

Life Sciences

Contributing editor
Alexander Ehlers



2017

GETTING THE
DEAL THROUGH

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Life Sciences 2017

Contributing editor

Alexander Ehlers

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Preface

Life Sciences 2017

Eighth edition

Getting the Deal Through is delighted to publish the eighth edition of Life Sciences, which is available in print, as an e-book and online at www.gettingthedealthrough.com.

Getting the Deal Through provides international expert analysis in key areas of law, practice and regulation for corporate counsel, cross-border legal practitioners, and company directors and officers.

Throughout this edition, and following the unique **Getting the Deal Through** format, the same key questions are answered by leading practitioners in each of the jurisdictions featured. Our coverage this year includes new chapters on Lithuania and Slovenia.

Getting the Deal Through titles are published annually in print. Please ensure you are referring to the latest edition or to the online version at www.gettingthedealthrough.com.

Every effort has been made to cover all matters of concern to readers. However, specific legal advice should always be sought from experienced local advisers.

Getting the Deal Through gratefully acknowledges the efforts of all the contributors to this volume, who were chosen for their recognised expertise. We also extend special thanks to the contributing editor, Alexander Ehlers of Ehlers, Ehlers & Partner Rechtsanwalts-gesellschaft mbB, for his continued assistance with this volume.

GETTING THE
DEAL THROUGH 

London
November 2016

Introduction

Alexander Ehlers

Ehlers, Ehlers & Partner Rechtsanwaltsgesellschaft mbB

Life sciences law, the entire range of legal practice for the life sciences industry, has become increasingly important in recent years. This can be said because the number of additional legal provisions and regulations regarding drug safety, pharmacovigilance, quality management, distribution, reimbursement and collaboration with healthcare professionals or patient organisations has increased significantly. However, this is not the only reason. Heeding Warren Buffett's famous warning, 'It takes 20 years to build a reputation and five minutes to ruin it,' pharmaceutical manufacturers and manufacturers of medical devices are increasingly willing to comply with these additional legal requirements and rules, in particular regarding collaboration with healthcare professionals and patient organisations. After the breast implant scandal in late 2011, pharmaceutical and medical device companies are now, more than ever, under public pressure to observe the respective requirements set out by legal provisions, directives and industry guidelines.

Further, the market for medicines and medicinal devices is highly competitive, and rule breaking is often pointed out and pursued by competitors. Conditions are complicated even further since the activities of manufacturers of medicines and medical devices are rarely limited to one country and, therefore, compliance with several rules and pieces of legislation must be ensured. Nevertheless, it is not only the

broad range of applicable rules and the competitive environment for manufacturers that have made life sciences law one of the most important legal areas in the recent past. Because of tightening public finance constraints, the reimbursement of medicines and medical devices has become subject to strict requirements in several countries, and consequently a great demand for legal advice with respect to reimbursement has arisen.

With this in mind, the following legal outline should serve as a guide for manufacturers of medicines and medical devices. It provides a helpful overview of the applicable rules for a variety of activities, with particular attention given to recent legal or political reforms. Furthermore, as the chapters cover several different jurisdictions, this edition of *Getting the Deal Through: Life Sciences* is also a comparative legal guide for cross-border activities or activities in a number of countries. I am honoured by the great success of seven previous editions of *Life Sciences* and am very pleased to once again be contributing editor of the eighth edition.

Of course, this legal outline is no substitute for case-related legal advice. Along with the other lawyers who have written chapters, I would be pleased to provide you with further insight based on our experience in this important and challenging legal area.

Australia

Kim O'Connell and James Ellsmore

King & Wood Mallesons

Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

Australia's healthcare system is organised, administered and funded by multiple levels of government and supported by a private health insurance system.

At the federal level, the government (through the Department of Health) is responsible for directing and coordinating healthcare policy, funding and regulation. The government administers Medicare, Australia's public health insurance scheme. Medicare encompasses the provision of free or subsidised medical services (through the Medicare Benefits Schedule), free or subsidised medicines (through the Pharmaceutical Benefits Scheme (PBS)) and free hospital treatment as a public patient.

Australia's eight states and territories are responsible for providing public health services, including public hospitals, and regulating private healthcare services and facilities.

Australians also have the option of taking up private health insurance with a registered health insurer. Private health insurance provides insurance cover for hospital treatment as a private patient, 'extras' cover (for services like physiotherapy, optical care and dental care) and ambulance cover.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

Australia's healthcare system has a complex funding structure. The Medicare system is partially funded through tax paid by Australians, as well as by an income-tax surcharge (whereby Australian taxpayers who earn over a certain amount pay a Medicare levy and a further amount if they do not have an appropriate level of private health insurance). In return, Australian residents are paid a benefit (rebate) for healthcare services they require. The federal government also provides a health insurance rebate of up to 35.722 per cent to Australians who take out private health insurance, depending on a person's age and income. Through this system, the federal government encourages Australians to take out private health insurance.

Medicare benefits are set according to an itemised schedule of fees for medical services (although doctors may set their own fees at more than the scheduled fee). The PBS provides subsidised access to over 860 medicines (and over 4,000 brands of those medicines) in Australia. Under the PBS, patients contribute up to a specified co-payment (currently A\$38.30) for each prescription item for medicines listed on the PBS.

Australia's public hospitals are funded jointly by the federal government and the states and territories. These levels of government also fund other health services, programmes and research.

Compliance - pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

Australia's therapeutic goods laws (including the Therapeutic Goods Act 1989, Therapeutic Goods Regulations 1990 and Therapeutic Goods Advertising Code (TGA Code)) and competition laws (including the Competition and Consumer Act 2010) govern the advertising of medicinal products in Australia.

The Therapeutic Goods Administration (TGA), an office within the Department of Health, administers Australia's laws relating to therapeutic goods. The Australian Competition and Consumer Commission (ACCC) is Australia's primary competition and consumer protection authority that administers Australia's competition laws.

Advertisements may also need to comply with applicable industry codes of practice. These codes include:

- the Medicines Australia Code of Conduct (MA Code) for advertisements of branded prescription products;
- the Generic and Biosimilar Medicines Australia Code of Practice (GBMA Code) for advertisements of generic prescription products;
- the Australian Self-Medication Industry Code of Practice (ASMI Code) for advertisements of non-prescription (over-the-counter) products; and
- the Complementary Medicines Australia Marketing and Supply Code of Practice: Complementary Medicines for advertisements of complementary medicines.

There are also state laws that apply (such as fair trading legislation).

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

In Australia, the type of medicinal product will determine the rules and principles that apply to advertising that product to healthcare professionals.

Prescription medicines

In addition to Australian competition laws, advertising prescription medicines to healthcare professionals is regulated by the Therapeutic Goods Act and the MA Code. The MA Code is a self-regulating code that is binding on all member companies of the MA (although membership of the MA is voluntary).

The main rules and principles for advertising prescription medicines to healthcare professionals include:

- only medicines included in the Australian Register of Therapeutic Goods (ARTG) may be advertised;
- advertisements can only refer to indications included in the ARTG for that particular medicine;
- all advertising must include certain minimum product information;
- information, claims and graphical representations must be current, accurate and fully supported by the product information for the medicine;
- comparisons of products must be factual, fair, capable of substantiation and referenced, and must not be disparaging; and
- a clear and prominent PBS disclosure statement must be included.

The GBMA Code also requires member companies, which agree to be bound by its Code, to comply with the Code and to consider other codes (including the MA Code) in advertising to healthcare professionals.

Non-prescription (over-the-counter) medicines

Advertising non-prescription medicines to healthcare professionals in Australia must comply with the Therapeutic Goods Act and the ASMI Code. The advertising rules contained in the ASMI Code largely reflect the requirements in the MA Code, although there are specific rules in relation to the promotion of pharmacy medicines and pharmacist-only

medicines. Like the MA Code, the ASMI Code is a self-regulating code that is binding on its members.

Australia's competition laws also apply to the advertising of both prescription and non-prescription medicines.

5 What are the main rules and principles applying to advertising aimed at the general public?

Advertising prescription medicines to the general public is not permitted in Australia.

Advertising non-prescription medicines to the Australian public is permitted. Such advertisements must comply with the Therapeutic Goods Act, Therapeutic Goods Regulations, TGA Code and ASMI Code.

The main rules and principles for advertising non-prescription medicines to the public include:

- advertisements on television and radio, in newspapers and magazines, on public displays and in cinemas must be approved by the TGA Code Council before publication;
- approval is not required for advertisements that display only the name, picture or price of the medicine without any therapeutic claims;
- advertisements must not:
 - arouse unrealistic expectations of effectiveness;
 - lead to consumers self-diagnosing or inappropriately treating potentially serious diseases;
 - exploit the lack of knowledge of consumers or contain language that could bring about fear or distress;
 - lead persons to believe they are suffering from a serious ailment or that harmful consequences may result from the medicine not being used;
 - encourage inappropriate or excessive use;
 - contain any claim that the medicine is effective in all cases, is safe or has no side-effects;
 - be directed to minors (with some exceptions); and
 - comparative advertisements must be factual and not misleading; and
- advertisements must not contain certain prohibited representations; and
- advertisements must not refer to certain serious diseases or conditions (without prior approval).

Australia's competition laws also apply to the advertising of both prescription and non-prescription medicines.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

Common infringements of the TGA Code include advertisements that arouse unwarranted and unrealistic expectations of product effectiveness, lead to consumers self-diagnosing or inappropriately treating potentially serious diseases, or are misleading.

Common infringements of the MA Code include advertisements that:

- are not balanced, accurate, correct or fully supported by the product information document;
- contain comparative statements that are not factual, fair or substantiated; or
- are misleading.

Misleading advertising is the most common infringement of the ASMI Code.

Manufacturers should ensure all advertising claims are balanced, accurate and reflect the scientific evidence. In particular, manufacturers should ensure that any comparative statements (eg, that a product works faster, is more effective or lasts longer) are accurate and can be substantiated.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

A pharmaceutical company may only provide information regarding an unapproved indication (of a prescription product) to a healthcare professional if that professional makes an unsolicited request. The information must be prepared by the company's medical department, not a member of the commercial team. Information relating

to an unapproved indication may also be displayed at international or Australian congresses held in Australia, provided the indication is approved overseas and there is a prominent notice that the indication is not approved in Australia.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

The relationship between pharmaceutical companies and healthcare professionals in Australia is governed by the MA Code, GBMA Code and ASMI Code. These codes govern the conduct of their members (addressed above). The main rules and principles by which members must abide are addressed in question 9.

Healthcare professionals' relationships with the pharmaceutical industry are also governed by their professional bodies. For example, for medical practitioners (doctors), the Australian Medical Association's (AMA's) Code of Ethics and the AMA guideline document 'Medical Practitioners' Relationships with Industry' contain guidelines that regulate how doctors should interact with pharmaceutical companies. Such codes apply to healthcare professionals generally and do not distinguish between doctors in the outpatient and in-patient sectors.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

Under the MA Code, GBMA Code and ASMI Code, collaboration between pharmaceutical companies and healthcare professionals must have the primary objective of enhancing medical knowledge and improving the quality use of medicines in Australia.

All interactions between pharmaceutical companies and healthcare professionals should be capable of withstanding public scrutiny and should not discredit or reduce confidence in the pharmaceutical industry. The provision of hospitality to healthcare professionals must be appropriate to the occasion, reasonable and of modest value. The offering of gifts, benefits in kind or pecuniary advantages as an incentive to recommend or prescribe a company's product is prohibited. In addition, there are specific rules relating to the organisation of educational events, trade displays, sponsorship, consulting arrangements, financial support and market research.

Pharmaceutical companies may also have reporting obligations under the MA or GBMA Codes. These obligations require such companies to report certain specified information, such as payments to healthcare professional consultants and advisory boards and educational events supported by the company.

Healthcare professionals may also have a professional responsibility to adhere to guidelines, including the AMA's Code of Ethics and guideline document 'Medical Practitioners' Relationships with Industry', as well as the Medical Board of Australia's 'Good Medical Practice: A Code of Conduct for Doctors'. These guidelines regulate interactions with industry consistent with the provisions in the MA, GBMA and ASMI Codes.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

The MA receives few complaints regarding collaboration between pharmaceutical companies and healthcare professionals. In the past three years, the MA has considered cases relating to the provision of accommodation expenses and the offer of gifts; however, breaches of the MA Code were not established.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

Rules governing collaboration with health consumer organisations are contained in the MA, GMIA and ASMI Codes. Notably, a company cannot be the sole funder of a health consumer organisation, must not make public use of an organisation's logo (or proprietary material) without that organisation's consent and must not seek to influence an organisation in a manner favourable to its own commercial interests.

The MA and the Consumers Health Forum of Australia have developed a guideline document, 'Working Together - A Guide

to Relationships between Health Consumer Organisations and Pharmaceutical Companies', which provides some principles for collaboration between health consumer organisations and companies, including respecting independence, maintaining public trust, fairness, transparency and accountability.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes. The ACCC is responsible for enforcing the Competition and Consumer Act, which includes the Australian Consumer Law (ACL).

In addition to pursuing pharmaceutical companies for contraventions of the ACL, and for misleading and deceptive conduct and other consumer-protection measures, the ACCC will also pursue companies that engage in anticompetitive conduct in breach of the Competition and Consumer Act. Such conduct includes conduct that substantially lessens competition in the market, exclusive dealing and third-line forcing, resale price maintenance, collective bargaining, price-fixing and market-sharing arrangements (including cartel conduct).

The ACCC has a variety of enforcement powers. Compliance and enforcement tools available to the ACCC include voluntary industry self-regulation codes, administrative resolutions (such as a signed agreement between the ACCC and a trader), infringement notices, court-enforceable undertakings and legal action. If legal action is taken for conduct in breach of the Competition and Consumer Act, a court can grant injunctions, order corrective advertising, damages, non-punitive orders (eg, requiring the offending trader to implement a compliance training programme), and impose pecuniary penalties and prison sentences for serious cartel conduct.

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes. A person (including a corporation) who has suffered loss or damage as a result of the conduct of a pharmaceutical company in contravention of the Competition and Consumer Act can bring an action against that manufacturer. Private antitrust litigation can be brought by competitors, purchasers and other persons who have suffered loss or damage as a result of the company's conduct.

Class actions may also be brought against manufacturers with respect to anticompetitive conduct.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

Pharmaceutical companies' transfers of value to healthcare professionals are now subject to more onerous reporting requirements. A more stringent transparency reporting regime, contained in the current MA Code, came into effect on 1 October 2015. The changes to the MA Code have strengthened the obligations regarding transfers of value from MA members to health professionals for the provision of services and where support is provided for education. The MA Code is authorised by the ACCC. Authorisation provides statutory protection from court action for conduct that might otherwise raise concerns under the competition provisions of the Competition and Consumer Act. Broadly, the ACCC may grant an authorisation when it is satisfied that the public benefit from the conduct outweighs any public detriment.

Pharmaceutical manufacturers are also subject to Australia's anti-corruption laws at both Commonwealth and state level. Generally, anti-corruption and bribery provisions are not limited to dealings with governments, they can also apply to employees or agents of private or public companies and individuals, as well as in dealings with foreign governments and government-owned entities.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Yes. Advertising medical devices and the collaboration of medical device companies with healthcare professionals and patient organisations is closely regulated.

Medical devices must be included on the ARTG and are regulated by the Therapeutic Goods Act, Therapeutic Goods (Medical Devices) Regulations 2002 and TGA Code. The Medical Technology Association of Australia (MTAA) is the representative industry body for medical device manufacturers and other businesses involved in the medical device industry in Australia. The MTAA Medical Technology Industry Code of Practice (MTAA Code) is a self-regulating industry code that is binding on MTAA member companies. The MTAA Code outlines requirements for the advertising and promotion of medical devices, and interactions with healthcare professionals and consumers.

The main advertising requirements for medical devices include the following:

- a medical device cannot be advertised as being for a purpose other than that for which it is included on the ARTG;
- advertisements cannot be misleading or deceptive, or likely to mislead or deceive;
- advertisements must not claim that a medical device is unique or has some special merit, quality or property unless the claim can be substantiated;
- all claims must be capable of substantiation by reliable technical, scientific or other support;
- comparative claims should be supported by unequivocal evidence; and
- advertisements to healthcare professionals must contain certain specified information.

The MTAA Code requires companies to undertake ethical business practices and prohibits any inappropriate inducement to use its products. The MTAA Code contains detailed rules covering company-sponsored training and educational events, hospitality and entertainment, trade displays, consulting arrangements, market research, gifts, competitions and research grants.

Companies may enter into relationships with health consumer organisations with the objective of enhancing the quality use of medical technology and supporting better outcomes for the Australian community.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The Australian regulatory framework for granting marketing authorisations and placing medicines, biologicals and medical devices on the market involves legislation at both the federal level and the state and territory level. Relevant federal legislation includes the Therapeutic Goods Act and the Therapeutic Goods Regulations, together with related legislation, orders and standards (including the Poisons Standard).

Each state and territory also has its own legislation governing medicines and related products. For example, in New South Wales, the Poisons and Therapeutic Goods Act 1966 and the Poisons and Therapeutic Goods Regulations 2008 are the applicable laws. State legislation supplements federal legislation and is administered by offices within each state or territory's department of health.

17 Which authorities may grant marketing authorisation in your jurisdiction?

Marketing authorisations for medicines, biologicals and medical devices are granted by the TGA. Medicines, biologicals and medical devices cannot be supplied unless they are included on the ARTG.

For prescription medicines and biologicals, it is also usual for such medicines to be included on the PBS. To be included on the Scheme, a prescription medicine or biological must be approved by the Pharmaceutical Benefits Advisory Committee, which is a statutory committee administered by the Department of Health.

18 What are the relevant procedures?

An application must be made to the TGA to include a medicine or a biological or medical device on the ARTG before that medicine or device can be manufactured or supplied. When a product is included on the ARTG, the TGA will issue a certificate. That certificate is akin to obtaining a marketing authorisation.

A person wanting to supply a medicine or medical device in Australia is known as a sponsor. The sponsor must be an Australian resident or a corporation with an Australian-resident representative.

The procedure for including a therapeutic good (ie, a medicine or medical device) on the ARTG will depend on the type of good. Medicines included on the ARTG are divided into different categories: prescription medicines, non-prescription (over-the-counter) medicines and complementary medicines are the most relevant. Medical devices (diagnostic tools, bandages and dressings, etc), biologicals (eg, stem cells and bone grafts) and other therapeutic goods (including tampons and disinfectants) also have their own procedures. The ARTG provides detailed regulatory guidelines outlining the specific requirements for registering each category of therapeutic good. One particular distinction to note is that 'higher-risk' medicines (which include all prescription medicines and most over-the-counter medicines) are registered on the ARTG, while complementary medicines (such as vitamin supplements and herbal medicines) are listed on the ARTG.

While the procedure for applying to have a product included on the ARTG differs slightly depending on the category of the good, the process is broadly the same.

A sponsor must determine the relevant category for the good sought to be included and ensure that it complies with the TGA's standards for manufacturing, marketing and labelling. For goods manufactured outside Australia, the sponsor must obtain good manufacturing practices clearance for all manufacturing sites.

The sponsor must submit the relevant application to the TGA, along with data establishing the quality, safety and (if the application is for a registered good) efficacy of the good, as well as pay the relevant application fees.

The TGA will assess the application and determine whether the good should be included on the ARTG.

Once a therapeutic good is included on the ARTG, the sponsor must maintain certain information on the ARTG (including manufacturer information), pay annual fees, comply with any registration or listing requirements, and report any adverse events, recalls or other problems associated with the good.

If the TGA refuses to include a good on the ARTG, there is a formal appeals process by which the sponsor can appeal the decision.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

No. There is no time limit within which marketing must commence in relation to a medicine included on the ARTG. Once marketing approval has been obtained, it continues as long as annual renewal fees are paid.

20 Which medicines may be marketed without authorisation?

Because medicines (including most complementary medicines) are classified as 'therapeutic goods', they must be included on the ARTG to be marketed. Australian legislation defines 'therapeutic goods' as any products for use in humans that relate to:

- preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury;
- influencing, inhibiting or modifying a physiological process;
- testing the susceptibility of persons to a disease or ailment;
- influencing, controlling or preventing conception;
- testing for pregnancy; or
- the replacement or modification of parts of the anatomy in persons.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

There are some exemptions for the supply of unapproved medicines in Australia. They include:

- importation of unapproved therapeutic goods for personal use through the TGA's 'Personal Import Scheme';
- the TGA's 'Special Access Scheme', which allows a person to import or supply, or both, an unapproved therapeutic good to a single patient on a case-by-case basis (subject to qualifying under the scheme and once approval is granted);
- supply by an 'authorised prescriber', through which a doctor may be granted authority to prescribe an unapproved therapeutic good (or class of unapproved therapeutic goods) to specific patients (or classes of patients) with a particular medical condition; and

- supply in the course of an authorised clinical trial through the TGA's 'Clinical Trial Exemption Scheme' or 'Clinical Trial Notification Scheme'.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

The market price of a medicinal product is governed by law or regulation to the extent that the product is listed on the PBS (the structure of which is governed by the National Health Act 1953 and the National Health (Pharmaceutical Benefits) Regulations 1960).

The Department of Health lists selected subsidised medicines on the PBS and sets a price for those medicines.

Eligible persons (Australian residents with a Medicare card and those visitors from countries with which Australia has a Reciprocal Healthcare Agreement) make a co-payment for each PBS-listed medicine they purchase. There is a concessional rate (determined by eligibility for a range of welfare payments) as well as a general rate. As of 1 July 2016, a patient eligible for the general rate pays up to A\$38.30 for most PBS-listed medicines or A\$6.20 if the patient is eligible for the concessional rate. The federal government pays the remaining cost of the medicine.

There are also safety nets. This means that, for a given year, when a patient with a concession card reaches a threshold of A\$372, they do not have to pay a PBS patient contribution. When a patient eligible for the general rate reaches a threshold of A\$1475.70, their PBS patient contribution falls to A\$6.20. The safety net threshold may be reached by completing forms that are available at available at both community pharmacies and outpatient pharmacies at public hospitals.

Medicines not listed on the PBS are also supplied in Australia (provided they are listed on the ARTG). These medicines are not supplied at a subsidised price. The price of medicines not listed on the PBS is not governed by law or regulation, except to the extent that such prices are subject to Australian competition laws.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

Pharmaceutical manufacturers in Australia are not required to negotiate their prices with public healthcare providers where those products are to be listed on the PBS. Rather, pharmaceutical manufacturers negotiate the prices of their products with the Department of Health. In this way, the Department of Health acts as a gatekeeper in relation to the pricing of medicines on the PBS.

Under the National Health Act, the Minister for Health and the sponsor of a pharmaceutical product to be listed on the PBS may agree an amount that is taken to be the appropriate maximum price for sales of the brand of pharmaceutical item to approved pharmacists. This is known as a price agreement. Where a price agreement is not reached, the Minister may make a price determination under the Act of the amount that is taken to be the appropriate maximum price for sales of the brand of the pharmaceutical item to approved pharmacists. In May 2015 the federal government introduced a raft of changes designed to reduce consumer and government spending on PBS-listed drugs and encourage the uptake of generic medicines and biosimilars. For more information on these changes, see 'Updates and trends'.

The appropriate maximum price must be the same for all brands of the same pharmaceutical item listed on the PBS, except if there is an approved brand or price premium. Where there are two or more brands of the same drug on the PBS, the government subsidises each brand to the same amount - up to the cost of the lowest-priced brand. If a patient chooses a more expensive brand, the price difference is required to be paid by the patient as a brand premium. This cost is in addition to the patient's co-payment.

The maximum amount that a pharmacist can charge a person and the amount that the pharmacist receives from the government for the sale of a pharmaceutical item are regulated by the National Health Act. Under the Act, where the price exceeds the co-payment, a pharmacist is required to charge only the applicable co-payment amount (unless there is an approved brand premium). The amount (the co-payment) is retained by the pharmacist. From 1 January 2016, pharmacists have the option to discount the PBS patient co-payment by up to A\$1 per script, which may increase competition between pharmacies.

If the government price is less than the relevant co-payment, a pharmacist is only able to charge an amount up to the government price. When an approved pharmacist supplies a pharmaceutical benefit, the pharmacist is entitled to be paid by the government the difference between the government price and the co-payment (if any).

The government price is calculated by the Pharmaceutical Benefits Remuneration Tribunal. The Tribunal must determine the government price by referring to any applicable agreement between the Pharmacy Guild of Australia and the government (currently the Sixth Community Pharmacy Agreement between the government and the Guild). The agreed basis for the determination of the Commonwealth price is that it comprises:

- an amount for the costs of production, being the ex-manufacturer price;
- an amount for the wholesale distribution of the product, being the wholesale mark-up;
- an amount for handling and storage by the pharmacy, being the pharmacy mark-up; and
- an amount for the pharmacist's specialised skills in dispensing the product, being a dispensing fee.

The total amount of the ex-manufacturer price and the wholesale mark-up comprises the approved price to pharmacists.

In a competitive market, an approved pharmacist is not normally willing to pay a manufacturer or a wholesaler more than the total of the ex-manufacturer price and the wholesale mark-up. However, manufacturers and wholesalers negotiate and offer pharmacists discounts on the purchase of particular brands that are listed on the PBS. Those discounts can result in the pharmacist obtaining additional profits on the sale of a brand, given that the amount reimbursed by the Commonwealth, calculated by reference to the Commonwealth price, remains the same. Pharmaceutical manufacturers also enter into direct supply arrangements with hospitals.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

The national health insurance system will reimburse a proportion of the costs of medicines that are listed on the PBS as outlined above (in questions 22 and 23).

The term 'off-label use' refers to prescriptions of registered medicines for a use that is not included in the prescribing information or that is disclaimed in the approved information. This includes use outside government-approved indication, dosage, age and route (ie, the indication that appears on the ARTG registration and product information for the medicine in question). The term does not refer to the conditions (if any) imposed on prescription under the PBS. In this regard, the conditions for a PBS subsidy may be more limited than the ARTG listing for a particular brand of pharmaceutical item. Therefore, to the extent that a medicine is prescribed off-label, and that off-label use is outside the conditions on the product imposed by the PBS, there will be no reimbursement.

In addition, where certain medicines that are not registered on the ARTG are prescribed (eg, under the TGA's Special Access Scheme), those medicines (by reason of not being on the ARTG) are not listed on the PBS, and therefore there is no reimbursement for those medicines.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The Minister for Health (and his or her delegates and the Department of Health, including its various committees) is competent for decisions regarding the pricing and reimbursement of medicinal products that are listed on the PBS.

If a wholesaler or manufacturer of a medicinal product listed on the PBS wishes to challenge a decision made with respect to the pricing determined for that product, that person must seek judicial review of that decision in the Federal Court of Australia.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

As noted in question 23, a pharmacist is not normally prepared to pay a manufacturer or distributor more than the total of the ex-manufacturer price and the wholesale mark-up. However, manufacturers and

distributors often negotiate and offer pharmacists discounts on the purchase of particular brands that are listed on the PBS. Those discounts can result in the pharmacist gaining extra profits on the sale of a particular brand listed on the PBS, as the amount reimbursed by the government, calculated by reference to the government price, remains the same. The offer of discounts in these circumstances, however, is not a statutory requirement.

In circumstances where a manufacturer or distributor wishes to list a new brand of pharmaceutical item on the PBS, in addition to an existing brand, and the new brand is bioequivalent or biosimilar to the existing brand and has the same drug and manner of administration (usually where a generic product is first listed and an innovator company's brand is already on the PBS), the agreed price must be at least 16 per cent lower than the approved price to pharmacists. When such a new brand is added to the PBS, the National Health Act requires that the agreed price for the other brand already listed also be discounted by 16 per cent. That is, the introduction of the generic product to the PBS means that the price for the innovator's product (already on the PBS) is statutorily reduced.

There are also statutorily required price reductions for combination items under the National Health Act as well as circumstances (set out in the Act) in which staged price reductions are implemented. Price reductions may also be triggered in some circumstances where products are grouped together (in therapeutic groups) for pricing purposes.

Following market entry, there is further monitoring of the prices that are actually charged on the market, and if there is substantial discounting, further price reductions will be implemented under the PBS.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

With the assistance of the Australian Customs and Border Protection Service, the TGA monitors the market for counterfeit goods. Products are considered counterfeit if the labelling, presentation, advertising, formulation or source of the goods is false. Counterfeiting of medicines on a large scale is not a major problem in Australia. However, medicines available for purchase over the internet from international websites are not regulated by the TGA. The TGA recommends that if medicines are purchased over the internet, such purchases should be made through the websites of Australian pharmacies.

It is an offence under Australian law for a person to intentionally manufacture, supply, import or export counterfeit therapeutic goods if the person knows the goods are counterfeit or is reckless as to whether they are counterfeit. The offence is punishable by imprisonment or a fine, or both. Civil penalties are also available. Australian law also provides for the forfeiture of imported counterfeit goods to the government.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

The federal government, consumer groups, pharmacies and pharmaceutical companies all provide consumers with access to information about prescription-only medicines. The not-for-profit organisation NPS MedicineWise is a prominent source of information for the public about the prescription and use of medicines.

Although not a recent measure, Australian law requires that when a prescription-only medicine is dispensed, a 'consumer medicines information' leaflet must be made available. The leaflet is prepared by the manufacturer of the medicine and provides information about the safe and effective use of that medicine.

29 Outline major developments to the regime relating to safety monitoring of medicines.

The TGA monitors the safety of medicines. It does so primarily through an adverse event reporting system. There have been no major developments to the regime relating to safety monitoring of medicines since the revised Australian requirements and recommendations came into effect in November 2012. These requirements and recommendations set out mandatory reporting requirements for adverse reactions and significant safety issues, as well as information to assist sponsors in meeting their requirements, for both registered and listed medicines regulated by the TGA.

Update and trends

Review of the Australian therapeutic goods regulatory regime

Last year, we reported that an independent review was under way into the regulation of medicines and medical devices. The Stage One Report made 32 recommendations relating to the approval, registration, variation and classification of medicines and medical devices, recognition of and coordination with overseas national regulatory authorities, post-market monitoring, current legislative framework and regulatory organisational structure. In November 2015 the federal government released the Stage Two Report, which covers the regulatory frameworks for complementary medicines and the advertising of therapeutic goods. It makes 26 additional recommendations; 19 of which concern the regulation of complementary medicines. They include proposed changes to improve:

- the regulatory framework administered by the TGA under which it lists, refuses to list or retains complementary medicines on the ARTG;
- the information available to sponsors and the public;
- the flexibility and clarity of the processes by which sponsors can apply for registration, coupled with review and appeal rights;
- the management of risk associated with complementary medicines, including a variation notification system and more comprehensive post-market monitoring;
- the provision of information by the sponsor regarding its product; and
- the incentives for innovation to improve competition.

The remaining seven recommendations concern the therapeutic goods advertising framework. The panel recommended:

- that requirements for advertising be made consistent across all medicines and medical devices;
- that advertising of therapeutic products moves from a pre-approval and vetting scheme to a more self-regulatory scheme;
- the development of a new advertising complaints system; and
- a review of advertising review and enforcement powers.

The federal government released its response to the Review in September 2016. The government accepted (or 'accepted-in-principle' or 'supported the intent of') most of the panel's recommendations. It also deferred its consideration of a number of recommendations due to the complexity of the issues involved. The government rejected two recommendations on grounds that they were not supported by stakeholders in consultation. Those recommendations concerned changing the decision-making process for the inclusion of medicines and medical devices in the ARTG and the scheduling of medicines and their inclusion in the Poisons Standard.

The panel also recommended that further reviews be undertaken to potentially streamline the regulatory framework for low-risk products and increase consumer access to these products. The reviews to be undertaken fall into two main categories:

- review of appropriate regulatory frameworks for low-risk products; and
- review of the Scheduling Policy Framework for medicines, to provide for the development and adoption of a formal risk-benefit methodology to assess scheduling applications and for opportunities to enhance input from interested parties into the scheduling process.

These reviews will commence in 2016/17.

Amendments to the PBS

In May 2015 the federal government announced its 'PBS Access and Sustainability Package'. The package was developed following stakeholder consultations and includes measures relating to the Sixth Community Pharmacy Agreement between the government and the Pharmacy Guild of Australia, agreed on 24 May 2015. The major elements of the package include:

- A one-off 5 per cent statutory price reduction for single brand medicines after being listed on the F1 formulary (the F1 formulary contains drugs that have only one brand of each form and strength listed on the PBS) for five years.
- Changing price disclosure arrangements for multiple-brand medicines which have been listed on the F2 formulary (the F2 formulary contains drugs for which there are more than one brand, and those brands are flagged as interchangeable) for three years or more.
- Applying flow on price disclosure reductions from component drugs (listed drugs that are constituents of combination drugs) to

multiple brand combination medicines on the F2 formulary.

- Allowing approved pharmacists to discount patient co-payments by a maximum of A\$1 for each PBS supply on a prescription.
- Extending the safety net early supply rules to apply to more medicines.

Review of PBAC Guidelines

A review of the Pharmaceutical Benefits Advisory Committee Guidelines (PBAC Guidelines) was completed in September 2016. The Guidelines were released in October 2016. The pharmaceutical industry uses the PBAC Guidelines to prepare submissions to the PBAC when applying to include a drug on the PBS. The new Guidelines constitute the first major revision and reorganisation of the text since November 2006. The Guidelines are designed to facilitate the evaluation and translation of the best available comparative clinical evidence for the requested PBS listing, followed by the most appropriate economic evaluation. Although the Guidelines present the currently preferred approach to the preparation of submissions to the PBAC, they stipulate that the approach is not prescriptive. Alternative approaches are permitted when adequately justified and supported by data.

Productivity Commission inquiry into Australia's intellectual property system

The Australian government asked the Productivity Commission to undertake a 12-month public inquiry into Australia's intellectual property system. The Commission released the Draft Report on 29 April 2016. A number of the findings intersect with the regulation of pharmaceutical products. Relevantly, the Draft Report included the following findings:

- Australia's patent system grants protection too easily, allowing a proliferation of low-quality patents, frustrating the efforts of follow-on innovators, stymieing competition and raising costs to the community. To raise the quality of patents, the Australian government should increase the degree of invention required to receive a patent, abolish the innovation patent, redesign extensions of term for pharmaceutical patents, limit business method and software patents, and use patent fees more effectively.
- Commercial transactions involving IP rights should be subject to competition law.
- Multilateral and bilateral trade agreements are the primary determinant of Australia's IP arrangements. These agreements substantially constrain domestic IP policy flexibility.

In relation to pharmaceutical patents specifically, the Commission recommended that:

- The Australian government should reform extensions of patent term for pharmaceuticals such that they are calculated based only on the time taken for regulatory approval by the TGA over and above one year.
- Regardless of the method of calculating their duration, extensions of term in Australia should only be granted through a tailored system that explicitly allows for manufacture for export in the extension period.
- There should be no extension of the period of data protection, including that applicable to biologics.
- The Australian government should introduce a transparent reporting and monitoring system to detect any pay-for-delay settlements between originator and generic pharmaceutical companies.
- The Australian government should reform section 76A of the Patents Act 1990 (Cth) to improve data collection requirements. Thereafter, extensions of term should not be granted until data is received in a satisfactory form.

The final report was handed to the Australian government in September 2016 and will be published by the Commission soon.

Australia's competition regulator wins proceedings against Reckitt-Benckiser

In April 2016, the Federal Court ordered Reckitt Benckiser (Australia) Pty Ltd to pay a penalty of A\$1.7 million for engaging in misleading conduct in relation to its Nurofen Specific Pain products, in proceedings brought by the ACCC. The Court found that the company had contravened the ACL by making false representations on its website and packaging that Nurofen Specific Pain products were each formulated to specifically treat a particular type of pain. In fact, each product contained the same active ingredient, ibuprofen lysine 342mg, which treats a wide variety of pain conditions.

In May, the ACCC appealed the amount of the penalty. The ACCC had submitted to the Court that a penalty of at least A\$6 million was appropriate in order to send a strong deterrence message. ACCC Chairman Rod Sims said: 'The ACCC will submit to the

Full Court of the Federal Court that \$1.7 million in penalties imposed on a company the size of Reckitt Benckiser does not act as an adequate deterrent and might be viewed as simply a cost of doing business.' The hearing of the appeal is scheduled for November 2016.

Each year the TGA receives more than 12,000 reports of suspected adverse events to medicines and vaccines. About 40 per cent of these reports come via pharmaceutical companies. All other reports are made directly to the TGA by general practitioners (about 15 per cent of all reports), hospitals (20 per cent) and specialists, community pharmacists, state and territory health departments and consumers.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

Although vaccination is not compulsory in Australia, immunisation coverage data for fully immunised children indicates Australia is meeting WHO targets, achieving 90 to 92 per cent coverage.

The Immunise Australia Program is a joint programme of the federal, state and territory governments and is administered by the Department of Health. The Program implements Australia's National Immunisation Program Schedule, funds free vaccination programmes, administers the Australian Childhood Immunisation Register and communicates information about immunisation to the public and to healthcare professionals.

Legislation in each state and territory specifies those authorised to administer vaccines. In New South Wales, for example, medical practitioners, nurses and midwives can administer vaccines.

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The Austrian healthcare system is characterised by the federalist structure of the country, the delegation of competences to self-governing bodies in the social security system, and the cross-stakeholder structures at the federal and provincial levels, which possess competences in cooperative planning, coordination and financing. With the exception of the hospitals sector, almost all areas of the healthcare system are primarily the regulatory responsibility of the federal authorities. In the hospitals sector, the federal legislator is only responsible for enacting basic law; legislation on implementation and enforcement is the responsibility of the nine federal provinces. In the outpatients' sector, as well as in the rehabilitation sector and in the field of medicines, healthcare is organised by negotiation between the 19 health insurance funds and the Federation of Austrian Social Security Institutions on the one hand, and the chambers of physicians and pharmacists (which are organised as self-governing public law bodies) and the statutory professional associations of midwives or other health professions on the other.

The various sectors of the healthcare system have traditionally been characterised by different stakeholders and regulation and financing mechanisms. However, in recent years there have been increased efforts to introduce decision-making and financing flows that are effective across all sectors. Since 2000, all federal provinces (except Vienna), as well as some of the private non-profit owners, have privatised their hospitals in the form of organisational privatisations. The various private operating companies have one thing in common: they are responsible for the management of hospitals, whereas the provinces or local authorities, as (majority) owners, usually act as guarantor. The Austrian healthcare system has developed almost completely into a model based mainly on decentralised contracts with all service providers.

In an effort to reduce the annual growth of public healthcare expenditure, the Parliament adopted a Healthcare-Targets Steering Act in 2013, which shall achieve cost containment through providing curative care at 'best point of service', enforcement of innovative outpatient care, targeted health promotion and prevention, establishment of a monitoring system, and effective and efficient application of medicines. To achieve these aims, the Federal Health Commission shall develop efficiency-oriented financing models for hospitals, establish financing guidelines, define health aims and indicators for monitoring and develop a documentation and information system. As a first step, the annual growth of public healthcare expenditure shall be reduced to 3.6 per cent until 2016.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

In 2014, total healthcare expenditure in Austria according to the Organisation for Economic Co-operation and Development system of health accounts accounted for €36.253 billion, or 11 per cent as a share of the Austrian gross domestic product (GDP). Thereof, current health expenditure amounted to €32.729 billion and gross capital formation in healthcare provider industries contributed €2.405 billion to the total expenditure on healthcare. Austrian healthcare expenditure (at current prices) increased on average by 5 per cent annually from 1990 to 2014.

As a share of GDP, total health expenditure increased from 8.4 per cent in 1990 to 11 per cent in 2014. The figures for 2015 are not yet available.

Public current healthcare expenditure consists of general government expenditure, which includes expenditure by federal, provincial and local governments as well as social security funds. In 2014, public current expenditure on health amounted to €25.642 billion. Total public expenditure, which also takes gross capital formation into account, amounted to €27.117 billion and corresponds to a share of 74.8 per cent of total healthcare expenditure. The biggest share of general government expenditure on healthcare (46.1 per cent) was spent on in-patient care in 2014. The other main spending categories were outpatient care (24.7 per cent), pharmaceutical products, medical durables and non-durables (13.3 per cent), and home-based long-term nursing care (9.1 per cent).

In 2014, private households and private insurance enterprises spent €8.153 billion on healthcare. With a share of 36.4 per cent, the largest expenditure category of private households and private insurance enterprises was outpatient care. A further 28.5 per cent went to in-patient care, while the third-largest share (27.8 per cent) was spent on pharmaceutical products, medical durables and non-durables.

Healthcare expenditure by private households and insurance enterprises grew from €2.576 billion in 1990 to €8.153 billion in 2014.

In total, 74.8 per cent of current health expenditure was financed by public sources. Private households, insurance enterprises, non-profit institutions and corporations financed altogether 25.2 per cent of current healthcare expenditure.

All those insured by the social health insurance system have a legal entitlement to benefits in kind and cash benefits within the legal framework of the specified (wide) range of benefits. Alongside statutory obligatory benefits, the health insurance funds also provide various levels of voluntary benefits according to their statutes, such as in the field of prevention.

Outpatient sector

Those covered by health insurance can choose freely between physicians in the outpatient sector, the majority of whom work in individual practices. In addition, approximately 800 outpatient clinics and hospital outpatient departments offer outpatient care. In 2015, about 45 per cent of the approximately 17,800 self-employed physicians in private practice have a contractual relationship with one or more health insurance funds. Around 55 per cent work as non-contracted physicians. Insured persons who consult non-contracted physicians are reimbursed with 80 per cent of the fee that the health insurance funds would pay to the contracted physicians. The population density of practising (employed and self-employed) physicians is around 5 per 1,000 inhabitants, but there is a considerable variation in this figure between the nine provinces.

Outpatient physician treatment is financed by (mandatory) insurance contributions, the premiums from private supplementary insurance and co-payments of private households. The payment of physicians in private practice is, in principle, set so that operating costs and investments for the practice can be amortised. The physicians' chambers at province level negotiate annual general agreements with the Federation of Austrian Social Security Institutions on the provision of contracted physician services. This has to be approved by the individual health insurance funds. The general agreements include, in

particular, payment regulations, agreements on service volumes and a capacity plan (location plan). On this basis, individual contracts are awarded to those physicians in private practice in accordance with the location plan. Contracted physicians receive a mixture of their capital payments for basic services and a fee-for-service payment for services that go beyond the scope of basic services. The distribution of these payment elements varies according to speciality, province and public due to the type of health insurance fund. In part, agreements on volume limitations for physicians' services are combined with decreasing payment scales. In principle, the utilisation of resources in the outpatient sector is subject to monitoring by the supervisory physicians or head physicians employed by the health insurance funds.

In-patient sector

Hospitals that are listed in the hospitals plan of a federal province (fund hospitals) are subject to public law and have a statutory requirement to provide care and admit patients. They are entitled to legally prescribed subsidies from public sources for investment, maintenance and operating costs. The ratio of 7.65 beds per 1,000 persons is clearly above the EU average. The admission rate of 27.9 per 100 inhabitants is one of the highest in the EU.

Public and non-profit hospitals, which are licensed to provide acute in-patient care in the hospitals plan of the respective province, have a mandate to provide care to all inhabitants. In return, they have a right to subsidies and to the reimbursement of operating costs. The expenditure on these hospitals amounts to around €11.9 billion. Approximately 45 per cent is financed by social health insurance funds, 7.5 per cent by private insurance (for better accommodation), and 3 per cent by private households by means of co-payments and out-of-pocket payments. A further 10 per cent is financed by budgeted funding from the federal government, the provinces and local authorities. The remaining amount of approximately 35 per cent is borne by the owners of public hospitals, that is, from the provinces or private non-profit organisations.

Compliance - pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

Advertisement of medicinal products to the general public and healthcare professionals is governed by the Act on Medicinal Products, implementing Directive 2001/83/EC (Community code relating to medicinal products for human use).

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

With regard to healthcare professionals, advertising is only permitted for medicinal products with a marketing authorisation, registered traditional medicinal products, registered homeopathic medicinal products, medicinal products accepted for parallel import and official medicinal products. Any advertisement must describe the properties of the medicinal product objectively and without exaggeration. The information provided by the advertisement must not contradict the summary of the product characteristics (SmPC). Advertising aimed at healthcare professionals may contain information that supplements the SmPC, provided that this information does not contradict the SmPC but confirms or articulates its content without distorting it.

Advertising of medicinal products subject to the mandatory publication of product characteristics and made through printed matter, electronic media or by means of telecommunication has to contain clearly legible SmPC. All information has to be exact, up to date, verifiable and complete to allow the addressee a personal evaluation of the therapeutic value of the medicinal products. Citations, tables and other information have to be reproduced verbatim and must contain a reference to their source. Citations from literature have to provide the essential content objectively. Furthermore, it is prohibited to offer premiums or other financial or tangible benefits to healthcare professionals unless such benefits are of minor value and provide a medical or pharmaceutical benefit.

5 What are the main rules and principles applying to advertising aimed at the general public?

Advertising aimed at the general public is prohibited for medicinal products subject to prescription, (over-the-counter) medicinal products marketed under the same or a similar name as a medicinal product subject to prescription, and registered homeopathic pharmaceuticals. However, this prohibition does not apply to publicly funded vaccination campaigns (eg, flu, ticks). Advertising has to be clearly recognisable as such and must contain the name of the medicinal product, the international non-proprietary name (INN) of the active ingredient (if the medicinal product contains only one active ingredient), the necessary information for sensible medical usage and clearly discernible advice that the medicinal product might have adverse effects, and that therefore the directions for use have to be consulted or the advice of a physician or pharmacist should be obtained. In the case of audiovisual media, this information has to be provided both audibly and visually. Furthermore, advertising aimed at the general public must not:

- contradict or go beyond the SmPC;
- contain pictures of healthcare professionals;
- allege that:
 - a medical examination is unnecessary;
 - there are no side effects;
 - good health might be improved by using the medicinal product;
 - non-use of the medicinal product might be detrimental to good health; or
 - the reason for the safety or effectiveness of the medicinal product is the fact that it is a 'natural product';
- exclusively or primarily address children;
- refer to recommendations of scientists or healthcare professionals;
- equate the medicinal product to a food, a cosmetic or other consumer goods;
- entrap the consumer to a wrong self-diagnosis through a detailed description or presentation of the anamnesis;
- refer to convalescence descriptions in a misleading or worrying way;
- use misleading or worrying pictures of transformations of the human or animal body caused by diseases or impairments through diseases; or
- induce mail orders for medicinal products subject to prescription.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

Although there are no statistics available, based on the quota of cases published in legal journals, probably the most common infringements committed with regard to the advertisement rules are misleading (comparative) advertising.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

Since Austrian law prohibits the advertising of medicinal products that do not have a marketing authorisation (and off-label use is the use of a medicinal product for an indication beyond the product's marketing authorisation) and restricts advertising to the contents of the SmPC, it is almost impossible to lawfully provide information regarding off-label use. Information to healthcare professionals limited to the INN of the active ingredient and its administration without any reference to the product's name or trademark, thus not directly advertising the off-label use of a specific medicinal product, seems to be possible. Furthermore, to limit the risk of product liability, it is appropriate to indicate that – notwithstanding the results of clinical studies – a marketing authorisation for this off-label use has not yet been obtained.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

The collaboration of the pharmaceutical industry with healthcare professionals both in the outpatient and in-patient sectors is governed by the Act on Medicinal Products (and in case of medical devices by the Act on Medical Devices). Neither the Act on Medicinal Products nor the Act on Medical Devices distinguishes between physicians in the outpatient and in-patient sector. Specific anti-corruption rules,

however, apply to public officials and physicians in the in-patient sector are public officials if they work in a public hospital. See question 14.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals are sections 55a and 55b of the Act on Medicinal Products. They prohibit the supply, offer or promise of gifts, pecuniary advantages or benefits in kind to persons qualified to prescribe or supply medicinal products unless they are inexpensive and relevant to the practice of a healthcare profession. The provision shall not prevent hospitality including travel expenses and accommodation offered directly or indirectly at events for purely professional and scientific purposes; such hospitality shall always be strictly limited to the main scientific objective of the event, and it must not be extended to persons other than healthcare professionals (such as the doctor's spouse). Persons qualified to prescribe or supply medicinal products shall not solicit or accept any such inducement. The federal Minister of Health may establish guidelines on the acceptable value of benefits, type and scope of hospitality, and may establish criteria for the qualification of exclusively business-related scientific events, but has not yet done so.

The offer or promise of discounts in kind to persons qualified to prescribe or supply medicinal products is allowed, unless such medicinal products are included in the Code of Reimbursement established by social security. In any case, persons qualified to prescribe or supply medicinal products must not solicit or accept discounts for medicinal products included in the Code of Reimbursement.

Product samples may be granted only for medicinal products having already obtained a marketing authorisation. The packages have to be the smallest package in the market labelled with 'Doctor's sample - not for sale'. The number of samples is limited to the use of 10 patients and 30 samples of a medicinal product per physician in the first year after the marketing authorisation and, thereafter, to two samples per request up to a maximum of five samples per year.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

Although there are no statistics available (and no cases published in legal journals), probably the most common infringement is excessive hospitality.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

The association of the pharmaceutical industry in Austria, Pharmig (www.pharmig.at), has issued a Code of Conduct that also deals with the industry's cooperation with patient organisations. Pharmig's Code of Conduct provides that cooperation between patient organisations and the pharmaceutical industry is based on common interests and has to take place in an ethical and transparent way. Support of patient organisations shall serve solely the interests of the patients and their families. Any support may only be provided on the basis of a written agreement, which shall in any event contain information about the nature and scope as well as a description of the support involved and the consent of the patient organisation to disclosure by the pharmaceutical company. Pharmaceutical companies must not influence the editorial work of the publications of patients organisations supported by them without a justifiable factual reason (such as correction of inaccuracies of content or correction from scientific aspects). Pharmaceutical companies shall detail on their website all the patient organisations they support by giving information about the nature and scope as well as a description of the support involved. The assumption of costs for members of patient organisations, patients or their families as well as other invited participants in the course of educational events shall be limited to travel costs, accommodation abroad as well as the admission fee, and shall be appropriate.

12 Are manufacturers' infringements of competition law pursued by national authorities?

The European Commission has imposed fines on pharmaceutical companies for pay-for-delay agreements. The producers of generic drugs refrain from or delay the marketing of their products in return for substantial financial benefits. However, there is no record of manufacturers' infringements of solely national competition law, but the Federal Cartel Authority (FCA) has pursued competition infringements with increasing vigour in recent years.

In spring 2009, the FCA brought an action in the cartel court for fines relating to printing chemical wholesalers; the action was based on leniency applications. The cartel court imposed a fine of €1.5 million on the concerned undertakings in April 2010, which was upheld by the Supreme Court in October 2010. It is noteworthy that in this case a fine was also imposed on the crown witness for lack of cooperation. In autumn 2010, the FCA filed an action against sugar producers for alleged allocation of customers and price-fixing agreements. In 2011, the FCA brought actions for vertical price-fixing agreements against producers of insulating materials and retailers. In spring 2013, the cartel court imposed a fine of €20.8 million against REWE (a large grocery chain) for vertical price-fixing agreements with suppliers and in December 2014, fines of €17.4 million were imposed on companies engaged in the transport and freight forwarding industry because of illegal price-fixing. In 2015 the cartel court imposed a fine of €30 million against SPAR (Austria's second-largest grocery chain) for vertical price-fixing agreements with suppliers of dairy products; and in August 2016, the FCA imposed an additional fine of €10.21 million against SPAR for vertical price-fixing agreements with other suppliers.

13 Is follow-on private antitrust litigation against manufacturers possible?

Follow-on private antitrust litigation to recover damages is possible. However, there has been only one such case in Austria, awarding damages of €218 to a claimant for an illegal price cartel established by driving schools. In February 2010, several territorial authorities, transportation companies (especially railway companies) and real estate companies filed follow-on damage claims of approximately €100 million for antitrust infringements committed by lift manufacturers. These cases are still pending. Presently the Austrian Supreme Court has only ruled that these damage claims are coherent and conclusive, and not time-barred.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

The Austrian Criminal Code penalises passive bribery (the request or acceptance of a benefit by a public official or arbitrator in exchange for the execution of a service in breach of their duties) and active bribery (the grant, promise or offer of a benefit to a public official or arbitrator in exchange of a service in breach of their duties) by imprisonment of up to 10 years. Also, the illegal acceptance of an advantage (the request or acceptance of a benefit by a public official or arbitrator in exchange for a dutiful execution of their services) is punishable by up to five years' imprisonment. The granting of undue advantages (the grant, promise or offer of a benefit to a public official or arbitrator in exchange for the dutiful execution of a service) may be punished with imprisonment of up to five years.

A public official is any person working for, or authorised by, a national public service organisation, an international organisation or foreign state or an enterprise of which at least 50 per cent is directly or indirectly owned by a national or foreign political body.

There are no particular provisions provided by law in terms of transparency requirements. However, self-regulation under Pharmig's Code of Conduct provides for a disclosure of the cooperation of pharmaceutical companies with healthcare professionals. The Code of Conduct applies to Pharmig members only. According to article 9 of the Code of Conduct, pharmaceutical companies have to document and disclose any and all transfers of value granted to healthcare professionals and/or institutions. For details see www.pharmig.at/de/verhaltenscodex/pharmig-verhaltenscodex/verhaltenscodex.aspx.

Update and trends

The implementation of electronic health records began in 2015. As a first step, public hospitals in Vienna and Styria made health records available electronically, followed, in summer 2016, by accident and emergency. Additionally, electronic medication was introduced on trial in the district of Deutschlandsberg. Medicinal products administered to a patient are electronically registered so that other healthcare providers are aware of the patient's medication to avoid adverse effects. This application shall be rolled out across Austria in the coming years. It is expected that this tool will help to reduce duplicating examinations and adverse effects in medication. As in most countries that have introduced electronic health records, Austrian physicians are reluctant for this change to take place.

Currently, there is no legislation in the pipeline on a national level that will have a major impact on the current legal environment for medicines and medical devices in Austria. (On an EU level the draft regulation on medical devices will also have an impact on the legal environment for these products in Austria.)

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Sections 102 to 108 of the Act on Medical Devices offer similar provisions on the advertising of medical devices to healthcare professionals and the general public, but less detailed regulations with regard to the collaboration of manufacturers with healthcare professionals. This is because of the proprietary differences between medicinal products and medical devices and the fact that no detailed provisions under EU directives had to be implemented verbatim. The anti-corruption provisions of the Austrian Criminal Code also apply to manufacturers of medical devices (see question 14). With regard to medical devices, there are no transparency requirements similar to the rules established by Pharmig in respect of medicinal products.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The regulatory framework for granting marketing authorisations and placing medicines on the market is provided by the Act on Medicinal Products. The provisions closely follow Directive 2001/83/EC on the Community code relating to medicinal products for human use.

17 Which authorities may grant marketing authorisation in your jurisdiction?

Marketing authorisation is granted by the Austrian Federal Agency for Safety in Healthcare (BASG), unless an authorisation has been granted in accordance with Regulation (EC) No. 726/2004, read in conjunction with Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No. 1394/2007.

18 What are the relevant procedures?

A marketing authorisation may only be granted to an applicant established in the European Economic Area. The application shall be accompanied by the particulars listed in article 8, paragraph 3 of Directive 2001/83/EC. Forms for obtaining marketing authorisation are available on the Federal Agency's website (www.basg.gv.at). Easements apply to the marketing authorisation of generic medicinal products.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Marketing authorisations are granted principally for a period of five years. No earlier than one year and no later than nine months prior to expiry, the licence holder of a medicinal product for human use may apply for a prolongation provided the criteria for obtaining the marketing authorisation are still fulfilled. The applicant has to provide an overview

of pharmacovigilance data, if necessary a report discussing any data that could possibly influence the assessment criteria and a consolidated version of the particulars to be filed for obtaining the marketing authorisation with all amendments since registration. If the BASG extends the marketing authorisation it is unlimited in time, unless an explicit limit of another five years is set due to reasons of pharmacovigilance.

If the marketing authorisation is not used within three years by putting the medicinal product on the market, the licence becomes invalid. The BASG may provide for exemptions for reasons of health protection. If marketing of a medicinal product is only impossible due to patent protection, the grace period only starts after expiry of patent protection.

20 Which medicines may be marketed without authorisation?

Medicines described in an Austrian Pharmacopoeia monograph that are prepared in a pharmacy for direct distribution by that pharmacy may be marketed without authorisation. In addition, medicinal products prepared by a pharmacy according to the instruction of a qualified physician, dentist or veterinarian may be marketed without authorisation. Furthermore, certain veterinary medicinal products do not need a marketing authorisation.

A marketing authorisation is also not required for conducting a (pre-)clinical trial or upon prescription by a physician admitted in Austria in cases of urgent need to fend off a danger to life or a substantial detriment to health, and this purpose cannot be achieved through the use of a medicinal product that has already obtained a marketing authorisation. Finally, pharmaceuticals for medical treatment in cases of emergency (natural disaster, terrorism, war) may be marketed without a marketing authorisation.

Furthermore, no marketing authorisation is required for medicinal products if the BASG has permitted distribution of a medicinal product according to article 83 of Regulation (EC) No. 726/2004 under a compassionate use programme. The programme has to define a group of patients suffering from chronic or severe diseases causing invalidity or a danger to life that cannot be treated by available medicinal products that have obtained marketing authorisation.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Upon prescription by a physician admitted in Austria, medicinal products that have not yet obtained a marketing authorisation may be administered under the physician's responsibility provided that the medicinal product is urgently needed to fend off a danger to life or a substantial detriment to health, and this purpose cannot be achieved through the use of a medicinal product that has already obtained a marketing authorisation. The physician has to confirm these requirements. Based on this confirmation, a pharmacy or a pharmaceutical wholesaler may apply for an import certificate to be issued by the BASG.

Upon application by the manufacturer of a medicinal product (if he or she is the sponsor of an approved clinical trial) or by the applicant for a marketing authorisation according to article 6 of Regulation (EC) No. 726/2004, the BASG may approve marketing of a medicinal product without marketing authorisation under a compassionate use programme for a defined group of patients suffering chronic or severe diseases. The modalities for such application are governed by the guideline on compassionate use of medicinal products pursuant to article 83 of Regulation (EC) No. 726/2004. The BASG issues guidelines for applications for compassionate use programmes. The guidelines are available in English and German on the BASG website (www.basg.gv.at/fileadmin/user_upload/L_1217_Compassionate_use_AT_en.pdf).

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

Theoretically, the manufacturer or distributor of a medicinal product is free to establish the price for his or her medicinal products. Practically, however, social security only reimburses patients the costs of medicinal products listed in the Code of Reimbursement. The Code of Reimbursement is established by the Federation of Austrian Social Security Institutions according to the General Social Security Act. The details of the pricing and reimbursement process are described in question 25.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

Since social security only reimburses patients the costs of medicinal products listed in the Code of Reimbursement, pharmaceutical manufacturers must negotiate the prices of their products with the public healthcare providers to achieve inclusion in the Code of Reimbursement. The details of the process are described in question 25.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

Upon prescription by a physician (or dentist), the Austrian health insurance systems reimburse the cost of medicines. For medicines in the yellow or red box of the Code of Reimbursement, physician or dentist prescriptions may be subject to approval or review by the local health insurance fund's 'head physician'. In the case of off-label use or compassionate use, upon approval by the head physician, the cost of the medicine is reimbursed provided there is no other reasonable current treatment available in Austria that is likely to be successful, or such treatment has been unsuccessful and the off-label treatment has a reasonable probability of success.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

After obtaining marketing authorisation, the manufacturer or distributor may apply for the inclusion of the medicinal product into the Code of Reimbursement by suggesting a retail price. Upon the manufacturer's application the product is included in the red box of the Code of Reimbursement for a period of 90 days (or 180 days in cases where the Social Security Fund also decides on the price) and has to be deleted if the Social Security Fund decides that the product is non-reimbursable after this period has elapsed. The price commission investigates the EU average price and informs the Social Security Fund, which negotiates the reimbursement price with the manufacturer or distributor. With the establishment of the EU average price, the medicinal product remains in the red box for a maximum of two years. The manufacturer, however, may apply within that period for inclusion in the yellow box or the green box. This application has to be made at least 90 days prior to the end of the two-year period. Where a decision on the price is also made, the application has to be made at least 180 days prior to the expiry of this period. Prices are evaluated every six months; if the price commission finds the EU average price cheaper, the Social Security Fund may demand a price reduction from the manufacturer and repayment of the difference.

Generics may be included in the Code of Reimbursement, provided they are substantially (at least 48 per cent) cheaper than the original product. Upon inclusion of a generic product, the manufacturer or importer of the original product must reduce the reimbursement price by at least 30 per cent to avoid delisting. A second generic product is eligible for inclusion in the Code of Reimbursement if it offers a substantial price difference when compared with the first generic product. If a

third generic product is registered, the manufacturer or importer of the original product has to offer a further price reduction to avoid delisting.

In the outpatient sector, the patient is entitled to receive any medicinal product upon prescription by his or her physician free of charge in any pharmacy, except for the payment of a minor prescription fee.

In the in-patient sector, the administration of medicinal products is an integrated part of the hospital treatment so the patient does not have to pay additional charges for them. Hospitals may negotiate the prices of their supply of medicinal products directly. The Social Security Fund, however, does not compensate the purchase price of the medicinal products separately because these costs are included in the global reimbursement for hospitalisation paid by the Social Security Fund to the hospitals.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

From 2004 until 2006, manufacturers and distributors had to pay a discount of 2 per cent of their annual turnovers with the social security funds; however, currently there is no statutory discount applicable in Austria. In December 2015, the pharmaceutical industry and the Social Security Fund reached an agreement on a 'voluntary' discount of €125 million in 2016. In 2017 and 2018, €10 million per percentage point of cost increase shall be paid, up to a maximum of €80 million per year. This 'voluntary' agreement was reached because the Ministry of Health threatened to reintroduce a statutory discount.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Under the rules that generally prevent counterfeiting and illegal distribution of products, counterfeiting of medicines may infringe the originator's trademark or patent rights, or both. Moreover, the originator may induce customs action against goods suspected of infringing certain intellectual property rights under Council Regulation (EC) No. 1383/2003. The competent customs authority for actions taken under this Regulation is the Villach Customs Authority. Furthermore, the Austrian Medicines and Medical Devices Agency has the authority to start investigations and search premises, and to transport devices to control compliance with the Act on Medicinal Products and the Act on the Importation of Medicines.

The adoption of Directive 2011/62/EU amending Directive 2001/83/EC, as regards the prevention of the entry into the legal supply chain of medicinal products that are falsified, has been implemented in Austria by amendments to the provisions of the Medicinal Products Act.

The Ordinance on Distant Selling of Medicinal Products (BGBl II 105/2015) sets up specific rules pharmacies have to comply with for the purpose of distance selling of medicinal products (medicinal products may be sold only for customary personal use, only OTC-products may be sold, transportation has to be made through qualified third-party logistics providers, returns must not be put on the market again).



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28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

No measures have been taken in Austria to facilitate the general public's access to information about prescription-only medicines. Since advertising prescription-only medicines to the general public is prohibited, only information brochures aimed at improving patient compliance through general information are permitted. Such brochures, however, must not contain direct or indirect appraisals of the medicinal product, and must not create direct or indirect incentives to use a particular medicinal product.

29 Outline major developments to the regime relating to safety monitoring of medicines.

There have been no major developments to the regime relating to safety monitoring of medicines since the implementation of Directives 2001/83/EC and 2003/94/EC; however, through the Ordinance of 17 September 2008 BGBl II 324/2008, the Ministry of Health enacted a new Ordinance on the Production and Marketing of Medicinal Products 2009 that codified the various amendments to the Ordinance on the Production and Marketing of Medicinal Products 2005.

Following the adoption of Directive 2010/84/EU amending, as regards pharmacovigilance, Directive 2001/83/EC, the Austrian Act on Medicinal Products as well as the Ordinance on the Production and Marketing of Medicinal Products 2009 have been amended accordingly.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

The first vaccination recommendations for children were issued by the government in 1959. In 1973, a 'mother-child passport' was introduced to record and monitor the administration of vaccines. Since 1984, the Ministry of Health has issued an annual vaccination plan providing for free vaccination of infants and children as well as vaccination recommendations for adults. Notwithstanding free vaccination against diphtheria, tetanus, pertussis, polio, hepatitis B, mumps, measles, rubella and rotavirus for infants, and subsidised vaccination against influenza, pneumococcus and HPV, most vaccination rates are below the World Health Organization targets. This is probably because vaccination is not mandatory but only recommended, and no central register of vaccination is maintained.

Only doctors may administer vaccines in Austria.

Colombia

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

In 2015, the Health Statutory Act (Law 1751, 16 February 2015) was sanctioned, which establishes healthcare as a fundamental right for all citizens. In addition, article 49 of the Colombian Constitution states that all citizens shall benefit from public healthcare, and therefore the social security system should regulate public health services and establish conditions to grant access to the entire population.

The national government manages the healthcare system through the Ministry of Health and Social Protection (MoH) and the National Superintendency of Health. In 2012, the government eliminated the Health Regulatory Committee through Decree 2560, assigning its functions to the MoH. Also active in the healthcare system are Benefit Plans Administration Entities (EAPB), including professional risk managers and health institutions.

The social security system is mostly regulated by Law 100 of 1993, which establishes the duty of equity in access to health services and a mandatory health insurance for every citizen. Originally, the system had two regimes to achieve this – one contributive and one subsidised. The contributive regime stated that every employer had to affiliate their employees to the healthcare system, whereas through the subsidised regime, the national government would ensure that those without an employer or otherwise unable to contribute were affiliated. In 2008, however, the Constitutional Court declared this distinction illegal (see decision T-760, 2008) and stated that the national government should accomplish its duty through a single regime with equal conditions for the whole population. This decision, together with other endemic problems in Colombia's healthcare system, triggered a structural change to the health system. On 19 January 2011, the Colombian Congress issued Law 1438, which, inter alia, unifies access to health services as of 1 July 2012.

As of 1 July 2012, contributive and subsidised regimes have the same benefits regarding the national Mandatory Health Plan (POS). To complement the POS, users may choose to voluntarily pay for an additional health plan.

Medical care for those who are not affiliated to any regime is supposed to be provided by public health institutions or by private entities that have contracts with the government to provide such services.

Currently, the POS covers essential medicine and treatment for diseases. According to the Health Statutory Act (2015) the POS will only exclude the following treatments: (i) treatments whose main purpose is cosmetic or sumptuary and is not related to the recovery or maintenance of a functional or vital capacity; (ii) treatments where no scientific evidence exists on their safety and clinical efficacy; (iii) treatments whose use has not been approved by the competent authority; (iv) treatments that have not been validated; or (v) treatments that have to be provided abroad. To implement the 'all-inclusive' POS, the MoH issued Resolution 1328 of 2016 establishing the procedure to remove technical scientific committees, which were responsible for the approval of non-POS therapies and for the contributive regime, and to replace them with an online information system (prescriptions tool) to allow the government to monitor doctors' prescriptions. Exclusions could also be prescribed through this information system and approved by new professional committees.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The healthcare system is financed by the national government for the attention of general diseases and non-occupational risks. The National Fund for Solidarity (FOSYGA) manages the resources designed for healthcare. The MoH mandates this fund to fulfil its obligation to distribute the portion of the budget assigned to the social security system. The resources are distributed to the following accounts:

- catastrophic risks and traffic accidents; this account covers the costs of caring for victims of traffic accidents and victims of catastrophic events or terrorism;
- the compensation account, which finances the contributive regime;
- the solidarity account, which raises the resources provided by all parties in the subsidised system; and
- the promotion account, which finances educational activities for health promotion and prevention of diseases.

Articles 67 and 73 of the National Development Plan (Law 1753 of 2015) contain particular dispositions regarding rules on resource management and reimbursement procedures before the FOSYGA. Additionally, Law 1797 of 2016 was recently issued, containing fiscal and operational mechanisms seeking to ensure the financial stability of the healthcare system as well as the improvement of resource management and services quality.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

The advertising of medical products to the general public and HCPs is regulated by article 79 of Decree 677 of 1995, providing a general rule according to which pharmaceutical products may only be advertised in scientific or technical publications addressed to professionals in the field, with the exception of over-the-counter medicines that may be advertised through press, television or any other media following the parameters stated in Resolution 4320 (2004).

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

According to article 79 of Decree 677, the rules and principles for advertising aimed at HCPs relate to the nature of the information that such advertising may include. Information must be complete and include all of the mechanism of action (MoA), indications, therapeutic uses, contraindications, side effect risk management, and precautions and warnings about the drug without omitting any of those stated in the scientific literature or those known by manufacturers.

Advertising and information on medicines must be truthful and the benefits cannot be overstated.

Paragraph 4 of article 79 of Decree 677, prohibits the advertising of drugs when such advertising:

- is contrary to the general rules on health, therapeutic education and nutrition;
- expresses partial truths to mislead or lead to error; or
- imputes, defames, causes injury or is pejorative compared to other brands, products, services, companies or organisations.

The active pharmaceutical ingredient (API) must always be identified by its generic name.

Price lists and calendars may not bear the indications and uses of prescribed medicines.

Finally, marketing authorisation (MA) holders will be responsible for any transgression on the content of promotional materials and advertising, and for the consequences that may arise.

5 What are the main rules and principles applying to advertising aimed at the general public?

Only over-the-counter medicines can be advertised to the general public following the parameters stated in Resolution 4320 (2004). Over-the-counter medicines require an MA. The information provided must include appropriate guidelines for the final user, as well as impartial information about the product's benefits, indications and contraindications.

In addition, advertising material cannot use elements that attract the attention of children, and must always include the product's MA number, together with statements that the product is a drug, and that the user should read indications and contraindications, should not exceed the stated dosage and should consult a doctor in the event that symptoms persist.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

In practice, the most common violations of advertising rules relate to the circulation of international magazines or flyers that include prescription drug advertisements aimed at the general public. These sorts of advertisements are mostly found in pharmacies and health facilities. Additionally, there have been some sanctions from the National Food and Drug Surveillance Institute (INVIMA) due to the existence of web pages allowing patients to access information, which is directed only to prescribers.

There have been a few cases of local manufacturers launching prescription medicines with aggressive advertisements aimed at end users containing indirect or hidden references to the product. Most of those campaigns are normally stopped either by the regulatory or unfair competition authorities.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

MA holders may not provide information regarding off-label use to HCPs according to Decree 677 of 1995, which states that drug advertisements cannot contain information or even suggestions about indications different from those approved in the MA.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

Article 17 of the Health Statutory Act (Law 1751 of 2015) states that:

Promotion or grant of any privileges or gifts to Professional Health Workers in the framework of his professional practice is expressly prohibited, be they in cash or in kind from suppliers, pharmaceutical companies, producers, distributors or traders of medicines or supplies, devices and/or medical or similar equipment.

In addition, article 106 of Law 1438 of 2011 also specifically states that pharmaceutical companies are not allowed to provide any sort of privilege or gifts to any player in the healthcare system, including HCPs and physicians. No distinction is made regarding outpatient or in-patient sectors.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

In addition to the general rules already mentioned in question 8, the Association of Pharmaceutical Laboratories for Research and Development (AFIDRO) launched in 2015 a Code of Ethics (ACE) containing guidelines concerning business conduct, promotional and

educational activities and interrelationships of the pharmaceutical industry with all relevant actors of the Colombian Health System.

Although not legally binding, the ACE is a voluntary self-regulation of the pharmaceutical industry that establishes some general guidelines to 'promote an atmosphere of healthy competition and development of promotional strategies consistent with unified ethical criteria.' In particular, some of the most relevant provisions regarding the collaboration of the pharmaceutical industry with HCPs in the ACE are as follows: (i) any drug promotion carried out by the pharmaceutical industry must be based solely on arguments, facts and scientific data; (ii) promotional items or medical samples must not individually exceed a sum equal to 10 per cent of a current legal monthly minimum wage (approximately US\$20) and it may be delivered in minimum quantity, if it relates to the work of the healthcare professional who receives it. These items cannot, under any circumstances, consist of gifts, cash or its equivalent for the personal benefit of the healthcare professional; and (iii) one may hire HCPs as consultants and advisors in activities such as speakers or moderators, where the remuneration for said activities must be monetary and obey market criteria.

AFIDRO has an ethical tribunal that includes, among its responsibilities, reviewing violations of the ACE.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

Manufacturers are usually tempted to provide information covering off-label use to HCPs or information about prescription medication that does not comply with the regulations in article 79 of Decree 677 of 1995 (see question 4). Less frequently, pharmaceutical companies provide HCPs with expensive gifts (such as tablets, free dinners or travel), giving the reason that such gifts contribute to furthering the education of the professional. There have been no recorded breaches of the Health Development Act, but, new investigations are ongoing.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

There is no specific regulation regarding this matter. However, in practice, the collaboration between pharmaceutical companies and patient organisations is based on research activities and general support of patient care.

The ACE establishes some general principles based on which aspects of the relationship between industry and patient organisations should be addressed, as follows: (i) independence and autonomy of the patient organisations; (ii) cooperation between patient organisations and companies so that equal weight is given to the points of view and decisions of each party; (iii) support to patient organisations will not be used for inducing drugs promotion or prescription; (iv) any support and scope of any collaboration given to a patient organisation will always be clearly recognised; and (v) funding of patient organisations shall ideally come from various sources.

The ACE also provides some guidelines regarding the interaction of the pharmaceutical industry with patient organisations. The referenced provisions are the following: (i) no pharmaceutical company may use the logo or sign that identifies the patient organisation, except in joint activities with the patient organisation; (ii) when companies sponsor material or a publication of patient organisations, they shall not seek to influence its content so that it can favour their own commercial interests; (iii) patient organisations may provide advisory or consulting services to companies, where the remuneration must be monetary and obey market criteria.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Unlike the regulatory authorities, the competition authorities cannot pursue ex officio investigations of unfair competition acts related to pharmaceutical products. However, the pharmaceutical industry is very active in this regard, and it is relatively common for competition authorities to be asked to take action regarding conduct that may affect the market or the end consumer of a given product.

13 Is follow-on private antitrust litigation against manufacturers possible?

There is no legal norm specifically providing for follow-on private antitrust litigation. Affected third parties may bring an ordinary declaratory civil suit seeking damages caused by the proven anticompetitive behaviour. However, to our knowledge, there has been no follow-on litigation against manufacturers. Nevertheless, recent pricing pressures and enforcement of price control mechanisms (see 'Update and trends') may make follow-on litigation more attractive in the future.

The Deputy for Verification and Control of Technical Regulation and Legal Metrology of the Superintendence of Industry and Commerce, which is in charge of supervising the compliance of technical regulations, has recently sanctioned and initiated investigations against pharmaceutical companies for selling pharmaceutical products exceeding the regulated price.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

Article 17 of the Health Statutory Act (Law 1751 of 2015) expressly prohibits promoting or granting any privileges or gifts to HCPs in a professional practice framework, be they in cash or in kind, from suppliers, pharmaceutical companies, producers, distributors or traders of medicines or supplies, devices or medical or similar equipment.

Article 28 of the Anti-Corruption Act states that whoever commits fraud or exerts undue influence over an official employee with the purpose of obtaining an economic benefit will have committed a crime. This article provides a four- to eight-year prison term and fines up to US\$4,448 (2016).

Article 29 of the Anti-Corruption Act states that when a public servant or an official employee, or whoever has held public office, obtains for him or herself or from another an unjustified increase in his or her assets, will have committed a crime. This article provides a nine- to 15-year prison term and fines up to US\$5,448 (2016).

Article 106 of Law 1438 of 2011 also specifically prohibits pharmaceutical companies from providing any sort of privilege or gifts to any HCP.

Law 23 of 1981 (Physicians Code of Ethics) also expressly prohibits a physician from receiving commercial benefits from pharmacies, laboratories, optical or orthopedic establishments and other organisations and similar institutions that are suppliers of items subject to medical prescription. Violations to this Code can lead to the following sanctions (which may be applied without prejudice to criminal or civil sanctions):

- a private warning;
- censure;
- suspension in the practice of medicine for up to six months;
- suspension in the practice of medicine for up to five years; and
- the sanction may be applied without prejudice to criminal or civil sanctions.

A regulatory attempt to force HCPs to disclose payments and transactions derived from their relationships with pharmaceutical companies was blocked by the medical community last year. However, Resolution 1328 of 2016 provided the creation of a prescription database (to be implemented in the coming months) in order to, inter alia, determine if physicians have any relationship with the company selling the medicines they prescribe, especially if they are high-cost medicines.

The Anti-Bribery Act (Law 1778 of 2016, Resolution No. 100-002657 and Circular No. 100-03 of 2016) defines the scope of transnational bribery in Colombia.

Finally, the ACE contains useful guidelines concerning business conduct and, more particularly, the interrelationship of the pharmaceutical industry with HCPs. Section 6(f) the ACE provides guidelines over specific scenarios in regard to interactions with HCPs.

Article 5.1.4 of the ACE states that pharmaceutical companies must avoid interactions with third parties whose resources come from illegal activities and must conduct due diligence. To this end, they should require such third parties to disclose all their business relationships in order to confirm that they are not subject to sanctions or investigations for corruption or money laundering.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Advertising of medical devices and the collaboration of manufacturers of medical devices with HCPs and patient organisations, although not specifically regulated, will most probably be governed by the general principle of article 17 of the Health Statutory Act (1751 of 2015) and article 106 of Law 1438.

In connection with the advertisement of medical devices, INVIMA stipulates that a disclosure must be made in accordance with the MA and with technical and legal standards. Class I medical devices can be advertised in mass media, but medical devices in Classes IIa, IIb and III can only be advertised in scientific and technical magazines (notwithstanding that INVIMA may authorise advertising in other media). No prior authorisation from INVIMA is required for the advertisement of medical devices unless permission to advertise moderate to high-risk medical devices (Class IIa, IIb, and III) in mass media is requested. INVIMA usually monitors medical device advertising after launch. The advertisement is valid for the time the MA is in force.

Additionally, there is a self-regulation guideline for the medical devices industry similar to the ACE, entitled the Medical Devices and Health Supplies Code (2015) issued by the National Association of Entrepreneurs of Colombia, which provides minimum standards applying to the interaction between manufacturers of medical devices and HCPs and patient organisations. Among others, advertising and promotional standards of medical devices are established.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The regulatory framework for granting MAs for medicines is set out in Decree 677 of 1995. This regulation, however, has undergone several amendments and modifications, including those in Decree 2227 of 1996, Decree 2091 of 1997, Decree 1792 of 1998, Decree 822 of 2003, Decree 2510 of 2003, Decree 2888 of 2005, Decree 426 of 2009, Decree 2086 of 2010, Decree 1313 of 2010 and Decree 843 of 2016.

Decree 4725 of 2005 regulates the procedure for obtaining MAs for medical devices in Colombia and Decree 1782 of 2014 regulates the procedure for biological and biotechnological products. Resolution 1606 of 2014 provides the technical guidelines for the submission of information on vaccine control.

The foregoing regulations can be roughly summarised by the following principles:

- medicines, pharmaceutical preparations based on natural resources, biological and biotechnological products, vaccines and medical devices require an MA from INVIMA for their manufacture, trade, import, packaging, processing and sale in Colombia;
- the above products must fulfil the technical and quality requirements established by INVIMA;
- marketing approvals are valid for a five-year term counted from the issuance of the registration, and may be renewed for the same period upon request of the interested party. The renewal application shall be filed at least three months before the expiration of the marketing approval, and will follow the same procedure as the first application;
- there are two types of pharmaceutical products according to Decree 677:
 - new medicines (not to be confused with new chemical entities, which is a subcategory related to regulatory test data exclusivity): namely, those whose API has not been included in the Pharmacological Code, or whose API is already included, but is related to new associations, fixed dosages, new indications or new pharmaceutical forms; and
 - medicines already included in the Pharmacological Code (generics); and
- pharmaceutical and biological manufacturing facilities require an operating licence issued by INVIMA after verification of good manufacturing practice compliance.

In addition, article 72 of the National Development Plan (Law 1753 of 2015) established an economic (cost/benefit) evaluation to be undertaken by the Institute of Health Technology Assessment (IETS) as a requisite for obtaining or renovating an MA. This requirement is yet to be regulated.

17 Which authorities may grant marketing authorisation (MA) in your jurisdiction?

According to article 245 of Law 100 of 1993, the competent authority for granting MAs for pharmaceuticals is INVIMA.

18 What are the relevant procedures?

An authorisation from INVIMA is required to obtain operating licences, MAs for new medicines and MAs for medicines included in the Colombian Pharmacological Code.

To obtain MAs for new medicines, the applicant must first submit a pharmacological evaluation application. The pharmacological evaluation studies the safety and efficacy of the drug and is performed by the Medicines Reviewing Committee, which takes into account the following features: efficacy, safety, dosage, indications, contraindications, warnings, toxicity, trading conditions and restrictions. Alternatively, article 27, paragraph 1 of Decree 677 provides an abbreviated procedure by which INVIMA can forego conducting a pharmacological evaluation (safety and efficacy) of a product whenever such product is already approved in at least two reference countries and has not been rejected in any of the other reference countries. Furthermore, article 72 of the National Development Plan (Law 1753 of 2015) now also requires an additional economic (cost/benefit) evaluation to be performed (by the IETS in parallel to the pharmacological evaluation. The results of the economic evaluation will hence be a prerequisite for obtaining an MA. However, regulations of article 72 are still under development, which is why this economic evaluation is not yet being applied.

Regarding biological and biotechnological products, a pharmacological evaluation must be performed even if the active ingredient (drug substance) is already included in the Colombian Pharmacological Code. This evaluation assesses the efficacy (indications, contraindications, interactions, precautions, warnings, pharmacokinetics, pharmacodynamics, dose, risk-to-benefit ratio) and safety (adverse effects, immunogenicity, trading conditions, special restrictions and risk-to-benefit ratio). Specific requirements for the submission of information for pharmacological evaluation are detailed in Decree 1782. This Decree contains an abbreviated route, by means of which biosimilar products should not have to submit clinical trials, nor head-to-head comparability assays to demonstrate its safety and efficacy. The same has been questioned by biotech R&D manufacturers and sanitary authorities worldwide.

Once the pharmacological evaluation is approved, the new medicine is included in the Colombian Pharmacological Code (when not previously included, in the case of biologicals). Subsequently, an MA application can be filed, which involves a pharmaceutical and a legal evaluation.

The pharmaceutical evaluation shall evaluate the capabilities of the manufacturing process and the product's quality (chemistry manufacturing and controls). The legal evaluation focuses on the legal documentation filed by the applicant, in compliance with the legal regulations governing this matter.

Finally, to obtain MAs for medicines already included in the Pharmacological Code (excluding biological products), generic applicants can proceed directly to filing the MA application (limited to the pharmaceutical and legal evaluation of the product). Decree 2085 of 2012 provides for regulatory test protection, and a generic applicant is blocked from pursuing approval for five years when this protection exists.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

According to Decree 843 of 2016, MA holders must notify INVIMA immediately when commercialisation of the product is interrupted temporarily or permanently. In order to protect the health of the community, an MA will lapse and cease to be valid if the pharmaceutical product ceases to be effectively marketed in Colombia. The non-commercialisation must be reported to the Drug Price Information System (SISMED). Additionally, permanent and temporary (six to 24

months) suspensions of the commercialisation must be notified to INVIMA, otherwise the MA will be cancelled. This changes the prior position of INVIMA where cancellations were not viable if the product was commercialised at least once within 24 months from the granting of the MA.

20 Which medicines may be marketed without authorisation?

As a general rule, all pharmaceutical products require an MA from INVIMA to be marketed in Colombia. However, article 96 of Decree 677, amended by article 1 of Decree 822 of 2003, states that INVIMA may allow the importation of pharmaceutical products without an MA in the following exceptional cases:

- when the MoH or INVIMA authorises a clinical trial of the product;
- when a health emergency is declared by the MoH; or
- when the MoH is obligated to provide a pharmaceutical product required by the Immunisation Programme to control diseases affecting the public health, and such product is unavailable on the domestic market.

Furthermore, Decree 481 of 2004 states that 'vital unavailable' medicines (those with low frequency of use and low returns) can be imported without an MA.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Named patient programmes – understood as the granting of access to a drug prior to its approval, under the specifications of an authorised healthcare professional, to a patient who has exhausted all alternative treatment options – are not provided for under the Colombian internal legislation. However, there has been at least one case where a patient was able to obtain access to a drug (that had marketing approval for a different use than the one requested) through a constitutional action for the protection of fundamental rights (*tutela*). The decision was opposed by the manufacturer of the product and by the MoH, but the court upheld the ruling.

On the other hand, Decree 481 of 2004 allows the importation of 'vital unavailable' medication for an individual patient or a specific group of patients without requesting an MA, but restricts said benefit only for medicines containing active ingredients, which had already demonstrated safety and efficacy in other countries and that are not under clinical research.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

According to article 60 of Law 81 of 1988, Colombia has three regimes related to the market price of a medicinal product: (i) monitored freedom; (ii) regulated freedom; and (iii) direct price control.

Different regulations regarding medicines price control were issued prior to 2013; however, as of issuance of Circular 03 of 2013, only monitored freedom and direct price control applies for medicines in Colombia.

Circular 03 of 2013 (issued on 21 May 2013) establishes the methodology for the application of direct price control for medicines marketed in the national territory. This methodology involves:

- defining the relevant market;
- determining the degree of market concentration;
- establishing the reference prices; and
- fixing the maximum retail price.

A product will be covered by this direct price control regime if its relevant market is highly concentrated and if the national reference price is above the international referenced price. Holders of MAs of medicine must periodically report their sales, which are then published in the SISMED.

According to article 245 of Law 100 of 1993 and article 1 of Decree 705 of 2016, the National Pharmaceutical Price Commission (NPPC) will regulate medicines and medical devices price methodologies.

Recently, the NPPC issued a draft circular containing a particular methodology for the price calculation of products subject to a declaration of public interest (a step within the patent Compulsory Licensing procedure). This new proposed methodology states that the maximum

Update and trends

In recent years the government, headed by the MoH has been taking different measures in an effort to protect the financial stability of the health system. Regarding pharmaceutical products these measures involve the development of a national pharmaceutical policy concerning: (i) medicine and medical device price control using international referencing methodology; (ii) stimulating market competition and facilitating entry of generic products such as issuing the Biologics and Biotechnologies Act, and reinforcing the possibility of using compulsory licences or declaring a health emergency; and (iii) promoting rational use of medicine therapies and technologies. Related measures also involve regulating the price of medicines and technologies at their entry into the market (requesting a 'cost benefit evaluation' as a prerequisite for obtaining an MA); and creating a medicines data standard (medicines unique identifier) allowing the gathering of information about the chemical, pharmacological and pharmaceutical features of the medicine as well as its commercial data (including patent protection). During 2016, different regulations for the Health Statutory Act and National Development Plan were issued. It is expected that the coverage of the health system during 2017 will be based on exclusions and not limited to particular inclusions.

Health Statutory Act Law 1751 of 2015

Resolution 3951 was issued in 2016 (and is expected to be enforced as of 1 December 2016) with the purpose of regulating the transition period the healthcare system is going through passing from a limited to an all-inclusive benefits plan (the POS) as determined within the Health Statutory Act.

Law 1797 of 2016

This Law was recently issued and contains fiscal and operative dispositions seeking the economic recovery of the healthcare system as well as the improvement of resource management and service quality.

This Law contains particular dispositions regarding the use of assigned revenues (gambling, alcohol, lottery) to pay non-POS services in the subsidised regime, royalties to provide financial support to health maintenance organisations with governmental participation; and periodic debt reconciliation among system stakeholders. Subsidised regime providers may obtain direct payments from the MoH through a simplified procedure. Regulations of this Law are still under review.

National Development Plan (Law 1753 of 2015)

New legislation developing article 72 of the National Development

Plan, which establishes new requirements for obtaining or renewing an MA by determining which therapies and medicines must be subject to an economic (cost/benefit) evaluation (performed by the IETS), is under discussion in Congress and is expected to be in force by the end of 2017.

This evaluation requires that R&D companies provide analysis comparing the 'innovator technology' with similar therapeutic alternatives or with the available therapy in the country (demonstrating improved clinical outcomes versus cost (Decree 1782 of 2014)).

Decree 1782 of 2014 (issued on 18 December 2014), which is currently pending, establishes the procedures for obtaining an MA for biological and biotechnological medicines. The Decree will enter into force once the guidelines for stability and immunogenicity of biologicals enter into force. Resolution 3690 containing the Stability Guideline was issued on 17 August 2016 and will be in force by 17 August 2017. Similarly, Resolution 4490, containing the immunogenicity guideline, was issued on 27 September 2016 and will be in force by 27 September 2017.

Referencing prices for medicine

The MoH has announced adjustments to the International Referencing Methodology for medicine price control. Although these adjustments are still uncertain, they may occur in the near future.

Proposed new methodology for medicines subject to a DPI

Recently, the NPPC issued a draft circular containing a particular methodology for the price calculation of products subject to a DPI. This new proposed methodology states that the maximum price for a drug subject to a DPI will be equal to the lowest price of any competitor in any referenced country. This circular is still in a preliminary stage.

Anti-Bribery Act (Law 1778 of 2016, Resolution No. 100-002657 and Circular No. 100-03 of 2016)

This legislation defines the scope of transnational bribery in Colombia and determines that headquarters operating abroad are liable for acts committed by, or attributable to, its affiliate in Colombia. Additionally, the Anti-Bribery Act provides legal competence to the Superintendency of Corporations to initiate, prosecute and sanction corporations whose conduct is contrary to Colombian regulations. Violations to this Act may lead to fines of up to US\$47 million and a five-year exclusion from government incentives or grants.

price for a drug subject to a declaration of public interest (DPI) will be equal to the lowest price of any competitor in any referenced country. This Circular is still in a preliminary stage and subject to very strong objections from the pharmaceutical industry.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

Article 71 of the National Development Plan (Law 1753 of 2015) amends article 88 of Law 1438 in order to enable the MoH to establish mechanisms to undertake centralised negotiations and to perform direct purchase of medicines, supplies and devices. The prices resulting from centralised negotiations are mandatory for health services suppliers and buyers, and cannot be increased.

In practice, however, companies that tried in the past to negotiate with public healthcare providers or the government were at a disadvantage because their competitors (mostly national companies) demanded access to the pricing information exchanged during the negotiation.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

In theory, the national government, through the FOSYGA fund, will reimburse the cost of medicines. The Electronic Prescription Service (EPS) (a health maintenance organisation (HMO)) is responsible for organising and ensuring access to the medicines and treatments included in the POS to their users. The EPS transfers the payment of each user to the FOSYGA, and the FOSYGA returns to the EPS a capitation payment unit (UPC) for each affiliated person. The UPC should be equivalent to the actual value of the POS.

If any user requests the provision of a drug or medical service that is not provided by the POS, the EPS is entitled to charge the FOSYGA the value of that particular drug or treatment. With the issuance of the Health Statutory Act, the POS will now become 'all inclusive' and in theory all therapies must be covered by the UPC. Exclusions are rarely approved for reimbursement from FOSYGA. Resolution 3951 of 2016 establishes the procedure for the supply, control and payment of therapies not covered by the UPC.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

According to article 245 of Law 100 of 1993, the NPPC is the competent authority to make decisions regarding the pricing of medical products (including the calculation of the maximum value for payment and reimbursement). However, and the Health Statutory Act (Law 1751 of 2015) now gives the MoH the responsibility, among others, to maintain a solid National Pharmaceutical Policy, which includes medicines price control and POS exclusions.

26 Finally, it is also worth noting that it is common for courts to intervene and order medicines and treatments to be covered.²⁵ Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

There is no specific regulation that obligates either the manufacturers or the distributors of medicinal products to give a discount. However, in practice, global payment agreements involving payments-per-results may lead to discounts if said results are not entirely achieved.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Colombia provides administrative and legal actions to prevent the counterfeiting and illegal distribution of medicines. Particularly, the Colombian legislation encompasses regulations aimed to protect activities related to public health that are contained in Title XIII of Law 599 of 2000 (the Penal Code), which states sanctions such as the imposition of a prison sentence or the inability to exercise certain health-related professions. The crimes related to healthcare range from contamination, poisoning and tampering, as well as marketing, distribution and supply of contaminated or poisoned drugs, even when they are past their expiration date or in poor condition. In addition, it is also considered a crime to counterfeit drugs, which leads to an additional offence related to trademark infringement.

With regard to administrative actions, any interested third party may file a complaint before INVIMA requesting the investigation of an illegal action, and INVIMA is authorised to impose the corresponding sanction.

Decree 677 of 1995, by means of which the regime of health surveillance is regulated in relation to the manufacture, processing, packaging, sale, import, export and marketing of medicines also establishes procedures and administrative penalties for those involved in these activities.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

Colombia has healthcare information systems in both the public and the private sector, which unfortunately are not integrated. A government strategy to facilitate the public's access to information has been focused on implementing telemedicine and the Integrated Information System of Social Protection (SISPRO). The MoH promotes SISPRO, whose purpose is to incorporate information related to the entire social security system.

SISPRO has different information systems, including SISMED, which incorporates the pricing information of prescription-only

medicines for the general public. This information is provided by health promotion entities, health facilities and pharmacies.

Resolution 3166 of 2015 defines and implements the Medicines Data Standard for the development of a medicine unique identifier as a component of the National Pharmaceutical Information System, which could help to maintain reliable, timely and public information about access affordability and quality of medicines. This standard will allow gathering information about chemical, pharmacological and pharmaceutical features of the medicine as well as its commercial information (sales, prices, patents, etc)

29 Outline major developments to the regime relating to safety monitoring of medicines.

INVIMA, through the National Pharmacovigilance Programme, promotes the safe use of medicines by monitoring them after they are marketed. The Programme has two groups of parties: people (patients and HCPs, among others); and institutions (hospitals, health facilities, pharmaceutical companies, etc). The Programme allows INVIMA to gain knowledge of any adverse effects and other problems related to medicine use, helping to improve the healthcare information system and to promote the safe and proper use of pharmaceutical products in Colombia. Resolution 2004009455 of 2004 establishes that the MA holders, manufacturers and healthcare providers have an obligation to report periodically to INVIMA any adverse effect of the use of any drug or any alert issued by any other sanitary authority in the world. This information is consolidated in INVIMA's pharmacovigilance database and, when necessary, INVIMA can issue alerts regarding the safe use of medicines commercialised in Colombia.

Vaccination
30 Outline your jurisdiction's vaccination regime for humans.

The Expanded Immunisation Programme (PAI) contains the minimum vaccines and doses that the government considers a child must be immunised with before the age of five, and are provided free of charge. The PAI covers tuberculosis (BCG), hepatitis B, diphtheria-pertussis-tetanus, haemophilus influenzae type b, oral rotavirus, oral polio, measles-rubella-mumps, pneumococcus, yellow

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fever, hepatitis A, adult diphtheria-tetanus toxoid and human papilloma virus (for girls aged 11 to 17 years).

Other vaccines, such as for chicken pox and a-cellular vaccines, which are not included in the PAI but are recommended by global vaccination schemes, are available in Colombia at different costs.

France

Christophe Hénin and Julie Vasseur

Intuity

Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The French healthcare system is based on the principle of free patient choice. People can decide to visit their assigned doctor, a specialist in direct access, or a public or private health establishment.

However, the health system is controlled to a large extent by the state across three different levels to ensure that it is consistent, especially in times during which the social security system and corresponding budget are affected by huge deficits.

At the national level, the state is directly involved in the financing (social security system) and organisation of the healthcare system delivery, and consequently promotes uniform national coverage and an effective match between the different stakeholders.

The regional health agencies (ARS) are organised at a regional level to ensure consistent resource management and relevant coordination at the regional level. They adapt national policies to regional contexts through regional health programmes composed of regional plans for prevention within hospital or private practice, as well as socio-medical schemes provided for elderly or dependent patients.

At the local level, structures and health professionals are organised under the supervision of the ARS to allow optimal management of patients according to their health status: primary healthcare provided by a general medical practitioner providing referrals, or secondary healthcare provided by medical specialists and health facilities. This organisation relies on healthcare coordination between health facilities and primary care on the one hand, and a continuous ambulatory or hospital care reinforcement on the other.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The French healthcare system is financed by personal and social contributions, as well as several taxes borne by companies, such as pharmaceutical companies, active within the system.

The main sources of funding (76 per cent in 2014) resulting from social security contributions are paid by all individuals. Other funding sources are quite diverse, such as taxes (VAT for pharmaceutical and health products, taxes on promotion, direct sales, turnover, etc).

The French system does not distinguish between outpatient and in-patient sectors in terms of the financing and coverage of health expenses.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

In France, advertising for medicinal products is governed by provisions of the French Public Health Code (PHC), which comply with the relevant provisions of modified Directive 2001/83/EC on the Community Code relating to medicinal products for human use.

The advertising guidelines of the French National Agency for Medicines and Health Products Safety (ANSM) shall also be taken into account.

The pharmaceutical industry is also bound by the Code of practice on representatives in pharmaceutical products, signed between the professional organisation of the pharmaceutical industry (LEEM), the Economic Committee of Healthcare Products (CEPS) and the Code

of practice on the communication of pharmaceutical companies on the internet (signed between the LEEM and the ANSM). As the LEEM has signed the European Pharmaceutical Industries and Associations (EFPIA) Code of the Promotion of Prescription-Only Medicines, each pharmaceutical company and member of the LEEM must also respect all the provisions of this code.

Overall, the pharmaceutical industry has to fulfil the professional and ethical standards that meet all the ethical provisions applicable to pharmaceutical companies as of 1 September 2015.

These ethical provisions include the Disclosure Code, the EFPIA Code on the Promotion of Prescription-Only Medicines, the EFPIA Code of Practice on Relationships between the Pharmaceutical Industry and Patient Organizations, the IFPMA Code, the Charter on Information of 15 October 2014, the Charter on Communication and Promotion of Medicines as well as the Charter signed between the LEEM, the French Union of Advertisers and the the French Press and Publications Union for Health Professionals of 17 July 2015. Any infringement of these provisions shall be sanctioned by the Ethics Committee of the Pharmaceutical Industry, an independent committee set up by the LEEM in late 2011.

Pharmaceutical companies are also bound by the Consumer Code, which prohibits misleading or comparative advertising and is applicable to any type of product.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

The main rules and principles applying to advertising aimed at healthcare professionals are provided by articles L5122-2–L5122-5, L5122-9–L5122-12 and R5122-8–R5122-17 of the PHC, which state the following:

- the advert must not be misleading and must not present a risk to public health. The presentation of the medicinal product must be objective and encourage its proper use;
- the advert must comply with the provisions of the marketing authorisation, and with the information contained in the summary of the medicinal product characteristics;
- the advert must indicate a minimum level of information such as the name of the product, the name of the manufacturer, the product's pharmaceutical form, its administrative form, its dosage, its therapeutic indications and contraindications, adverse reactions, special warnings and precautions for use, medicinal and other interactions, and the status regarding reimbursement by the healthcare system;
- the information provided must be accurate, updated, verifiable and sufficiently exhaustive to enable healthcare professionals to make their own judgements on the therapeutic value of the product; and
- each chart, quotation or illustration taken from medical journals or scientific literature must be quoted faithfully. Their source must be precisely stated. Any written mention thereof must be clearly legible.

Since the enactment of Law 2011-2012 of 29 December 2011 and its implementation decrees, advertising for medicinal products intended for professionals – as in the case of advertising to the public – must be previously authorised by the ANSM. Failure to comply with this obligation constitutes a breach subject to a financial penalty.

The ANSM may impose, as such, an administrative penalty that shall not exceed 10 per cent of the annual turnover or €1 million.

The oral presentation of a medicinal product should only be delivered by medical sales representatives, who have specific diplomas and sufficient scientific knowledge that is regularly updated, and shall include a summary of the medicinal product characteristics, the classification of the product, its maximum selling price, its possible reimbursement, the daily treatment cost and the approval of public institutions. This practice is also framed by the Code of practice on representatives in pharmaceutical products.

5 What are the main rules and principles applying to advertising aimed at the general public?

Advertising of medicinal products intended for the public is only allowed under the following conditions:

- the product is not prescribed;
- the product is non-refundable by the social security scheme; and
- the marketing authorisation does not contain prohibitions or restrictions as regards advertising intended to target the public.

In addition, the advert must not be misleading and must not present a risk to public health. The presentation of the medicinal product must be objective and encourage its proper use, and must comply with the provisions contained in the marketing authorisation and the summary of the medicinal product characteristics.

Such advertising must be conceived so that the character of the advertising message is obvious and the product is clearly identified as a medicinal product.

Any advertising for a medicinal product intended for the public must comply with the provisions of the Consumer Code and shall also contain:

- the denomination, as well as the international non-property name when the product contains only one active ingredient;
- any essential information for proper use;
- an express invitation to read the leaflet; and
- a message of caution, and a reference to the advice of a pharmacist and to the consultation of a medical practitioner.

Finally, advertising for medicinal products intended for the public shall be previously authorised by the ANSM. Failure to comply with this obligation constitutes a breach subject to a financial penalty.

The ANSM may impose, as such, an administrative penalty that shall not exceed 10 per cent of a company's annual turnover or €1 million.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The most common infringements committed by manufacturers are breaches of the Consumer Code provisions with regards to misleading or comparative advertising. The ANSM often issues decisions banning advertising that fails to fulfil the provisions of the marketing authorisation, or that constitutes indirect advertising that was not previously authorised pursuant to the law.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

According to article L5122-2 of the PHC, advertising of medicinal products must comply with a marketing authorisation. Pharmaceutical companies are under an obligation to refer to the ANSM off-label use practices.

Accordingly, advertising on off-label use of medicinal products is not permitted and is punishable by up to two years' imprisonment and a fine up to €30,000 (article L5422-1 of the PHC).

However, Law No. 2011-2012 of 29 December 2011 has allowed off-label use of medicinal products by prescribers when an authorised, appropriate alternative medicinal product does not exist and when:

- the physician duly considers that such a prescription is essential for his or her patient; or
- the ANSM has adopted a recommendation for therapeutic use (RTU) stating therapeutic indications or conditions of use. This recommendation, which is valid for up to three years, includes providing the necessary information to the prescriber for assessing the proper medicinal administration (such as dosage, adverse effects), and is published on the website of the ANSM. It is worth noting that the French RTU could be judged contrary to the EU law. As the

latter prohibits off-label prescriptions based on economic grounds, a complaint has been filed before the European Commission (the Commission) by the EFPIA against the French law promoting the off-label use of specific medicinal products.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

In addition to the legal framework provided by the French Criminal Code in connection with corruption and influence-peddling, the French Anti-Gift Act of 27 January 1993 has been introduced for the specific area of health.

Its provisions have been then supplemented by the French 'Sunshine Act' of 2011, itself recently completed by the Law on the Modernisation of the French Health System of 26 January 2016.

Furthermore, the relationship between pharmaceutical companies and healthcare professionals is strictly regulated by the Health Professions Council.

As mentioned in question 3, pharmaceutical companies that are members of the LEEM shall respect the professional and ethics standards that meet all the ethical provisions applicable to the pharmaceutical companies as of 1 September 2015, such as the Disclosure Code.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The Anti-Gift Act provides that healthcare professionals, including physicians, pharmacists and medical students, cannot receive any direct or indirect advantage, in kind or in cash, except for:

- advantages provided by an agreement whose express subject and real purpose are research activities or scientific evaluation. The agreement should be submitted before its implementation to the departmental council of the relevant professional body, and compensations should not be calculated on the basis of the number of prescribed services or products;
- hospitality being offered, directly or indirectly, at events for purely professional and scientific purposes when provided by agreement between the company and the health professional, and submitted before its implementation to the departmental council of the relevant professional body. This hospitality should be reasonable and limited to the main scientific and professional objective of the event. Such hospitality cannot be extended to persons other than the professionals directly involved; and
- gifts of negligible value, relating to the exercise of their activity.

Failure to comply with this provision is a criminal offence punishable by up to two years' imprisonment and a fine up to €75,000.

Consequently, pharmaceutical companies have also been required by the French Sunshine Act to make public the existence of agreements with health professionals and advantages granted (for an amount at least equal to €10) on the dedicated government website www.transparence.sante.gouv.fr.

A deliberate failure of companies to comply with this publication is punishable by a fine up to €75,000.

Following a ruling of the French Council of State dated 24 February 2015, the new Law on the Modernisation of the French Health System of 2016 has strengthened the French Sunshine Act in several respects, but mostly by introducing a new regime on healthcare professionals' remuneration disclosure. The Decree that determines the conditions of application of such a new transparency legal framework is still awaiting publication.

In addition, it should be noted that discounts, rebates and commercial and financial benefits, including commercial cooperation agreements on reimbursable medicinal products granted to pharmacists, may not exceed (for the calendar year and by product line) 2.5 per cent of the manufacturer's price excluding taxes, and 40 per cent for generic specialties, per pharmacy (since the Order of 22 August 2014 laying down limits for discounts, rebates and other commercial and financial benefits set out in article L138-9 of the Social Security Code). It is worth noting that pharmacists were previously eligible for generic discounts to the sole extent of 17 per cent. However, circumvention practices revealed by some 'hidden' discounts in the form of commercial

cooperation agreements encouraged the government to raise this limit up to 40 per cent.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

Owing to the recent modification of the law and corresponding provisions mentioned above, pharmaceutical companies are experiencing difficulties in portraying their contractual relationship with healthcare professionals, properly framing their global relationship with hospitals and their physicians, and orientating such possible close relations in a way that might induce anticompetitive behaviours.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

Beyond the EFPIA Codes mentioned in question 3, provisions relating to the mandatory declaration of 'interests' described in question 9 duly apply to patient associations. Furthermore, pharmaceutical companies are under the obligation to declare the list of potentially financed patient associations (in total or in part).

12 Are manufacturers' infringements of competition law pursued by national authorities?

The French Competition Authority regularly condemns pharmaceutical companies for anticompetitive behaviours, and especially for abuse of a dominant position.

Thus, the Competition Authority recently fined a pharmaceutical company €40.6 million (Decision No. 13-D-11 of 14 May 2013) and another company €15.3 million (Decision No. 13-D-21 of 19 December 2013) for a denigration strategy implemented to prevent the entrance of generic competitors.

Unannounced visits and seizure operations were also performed on 8 April 2014 in the area of the commercialisation of wet age-related macular degeneration (AMD) treatment. It is worth noting that the Competition Authority issued Opinion No. 13-A-24 on 18 December 2013 relating to the functioning of competition in the distribution sector of medicinal products for human use 'in town' ('distribution in town' means distribution from pharmacists as opposed to distribution in hospitals) to regulate the denigration practices that are most common in France.

13 Is follow-on private antitrust litigation against manufacturers possible?

Violations of competition law and restrictive practices may be enforceable before a competent tribunal by competitors in order to potentially request corresponding damages. Parallel litigations are common to exercise greater pressure on the dominant pharmaceutical company before the Competition Authority, as well as before a tribunal, to immediately request damages.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

Beyond the specific rules, which are only applicable to the pharmaceutical sector (see question 9), more general transparency provisions apply to all French and European manufacturers. Thus, in case of subcontracting with a threshold of €500,000, the manufacturer and the contractor are obliged to conclude a written agreement 'for any purchase of manufactured products, made at the request of the buyer in the view of being integrated into its own production', in respect with article L441-9 of the Commercial Code. Furthermore, following the adoption by the Commission, on 12 April 2016, of a draft directive that aims at strengthening the fiscal transparency, the manufacturer, which is part of a multinational, should be under a financial annual reporting obligation in France as well as in the countries in which the entity has at least one structure. Finally, in anticipation of the legislative calendar of the French draft law 'Sapin II', the manufacturer is advised to set up a procedure for prevention and detection of corruption or influence-peddling if the company has over 500 employees and has an annual turnover that exceeds €100 million.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Law No. 2011-2012 of 29 December 2011 introduced a new regulation on advertising for medical devices, which is generally less cumbersome than the regulation in force governing medicinal products, except for those that might induce a significant risk to public health (a list is laid down by one Decree dated 24 September 2012 for in vitro diagnostic medical devices and another Decree dated 22 March 2013 for other medical devices).

Advertising is forbidden for medical devices that do not bear a certificate of conformity. In addition, the advertising shall objectively describe the product and, where applicable, its performance and compliance with essential requirements for safety and health. It must not be misleading or present a risk to public health.

Finally, as under the relevant rules for reimbursed medicinal products, any advertising to the general public in favour of medical devices whose costs are supported at least partially by the national health system is strictly prohibited.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

In accordance with EU directives and regulations, the conditions to grant a marketing authorisation for human use (for innovated products as well as for generics), either nationally or through the centralised or decentralised procedure for human use, are contained and detailed within the PHC (articles L5121-8, R5121-21 and following) and generic products (articles L5121-10, R5121-5 and following).

17 Which authorities may grant marketing authorisation in your jurisdiction?

For many years, the French Health Products Safety Agency (AFSSAPS) was the relevant health administrative body to grant marketing authorisations and enforce the rules applicable to medicines and pharmaceutical firms. It was replaced by the ANSM on 1 May 2012 following the publication of Decree No. 2012-597 on 27 April 2012. As a public body under the supervision of the Ministry of Health, the ANSM took over the tasks of the AFSSAPS, and has been entrusted with new powers and responsibilities.

18 What are the relevant procedures?

Applications for marketing authorisations are submitted to the ANSM, which scientifically assesses the marketing authorisation file according to scientific criteria regarding quality, safety and effectiveness. A new product must provide a benefit-to-risk ratio at least equivalent to existing products.

The application is thus reviewed by the committees of the ANSM (and, in particular, by the commission in charge of the initial assessment of the risk-to-benefit balance of the health products) if a deeper examination and a supplementary peer opinion for such a case is required. Three outcomes can arise: a favourable opinion, a request for further information or an unfavourable opinion.

The final decision belongs to the General Director of the ANSM. A simplified procedure exists for generics in full accordance with article 10 of Directive 2001/83/EC (modified).

Any company marketing medicinal products without prior authorisation will incur two years' imprisonment and a maximum fine up to €30,000 (article L5421-2 of the PHC).

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

The marketing authorisation for a medicinal product and the registration of certain products (such as homeopathic or herbal medicines) lapse if they are not marketed in the territory within three years following the authorisation or registration, or if the corresponding product is no longer on the market for three consecutive years.

The ANSM may grant exemptions to such an applicable rule, either for public health reasons, or:

- when the medicinal product could not be legally marketed during the period;
- when the medicinal product was exclusively intended for export to a state that does not belong to the European Economic Area; or
- when the medicinal product is marketed in at least another member state of the European Union or of the European Economic Area while a different dosage or pharmaceutical form is marketed in France.

20 Which medicines may be marketed without authorisation?

Homeopathic medicines and traditional herbal medicines complying with the conditions respectively provided by articles L5121-13 and L5121-14-1 of the PHC are only subject to registration and not to the rigorous formalism of the procedure applicable to the medicinal products for human use.

Medicinal products not industrially manufactured (pharmacy preparations, hospital preparations and pharmaceutical preparations) have their own regulatory rules that do not involve the obligation to register the preparation or to obtain a marketing authorisation.

In addition, it is worth mentioning the possibility to obtain a temporary authorisation for use (ATU) when a medicinal product is considered essential by the prescriber, in view of the scientific knowledge, to improve or stabilise the clinical condition of the patient and when no other appropriate medicine exists.

The ATU is said to be 'nominative' when the product is prescribed at the request and under the responsibility of the prescriber and physician.

The 'cohort' ATU, referring to a group or subgroup of patients who are included within a clinical protocol for therapeutic use, might also be granted at the sole request of the holder of the corresponding rights concerned and under specific conditions.

It must be noted that the 2017 draft law on social security provides for an extension of the medicinal product's ATU for any of its therapeutic indication that has not been yet registered on the reimbursement lists.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

As mentioned in question 20, such a legal possibility, contained in article 5(1) of Directive 2001/83/EC, follows the 'nominative' ATU regime.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

In this regard, a key distinction has to be made between the hospitals market for in-patients and the pharmacies market for outpatients:

- for the hospitals market, pricing is free and prices are set through tender offers (except for medicines that can be also purchased by outpatients and for most innovative medicines for which maximum prices are set according to a procedure that is similar to the procedure applying to medicinal products reimbursable in retail pharmacies);
- for the retail pharmacies market, the ultimate goal of the pharmaceutical company is to obtain a reimbursable price that might meet its internal costs and margins. In such a case, the price is then fixed in a contract signed between the pharmaceutical company and the CEPS. If the result of the negotiation does not fulfil the objectives of the company, then the company might decide not to market its medicinal product in France; and
- prices are free for over-the-counter products.

The 2017 draft law on social security clarifies the criteria for the CEPS in order to set prices.

This draft law also proposes to maintain the principle of freedom of pricing for medicinal products subject to an ATU while imposing a repayment of the price difference that arose between the ATU (free price) and the post-ATU (negotiated price of conventional discounts) period.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

As mentioned above, depending on the market segment concerned, and especially in retail pharmacies, the negotiation is centralised through discussion with the CEPS. This leads to a signing of contracts that shall also impose other obligations on the pharmaceutical company, such as maximum volumes to be sold or rebates to be paid to the health insurance system if these maximum volumes are exceeded.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

To be reimbursed, the product has to be registered on two lists – one for hospitals and the other one for pharmacies in retail pharmacies pursuant to article L162-17 of the Social Security Code. This registration is granted with respect to a single criterion: the therapeutic value, which is fixed for each therapeutic indication. It is worth noting that a new Decree of 24 March 2016 has, however, strengthened the conditions to be registered on such lists.

Reimbursement of medicinal products subject to a RTU is decided by a ministerial order after the advice of the French National Union of the Medical Insurances (UNCAM). Medicinal products subject to an ATU are completely supported by health insurance. If, during the ATU's validity, the medicinal product has been granted a marketing authorisation, the health insurance payment continues until the ATU ceases to be valid.

Furthermore, arrivals of new polemical expensive treatments have required taking measures to ensure not only a broad access to innovative medicines and financial sustainability for health insurance. This is why the 2017 draft law on social security proposes the establishment of a Pharmaceutical Innovation Financing Fund that would moderate fluctuations of annual expenses with respect to these innovations.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The cost of pricing reimbursable medicinal products is regulated and set by a convention between CEPS and the firm. The process takes into account various criteria set out in article L162-16-4 of the Social Security Code, including the improvement of clinical benefit evaluated through the Transparency Commission of the French National Authority for Health, prices of other medicinal products within the same therapeutic class, the expected or recorded sales volume, and the actual and foreseeable use of the medicinal product.

For generics, the price set out by the CEPS is systematically 60 per cent lower than a referenced medical product.

The reimbursement rate is decided by the President of the French National Union of Health Insurances and is then endorsed by a ministerial order and published in the Official Journal of the French Republic.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

As mentioned in question 22, rebates might be due to the national insurance system in specific circumstances: for example, where maximum volumes of sales (agreements on price and volume), provided in the contract between the CEPS and the pharmaceutical company, have been exceeded.

Article 138-10 of the Social Security Code subjects pharmaceutical companies to an overall contribution where expenses of reimbursable medicinal products exceed the growth rate of the national health insurance spending objective (fixed by the parliament) whenever the pharmaceutical company has refused to sign a contract with the CEPS; however, this happens very rarely.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Order No. 2012-1427 dated 19 December 2012 and the Decree dated 31 December 2012 implement the provisions of Directive 2011/62/EU dated 8 June 2011.

These provisions introduced the definition of a falsified medicinal product and secured the distribution channel of medicinal products

(notably, definition of the 'trader' of medicinal products, as well as information to be added on the external packaging of the medicinal product in order to ensure its integrity). They also limited sales through the internet to websites initiated and managed by pharmacists and previously authorised by the ARS, and to pharmacists who also have a pharmacy establishment (see the Order of 20 June 2013 on good dispensing practice for medicinal products).

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

A Decree dated 27 September 2013 determined the creation (since 1 October 2013) of a public database of medicinal products, which collects administrative and scientific information on all pharmaceutical products (regardless of whether they are prescribed or reimbursed) on a single public website.

The information provided within the database includes the name of the product, its composition in active substances, a summary of the medicinal product characteristics, the package leaflet, the clinical or therapeutic value and the sale price. Such information is of particular interest now that the online sale of non-prescription medicinal products is allowed under French law.

In parallel, prescription assistance software aims to help healthcare professionals to prescribe the most appropriate treatment by comparing data on different medicinal products with those of the patient. Since a Decree of 15 November 2014, such software has to be certified by the ANSM before being used.

29 Outline major developments to the regime relating to safety monitoring of medicines.

No major pharmacovigilance reform has been introduced in France since the adoption of Law No. 2011-2012 dated 29 December 2011. However, two Decrees were recently published in the Official Journal.

The first decree implements the provisions of Directive 2010/84/EU and enhances the powers of the General Director of the ANSM with regards to medicinal product safety. For example, it provides the means, following the granting of a marketing authorisation, to ask a company to carry out safety and efficacy studies, or to impose a risk management plan.

The second Decree, dated 16 October 2013, transposes Directive 2012/26/EU dated 25 October 2012 in order to reinforce pharmacovigilance obligations on exporting companies to countries that are not members of the EU and on importing companies from these countries.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

French vaccination policy is the responsibility of the Minister of Health, who must consult the High Council for Public Health, as well as a technical vaccination committee.

The vaccination regime, as in many other countries, distinguishes between compulsory vaccines (such as tetanus and poliomyelitis) and vaccines recommended (such as pertussis, rubella, measles, mumps and chickenpox).

The procedure for setting the price and obtaining reimbursement for vaccines follows the medicinal products for human use regimes (see question 22).



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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The healthcare system in Germany is organised by the statutory health insurance system (GKV). Approximately 85 per cent of the population in Germany is insured within the GKV; the remaining population is privately insured. In the GKV, the legislature creates the legal framework for the provision of medical services, and the medical self-governing bodies, such as the associations (on a federal and regional level) of physicians (KVs), the statutory health insurance funds (SHI funds) and the German Hospital Federation, formulate and implement in detail which healthcare services will be provided and under what conditions.

The most relevant decision-making body in the system of the GKV is the Federal Joint Committee (G-BA), an association representing all relevant parties of the healthcare sector such as physicians, hospitals, sickness funds and patients. The G-BA issues directives and determines the benefit package of the GKV. The organisation of the GKV, the responsibilities of the G-BA and the other self-governing bodies, as well as the provisions for medical care, are laid down in the Social Code Book V (SGB V).

In addition, as a main principle, the SGB V sets out that the patient's entitlement to medical service within the system of the GKV is restricted by the 'efficiency principle', namely that the respective healthcare must be sufficient, appropriate and economically efficient, and must not exceed the extent of what is necessary. Recently, the SGB V has been subject to numerous legislative changes and amendments to enhance competition between the healthcare providers and the sickness funds.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

In the system of the GKV, the provision of medical care is funded by a statutory contribution system, which constitutes the major system of financing the healthcare of the insured. The insured and their employers must pay contributions to SHI funds in Germany, which transfer the contributions to a healthcare fund. The German Federal (Social) Insurance Office administers this fund and transfers the contributions to the SHI funds, according to the structure of their insurance. The amount to be paid by each person is dependent on his or her income and not on individual health risks. Finally, the healthcare insurance of an insured employee covers non-earning spouses and children, without any additional charges.

In the outpatient sector, the provision of healthcare is financed by payments of the SHI funds to the respective KV (section 85(1) of the SGB V), which conveys the payments to the medical service provider in the outpatient sector. In the hospital sector, the payments of the SHI funds are transferred directly to the respective hospital. Costs incurred in the hospital sector are covered by diagnosis-related groups (DRG). A DRG is calculated in consideration of the primary diagnosis, the necessary treatment, the co-morbidity, if relevant, and patient-related factors such as age and gender.

Compliance - pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

In Germany, the legal requirements for marketing activities of pharmaceutical companies addressed to healthcare professionals or the general public are laid down in the Advertisement of Medicinal Products Act (HWG). However, a (marketing) activity in general falls within the scope of the HWG only if the activity in question is product-related and intended to increase the sales of a respective product. Provided that the (marketing) activity is solely company-related, the rules of the Act Against Unfair Competition (UWG) are applicable. Finally, the Medicinal Product Act (AMG) also imposes legal requirements for interactions with healthcare professionals and patient organisations.

In addition, several industry guidelines apply to product or company-related marketing activities of pharmaceutical companies, either addressed to healthcare professionals or the general public. In particular, the AKG Code of Conduct, issued by the German Pharmaceutical Industry Association (BPI) and the FSA Code of Conduct of Healthcare Professionals, issued by the Association of Research-based Pharmaceutical Companies (VfA), are relevant. The aforementioned industry guidelines are binding for members of the BPI and the VfA, and compliance is monitored and sanctioned by the FSA and AKG arbitration board. Even if a pharmaceutical company is not a member of the BPI or the VfA, these regulations shall be observed by pharmaceutical companies, as these industry guidelines serve as a means of interpretation for the courts when assessing whether a marketing activity infringes the applicable legal provisions. This assessment applies, in our view, although a recent decision of the Higher Regional Court of Munich has also questioned the general application of such industry guidelines for non-members of the VfA. The above-mentioned industry guidelines are specific and detailed with regard to activities in the sector of the pharmaceutical industry. Therefore, in our view, one might expect that judges may continue to use such conclusive guidelines to assess whether a certain practice in the field of the pharmaceutical industry infringes the general legal provisions (which also apply to other industry sectors). Recently, the Codes of Conduct have been updated and extended to implement the EPFIA Code of Conduct.

Since mid-2016, legal provisions have been added to the Penal Code, paragraph 299a, b StGB, which regulate that corruption in the healthcare sector will be punished by law. In the healthcare sector, the new provisions have caused companies to change their activities significantly, although the punished actions are the same as those forbidden by the industry codes. The reason for this change of behaviour is that public prosecutor's offices are responsible for investigating.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

As a main rule and principle, product-related advertisements (the HWG, section 3) and company-related advertisements (the UWG, section 5) addressed to healthcare professionals must not be misleading or unfair: namely, the promotional statement must be correct and, if necessary, verifiable. The HWG and the UWG contain concrete examples of misleading or unfair competition. As far as product-related advertisement is concerned, most importantly, the law requires, inter alia, that the promoted medicinal product must not be ascribed therapeutic

efficacy or effects that it does not possess, and that the advertisement gives no false impression that success is guaranteed or that the recommended use has no side effects (the HWG, section 3 Nos. 1 and 2). A respective list of legal examples is set out in the UWG, which applies to company-related advertising statements (the UWG, sections 4 and 5). In addition, as further main principles applying to product-related advertisements, the advertisement should always provide the mandatory information regarding the promoted medicine, and the promoted indications must be in line with the marketing authorisation, the summary of product characteristics and the package leaflet.

5 What are the main rules and principles applying to advertising aimed at the general public?

The above-mentioned rules and principles with regard to advertisements addressed to healthcare professionals also apply to advertisements addressed to the general public. Thus, promotional statements addressed to the general public must not be misleading or unfair.

In addition, further legislative provisions apply to enhance the protection of the general public, as the public is considered to have no (profound) medical knowledge. For instance, the HWG sets out in section 10 that the advertisement of medicines available on prescription only is prohibited to the general public. This prohibition shall ensure that the healthcare professional decides independently on the prescription of a certain medicine and solely based on medical considerations that are not influenced by the patient. Furthermore, the HWG stipulates a list of examples of advertisements that shall not be directed to persons other than healthcare professionals, as they are potentially misleading or manipulative. These are, *inter alia*, advertisements containing:

- scientific or professional publications;
- statements alleging that the medicine is recommended, tested or used by healthcare professionals;
- foreign or professional terminology, insofar as these have not become part of the general German vocabulary; or
- publications that suggest self-diagnosis and treatment by the advertised medicinal product.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

According to our experience, the most common infringements committed by manufacturers with regard to the advertising rules are product-related advertisements for medicines available on prescription only addressed to the general public. The high number of infringements is due to established case law in Germany whereupon the requirement of a 'product-relation' of advertisement is widely interpreted. According to established case law, an advertisement is not only product-related if the respective promotional activity contains 'a naming of a concrete product' but also if 'at least information that enables the addressee to identify a medicine' is given. Therefore, the naming of the manufacturer associated with an active substance (of a medicine available on prescription only) within a promotional activity addressed to the general public is not admissible because of established case law in Germany (eg, the decision of the German Federal Court of 15 December 1994; case I ZR 154/92).

Furthermore, advertisements for the administration of medicines outside its authorised indications can be observed in many cases. This is because off-label use of medicines is a relevant factor in many indications, such as oncology, and the manufacturers therefore have a significant economic interest in the advertisement of such use.

Finally, according to the nature of product-related advertisement, promotional statements are often not accurate due to exaggerations concerning the therapeutic effect or features of a medicine. Most common are advertisements falsely implying success in treatment or containing an improper statement regarding the status of the medicine on the market, namely that the product is the best and maintains its position without competing products.

Provided that the competent local authority comes to the conclusion that an advertisement infringes legal provisions, it has the power to stop the further distribution and usage of such advertisement. The intentional infringement of legal provisions of the HWG may be sanctioned with imprisonment of up to one year, or with an administrative fine of up to €50,000; the negligent infringement may be sanctioned by an administrative fine of up to €20,000.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

The provision of information regarding off-label use to healthcare professionals is allowed if such information is provided within correspondence of a non-promotional nature, and is needed to answer a specific question (of a healthcare professional) about a particular medicine. This exemption is, *inter alia*, set out in section 1(5) of the HWG and section 1(3) No. 2 of the FSA Code of Conduct. However, if the pharmaceutical manufacturer provides off-label use information to healthcare professionals by way of such correspondence, it is advisable for the manufacturer to keep the respective (written) request from the healthcare professional in its records. If necessary, this enables the pharmaceutical manufacturer to prove that the information regarding off-label use has been given to the healthcare professional solely upon request, and that the above-mentioned legal exemption applies.

Furthermore, the provision of information regarding off-label use is allowed provided such information has a non-promotional character; for example, copies of publications regarding the outcome of a clinical trial (but not in connection with reprint carriers containing any advertisement) or purely scientific information that solely mentions the international non-proprietary name of the active substance.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

As for advertisements, the legal requirements for the collaboration of pharmaceutical companies with healthcare professionals are partly laid down in the HWG and the UWG. These statutes apply to healthcare professionals from the outpatient sector as well as to healthcare professionals who work in hospitals. Furthermore, the German Criminal Code (StGB) sets out in sections 299 and 331 legal requirements regarding attempts to influence healthcare professionals who work in public hospitals in their prescription of medicines.

In March 2012, the Grand Criminal Panel of the Federal Court of Justice decided – contrary to the former tendency of German courts to see physicians in the outpatient sector as designees of the SHI and to apply the respective legal provisions of the StGB to them – that physicians are in fact not designees of the SHI. They are neither public officials nor designees of the SHI. Sections 299 and 331 of the StGB are consequently not applicable to outpatient sector physicians.

As mentioned, the new provisions of 299 a, b StGB were introduced in mid-2016 to pursue corruption in the outpatient sector too and are applicable to all members of the medical profession.

Sections 31 and 33 of the Professional Code for Physicians (the official draft of the professional code for physicians, which is to a large extent implemented in the regional professional code) stipulate rules and principles for the interactions of physicians, either from the in-patient or the hospital sector, with the pharmaceutical industry.

In addition, several industry guidelines govern the interaction of pharmaceutical manufacturers with healthcare professionals. These are the FSA Code of Conduct of Healthcare Professionals, the respective AKG Code of Conduct, and the Common Position Concerning the Consideration of Cooperation between Industry, Medical Institutions and Staff from the Aspect of Criminal Law. As previously mentioned, these industry guidelines are binding for members of these industry associations, and shall furthermore be observed since they serve as a means of interpretation for German courts when assessing if certain collaboration with healthcare professionals infringes respective legal provisions.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The FSA Code of Conduct sets out in its introduction that all interactions and measures of collaborations with healthcare professionals 'must remain within certain appropriate bounds and in accordance with the law'. In this respect, the principles of separation, transparency, documentation and, for mutual service, the principle of equivalence (as stipulated in the Common Position Concerning the Consideration of Cooperation between Industry, Medical Institutions and Staff from the Aspect of Criminal Law) outline valuable reference points for the collaboration of the pharmaceutical industry with healthcare professionals

from the outpatient sector or those working in hospitals. Accordingly, the collaboration between pharmaceutical manufacturers and healthcare professionals must meet the following requirements:

- separation principle – the fee paid by the pharmaceutical manufacturer for the service provided by the healthcare professional must not constitute an inducement to recommend, prescribe, purchase, supply, sell or administer specific medicinal products;
- transparency principle – all collaborations with pharmaceutical manufacturers must be disclosed to the administration of the professional's medical institution; usually, a prior authorisation is required;
- documentation principle – all collaborations between pharmaceutical manufacturers and healthcare professionals must be set out in writing; and
- equivalence principle – the fee paid by the pharmaceutical manufacturer for the service must correspond to the market value of the service rendered by the healthcare professional.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

In our experience, it is most common that pharmaceutical manufacturers infringe the equivalence principle when collaborating with healthcare professionals. In many cases, the fee paid for the service rendered is not in accordance with the appropriate market value of the service. According to the latest decision of the FSA Board of Arbitration (the body responsible for the observance of the FSA Code of Conduct), a remuneration of €80.45 for a 30-minute qualified consulting service rendered by a healthcare professional is considered appropriate and reasonable (see decision of 3 February 2009 (2008.1-220)). However, this arbitration may only serve as a benchmark for an assessment of the appropriate market value of such a service. The respective assessment must, furthermore, be carried out on a case-by-case basis and in consideration of numerous factors, such as the difficulty of the service and the qualification of the healthcare professional. Please note that the above-mentioned amount is, for the time being, the highest sum considered appropriate in Germany.

With respect to the FSA Board of Arbitration, many cases result from gifts or services offered to healthcare professionals. As a general rule, the HWG and the respective industry guidelines set out that it is not admissible to offer products or services unless they are inexpensive and relevant to the practice of human medicine. According to the FSA Board of Arbitration and cipher 10.2 of the FSA Guidelines pursuant to section 6(2) FSA Code of Conduct (the FSA Leitlinien), a gift is considered as 'inexpensive' if it does not exceed the value of €5 (purchase price).

In addition, numerous infringements result from travel and accommodation granted to healthcare professionals by pharmaceutical manufacturers. For instance, healthcare professionals attending a job-related or science-oriented training event may not be offered accommodation and hospitality exceeding a reasonable limit. In this respect, a dinner must not exceed the value of €60 (see cipher 6.1 FSA Leitlinien), and the hotel should be classified under business class, not luxury class, and should not provide any extraordinary entertainments or services (see cipher 6.3 FSA Leitlinien).

As regards the new anti-corruption provisions of the penal code, there is no common use of the prosecutor's offices; but violations of the law can be punished by fees or imprisonment.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

In Germany, the relevant industry guidelines applying to the collaboration of pharmaceutical manufacturers and patient organisations are the FSA Code of Conduct on the Collaboration with Patient Organisations (FSA Code of Conduct on Patient Organisations) and the respective Code of Conduct issued by the AKG (AKG Code of Conduct on Patient Organisations). These codes of conduct define the term 'patient organisations' as follows:

Patient organisations are voluntary, non-profit organisations of patients and/or their families, whose activities involve group support in coping with diseases, disseminating information about

diseases and therapy options, lobbying in healthcare and social policy, publishing of media to inform and support patients and/or providing advisory services.

In our view, the scope of this definition is broader than the definition of patient organisations laid down in the European Federation of Pharmaceutical Industries and Associations (EFPIA) Code of Conduct on Relationships between the Pharmaceutical Industry and Patient Organisations (EFPIA Code of Conduct). Therefore, it has to be assumed that the German national Codes of Conduct also apply to interactions between patient organisations and pharmaceutical companies that are not subject to the EFPIA Code of Conduct.

As a main rule for collaboration of the pharmaceutical industry with patient organisations, it is stipulated in the AKG and FSA Code of Conduct on Patient Organisations that pharmaceutical companies may not establish any patient organisation on their own (separation principle). Further, the pharmaceutical manufacturer is obliged to respect the neutrality and independence of the patient organisation, in particular regarding the events organised by the patient organisation (principle of neutrality).

Besides these principles, pharmaceutical companies have to observe the principle of transparency, namely that the collaboration and support must be executed in a transparent and open manner. In consequence, pharmaceutical companies shall make available to the public a list of the patient organisations that are financially supported in Germany and throughout Europe, or that receive indirect or non-financial benefit. Accordingly, in collaborations with healthcare professionals, the documentation principle shall be observed by the pharmaceutical manufacturers, meaning that the collaboration may only proceed on the basis of a written agreement that spells out the basic elements of the collaboration, as far as a financial payment is provided.

12 Are manufacturers' infringements of competition law pursued by national authorities?

The competent national authorities in Germany are authorised to pursue infringements of rules for the protection of fair competition by pharmaceutical manufacturers. With respect to the HWG, it is laid down in section 64(3) of the AMG that the competent authority shall ensure that the provisions of advertisements in the field of medicines are observed. The competent authorities are the regional authorities in the respective federal states in which the pharmaceutical company is established, the regional administrative authorities (RPs).

However, in our experience, RPs rarely pursue pharmaceutical manufacturers for infringements of unfair competition law. In Germany, the market for medicinal products is mainly self-regulating, and it is common practice for competitors to apply for preliminary injunctions or to initiate regular court proceedings if a competitor fails to comply with the rules for the protection of fair competition.

13 Is follow-on private antitrust litigation against manufacturers possible?

A third party may claim that an infringement of antitrust constitutes a breach of fair competition legislation and may initiate respective legal proceedings against the infringer before the civil courts. However, the Federal Cartel Office is the body responsible for observing a company's compliance with antitrust rules as such.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

The new provisions of the StGB, paragraph 299 a, b StGB, are addressed to members of the medical profession and set out the punishment for corrupt practices. Therefore, corruption is no longer pursued only by the industry codes, but by the prosecutor's office as well.

For interpreting the new provisions, main anti-corruption principles (separation principle, transparency principle, documentation principle, equivalence principle) will be valid. In that regard, nothing has changed from what has been illegal before, however, it is anticipated that it will be prosecuted more in the future.

As regards transparency, the legal provisions do not request transparency, but this still is part of the industry code catalogue.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

The advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations are less regulated than they are in the pharmaceutical sector. For instance, it is not legally required that advertisements for medical devices display the mandatory information about the promoted product. Further, it is admissible to promote medical devices that are only available on prescription to the general public, and not solely to healthcare professionals. In addition, it is possible to promote a medical device in Germany before obtaining the CE mark. However, according to section 12 of the German Act on Medical Devices, the respective medical devices may only be shown if a visible sign clearly indicates that the medical device does not conform to the prerequisites and cannot be purchased until full and due compliance has been achieved. The reason for this more liberal approach of the legislature on advertisements and collaborations is a lesser risk of misuse. Medical devices function physically, and side effects and misuse by consumers are therefore very unlikely.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The AMG sets out the regulatory framework for obtaining a marketing authorisation and placing medicines on the market in Germany. According to section 21(1) of the AMG, a finished medicinal product may only be placed on the market after a marketing authorisation has been granted by the German Higher Federal Authority or the European Commission. Section 4(17) of the AMG defines placing on the market as the keeping in stock for sale or for other forms of supply, the exhibition and offering for sale and the distribution to others. The legal requirement to obtain an authorisation before placing the medicinal product on the market also applies to tissue preparations that are not manufactured in an industrial process, and whose essential processing procedures are sufficiently well-known in the EU and whose effects and side effects are known and evident from scientific data (AMG, section 21a(1)). In addition to the AMG, the Good Manufacturing Practice, as a legal prerequisite for the placing of medicines on the market, is laid down in certain national directives, such as the German Medicinal Products and Active Ingredients Manufacturing Decree.

17 Which authorities may grant marketing authorisation in your jurisdiction?

In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) is competent for the authorisation of finished medicinal products, unless either the Federal Institute for Vaccines and Biomedicines (PEI) or the Federal Office of Consumer Protection and Food Safety (BVL) is competent. According to section 77 of the AMG, the PEI is competent for sera, vaccines, blood preparations, bone marrow preparations, tissue preparations, allergens, gene transfer medicinal products, somatic cell therapy products, xenogeneic cell therapy products and blood components manufactured using genetic engineering. The BVL is responsible for medicinal products that are intended for administration to animals.

18 What are the relevant procedures?

The most relevant procedure to obtain a marketing authorisation for human medicinal products is the national authorisation procedure according to section 21(1) of the AMG, applicable to finished medicinal products. Finished medicinal products are medicinal products that are manufactured beforehand and placed on the market in packaging intended for distribution to the consumer or other medicinal products intended for distribution to the consumer, in the preparation of which any form of industrial process is used or medicinal products that are produced commercially, except in pharmacies (AMG, section 4(1)). Additionally, if the pharmaceutical manufacturer applies for a

marketing authorisation in more than one member state (provided that the respective medicinal product does not fall within the scope of the Regulation 726/2004/EC) and chooses Germany as the reference member state, the decentralised procedure (DCP) and the mutual recognition procedure (MRP) apply (AMG, section 25b; also see the DCP member states' SOP or the Best Practice Guide for DCP and MRP, issued by the Coordination Group).

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

The AMG sets out in section 31(1) No. 1 that a marketing authorisation expires if the authorised medicinal product is not placed on the market within three years after the marketing authorisation has been obtained, or if the medicinal product that was placed on the market in accordance with the marketing authorisation is not marketed for three successive years. The three-year period starts, according to the BfArM, on the date when the respective medicinal product could have been marketed. Therefore, the BfArM follows the European Medicines Agency (EMA) view (see 4.1 of the EMA Q and A document (Ref EMA /180079/2005) of 23 February 2006), and the Notice to Applicants (Volume IIa, Chapter 1, section 2.4.2). If a medicinal product was already on the market, the period will start from the time the medicinal product is no longer being marketed. However, the competent higher federal authority may allow exceptions to this 'sunset clause' if required to protect human or animal health (AMG, section 31(1) 2). In addition, according to the BfArM, this three-year period is suspended if marketing authorisation is suspended due to pharmacovigilance reasons. In any case, the obligation of the marketing authorisation holder to notify the cessation remains unaffected; that is, the marketing authorisation holder must notify the interruption of supply two months in advance to the competent authority (AMG, section 29(1c)).

20 Which medicines may be marketed without authorisation?

Section 21(2) of the AMG provides a list of medicinal products that may be placed on the market without a marketing authorisation. The most relevant exemption (to the rule that medicines shall only be placed on the market after a marketing authorisation has been granted) is set out in section 21(1). Thereafter, medicinal products that are intended for human beings, and of which the essential manufacturing stages are carried out in a pharmacy, in an amount of up to 100 packages in one day and within the framework of the pharmacy operating licence, shall be placed on the market without a marketing authorisation. In addition, the exemptions set out in section 21(2) Nos. 2 and 6 are of relevance. According to No. 2, medicinal products that are intended for use in clinical trials on human beings do not require a marketing authorisation as a prerequisite to being placed on the market. Finally, the same applies to medicinal products that are made available under conditions for compassionate use (AMG, section 21(2) No. 6). In this respect, the Federal Ministry of Health recently issued the Ordinance for Compassionate Use that stipulates the legal requirements for placing unlicensed medicinal products on the market in Germany before a marketing authorisation has been obtained by the pharmaceutical company. Besides the requirement to notify the compassionate use programme to the higher federal authority (BfArM or PEI), the requirements are, inter alia, as follows:

- the existence of objective evidence that the patients suffer from a life-threatening disease or a disease leading to severe disability;
- the existence of objective evidence that there is no other satisfying treatment option with medicinal products approved in the European Community; and
- the existence of objective evidence that a marketing authorisation application has been submitted for the medicinal product or that clinical trials with this medicinal product are still ongoing.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

The AMG states that finished medicinal products may only be placed on the market after a marketing authorisation has been granted. Named patient programmes are exempt from this general rule. The relevant legal provision of the AMG, which implements article 5(1) of Directive 2001/83/EC (see the ECJ's judgment in its decision dated 8 November 2007, C-143/06), reads as follows (non-official translation):

Section 73

(3) [...] finished medicinal products which are intended for use in human beings and which are not authorised for marketing [...] may be introduced into the purview of the present Act if

1. they are ordered by pharmacies on the basis of an order received from individual persons in a small quantity and are dispensed by these pharmacies within the framework of the existing pharmacy operating licence,
2. they may be legally placed on the market in the state from which they were introduced into the territorial scope of the present Act, and
3. no medicinal product for the therapeutic indication in question which is identical in terms of the active substance and comparable in terms of the strength is available in the territorial scope of the Act [...]. The ordering and dispensing of medicinal products from states other than member states of the European Union or other states parties to the Agreement on the European Economic Area require a prescription from a doctor or dentist. Further details shall be settled by the Pharmacies Operation Regulations.

Against this legal background, medicinal products may be placed on the market in Germany under named patient programmes provided that the respective medicinal product is a finished medicinal product, in other words, a medicinal product that is manufactured beforehand and placed on the market in packaging intended for distribution to the consumer. In addition, the medicinal product intended for named patient programmes in Germany must be lawfully placed on the market in the (third) country from which it shall be imported. Furthermore, the ordering and dispensing of the respective medicinal product must be carried out by a pharmacy. Section 73(3) sentence 2 No. 1 of the AMG expressly states that dispensing may only be carried out within 'the framework of the existing pharmacy operating licence'. Therefore, the dispensing must be carried out in the pharmacy and only by pharmaceutical personnel. Furthermore, it is legally required that a supply deficit does exist; in other words, no identical medicinal product for the therapeutic indication with respect to the active substance and no comparable medicinal product for the therapeutic indication with respect to the strength are available. Finally, the medicinal product shall be imported solely in small quantities for a single patient and supplied solely on the basis of a physician's prescription.

Section 8 of the HWG sets out that any promotion for the supply of medicinal products pursuant to section 73(3) of the AMG is prohibited. However, it would be lawful to provide information such as the name of the medicinal product, international non-property name, active substance, strength and price to healthcare professionals, since such information is not considered promotional (see the ECJ's judgment in its decision dated 8 November 2007, C-143/06).

Medicinal products supplied on a named patient basis according to section 73(3) of the AMG are only subject to reimbursement in the German statutory health system if certain requirements are fulfilled. According to the established case law of the German Federal Social Court (see its decision dated 14 December 2009, B 1 KR 12/06 R), the medicinal product must be administered for the treatment of a chronic and serious disease, a seriously debilitating disease, or a disease that is life-threatening, for which no other satisfactory therapy is available and for which reliable safety data can be obtained.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

In Germany, pharmaceutical companies are free to set their prices at will. However, some legal instruments do exist, in particular with regard to the outpatient sector, which might have an indirect impact on the price setting of medicines within the SHI. These instruments are stipulated in the SGB V, which are as follows:

- the reference price system (section 35(1) of the SGB V);
- the efficiency principle (sections 2 and 12 of the SGB V); and
- the therapy information (section 92(2) of the SGB V).

A reference price system can be set by the G-BA for medicines with the same active substance, medicines with therapeutically and pharmacologically comparable active substance, or medicines with

therapeutically comparable effects. The reference price is based on the price of all products of the group into which the medicines are categorised and constitutes the maximum amount being reimbursed for the respective medicines by the SHI. If the price has been set at a higher level by the pharmaceutical company, the difference must be paid by the patient receiving the medicine. However, according to the Basis for Decision-making by the Subcommittee-Medicines for Defining Reference Prices dated 19 July 2007, no reference price should be set for patent medicines based on a new principle and deemed to represent a significant therapeutic advance.

With respect to the efficiency principle, please note the findings mentioned above. The efficiency principle can be specified or defined by therapy information. In consequence, the medicine for which therapy information exists (issued by the G-BA) would only be reimbursed in the case of a certain therapy application. The Drug Price Ordinance sets out certain conditions for the pricing of medicines.

The Act for the Restructuring of the Drug Market (AMNOG) proposes a new form of price setting for innovative medicinal products and sets new conditions for pricing and reimbursement of medicinal products. Since 2011, the reimbursement of a new medicinal product has been aligned regarding its therapeutic value. According to the AMNOG, the value of an innovative medicinal product is determined in comparison with existing therapies. A higher price might be negotiated with the National Association of Statutory Health Insurance Funds (GKV-SV) only if an additional benefit can be proven to the G-BA with respect to existing therapies. Medicinal products without any additional benefit are only reimbursed at the level of comparable products or therapies.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

Since the Act for restructuring of the drug market in the statutory health insurance (AMNOG) came into effect on 1 January 2011, new legal requirements have applied regarding the pricing of medicinal products in the outpatient sector. The price for medicinal products is now subject to negotiations between the pharmaceutical manufacturer and the GKV-SV. In general, two different price negotiation procedures apply, depending on whether innovative medicinal products (ie, with additional benefit) are concerned.

To identify additional benefit, medicinal products with new active ingredients or new areas of application are to be assessed by the G-BA in 'early assessment procedures'. The G-BA is authorised to delegate the assessment to the Institute for Quality and Efficiency in Healthcare or to another third party. The assessment is based on a dossier that is drafted by the pharmaceutical manufacturer. The dossier must be submitted to the G-BA before the medicinal product is placed on the market for the first time. According to section 4(1) of the Ordinance for the Assessment of the Benefit of Drugs with New Active Ingredients (AM-NutzenV), the dossier must contain the following information:

- authorised application areas;
- medical benefits;
- additional medical benefit compared with the suitable comparative therapy;
- the number of patients and patient groups for which the therapeutically meaningful additional benefit exists;
- the costs for the therapy to the statutory health insurance; and
- the conditions for application in the requested quality.

If the pharmaceutical manufacturer submits no dossier to the G-BA, the additional benefit is deemed not proven. Provided that a dossier has been submitted by the pharmaceutical manufacturer, the G-BA conducts the assessment procedure within three months. As a matter of course, the G-BA notifies the result of the assessment to the pharmaceutical manufacturer, and publishes it on its website as well.

According to section 2(4) of the AM-NutzenV, the additional benefit of a medicinal product is defined as any quantitatively or qualitatively improved patient-relevant therapeutic effect, compared with the effect of a suitable comparative therapy (such as improvement of health, reduction of illness duration, extension of survival, reduction of side effects or improvement of the quality of life). A suitable comparative therapy must usually be determined based on conditions that result from the international standards of evidence-based medicine. Provided that more alternatives exist, more economical therapy should be selected, preferably a therapy with a reference price.

Update and trends

Just recently, the German parliament passed a law with which the benefit assessment of medical devices becomes mandatory for high-risk classes (section 137 h SGB V). It is notable that the system of benefit assessment is not only applied to medicinal products but becomes a common system for introducing new technologies and devices to the market. We suppose that within the next couple of years, benefit assessment will be the major instrument before any health service enters the reimbursement system.

The price for medicinal products without additional benefits is limited to the costs of the comparative therapy, either by including the medicinal product in the reference price system, or, if the requirements for reference price system are not fulfilled, by negotiating a respective price with the GKV-SV.

The price for medicinal products with additional benefit may be determined by the pharmaceutical manufacturer for a 12-month period, beginning when the medicinal product has been placed on the market. Within this 12-month period, the reimbursement amount is to be negotiated between the pharmaceutical manufacturer and the GKV-SV. This amount applies from the 13th month onwards.

According to section 130b of the SGB V, the GKV-SV and the pharmaceutical manufacturer must conclude a contractual agreement on a reimbursement amount. This contractual agreement applies to all health funds; in other words, to the statutory health insurance funds and to the private insurance funds. If no agreement is reached within six months, an arbitration board becomes involved and decides within three months. The arbitration board consists of seven members: three independent members, two members from the GKV-SV and two members from the pharmaceutical manufacturer. The applicable legal provisions provide no benchmark on how the price shall be stipulated by the arbitration board. With respect to medicinal products with additional benefit, the sales price in other European countries shall be taken into account (see section 130b(4) of the SGB V).

Provided that orphan drugs pursuant to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products are concerned, the additional benefit of the authorised orphan medicinal product does not have to be proven by the pharmaceutical manufacturer. According to section 130b (1) sentence 10 of the SGB V, orphan medicinal products need not prove any medical benefit or any additional medical benefit compared with the suitable comparative therapy, since this is legally acknowledged for orphan medicinal products by the marketing authorisation.

However, this privilege does not apply to orphan medicinal products with a turnover in the statutory health insurance fund above €50 billion in the past 12 months. The turnover is calculated by considering the sales price including value added tax. In this case, the G-BA may request evidence from the pharmaceutical manufacturer within three months with respect to the additional benefit of the orphan medicinal product as under the above-mentioned procedure.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

According to section 27(1) of the SGB V, persons insured within the SHI are entitled to treatment if necessary to diagnose a disease, to heal a disease, to reduce its deterioration or to reduce clinical pain. This includes the supply of medicines, pursuant to section 27(1) 2 No. 3 of the SGB V.

However, the reimbursement of medicines in the outpatient sector within the SHI is subject to numerous restrictions, such as:

- the medicine supplied to the insured must be legally placed on the market in Germany;
- the supply of medicines must be in line with the efficiency principle set out in sections 2 and 12 of the SGB V;
- the medicine must be available in pharmacies only (see section 31(1) of the SGB V); and
- the reimbursement by the SHI must not be excluded by section 34 of the SGB V.

Firstly, according to No. 3 of the Pharmaceutical Guideline issued by the G-BA, persons who are statutorily insured are entitled to the supply of medicines provided that the respective medicines are legally

placed on the market in Germany: that is, with a marketing authorisation or another respective authorisation (eg, a registration), or where no authorisation is required due to section 21(2) of the AMG. Secondly, with respect to the efficiency principle, please note the above. Thirdly, persons statutorily insured are entitled to medicines within the SHI solely if these medicines are classified as 'pharmacy-only medicine'. Fourthly, according to section 34 of the AMG, the medicine is excluded from the supply within the SHI if the medicine is not available on prescription, if the medicine is intended for the treatment of a minor ailment or if the medicine can be classified as a 'lifestyle' medicine.

With respect to off-label use, the administration of a medicine outside its licensed indications can be reimbursed by the SHI, provided that certain conditions are fulfilled. In many rulings, German courts have laid down that if a medicine is administered for the therapy of a chronic and serious disease, a seriously debilitating disease or a disease that is life-threatening, for which no other satisfactorily therapy is available and for which reliable safety data can be obtained, the medicine will be reimbursed within the system of the SHI. With respect to medicines administered in a compassionate use programme, the reimbursement (within the system of the SHI) has been subject to even stricter requirements than those applying to the reimbursement of medicines for off-label use. However, since the 15th amendment of the AMG was enacted (September 2009), medicines administered in compassionate use programmes are excluded from reimbursement within the system of the SHI.

The costs for medicines in the hospital sector are covered by DRGs. Each DRG is calculated to cover the costs of the hospital: namely, physicians' services, in-patient care and the necessary medicinal products. If the costs for a medicine are not sufficiently covered by the respective DRG, the hospital may agree with the relevant bodies in the SHI on a supplementary benefit, on a national or regional level, to ensure that the actual incurred costs for an in-patient treatment are covered. The responsible body for calculating DRGs in Germany is the Institute for the Hospital Financing System, and the respective DRG catalogue is enacted each year upon the collaboration of the GKV-SV, the Private Health Insurance Association and the German Hospital Federation.

Finally, the medicines must be incorporated in the Lauer-Taxe, regardless of whether the medicines will be reimbursed in the outpatient or the hospital sector. The Lauer-Taxe is an official databank that contains information of authorised finished medicinal products that are reported to the Information Centre for Proprietary Medicinal Products. After the inclusion in the Lauer-Taxe, the medicine receives a central pharmaceutical number (PZN), a nationwide identification key for products distributed by pharmacies. Beside the PZN, the Lauer-Taxe also includes information regarding the respective medicine such as product characteristics, form of administration, package size and package price. It is legally ruled that the PZN serves as an identification key for the reimbursement of medicines within the SHI (section 300 of the SGB V), and the PZN is, for this purpose, also listed on the prescription.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

As mentioned in question 23, the new pricing requirements, which introduced (further) requirements for the pricing and reimbursement of medicinal products, have applied since 1 January 2011. After a marketing authorisation has been granted, the G-BA reviews, in an 'early assessment procedure', whether a new medicinal product has any additional benefit regarding the existing therapies. The 'early assessment procedure' is carried out by the G-BA on the basis of a dossier submitted by the marketing authorisation holder. Provided that no dossier will be submitted by the marketing authorisation holder, the G-BA is under no obligation to become active, and the additional benefit is deemed to be not proven.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

Pharmaceutical manufacturers are legally obliged to grant a discount of 16 per cent on their finished medicinal products, based on the manufacturer price listed in the Lauer-Taxe. This has recently been extended with effect from 1 January 2014 until 31 December 2017, and applies to medicinal products that are dispensed by community hospitals for the outpatient sector and by hospital pharmacies for outpatient care. The

increase to the manufacturers' discount has been introduced jointly with a price moratorium, which considers the official price listed in the Lauer-Taxe on 1 August 2009. This was supposed to have the effect that pharmaceutical manufacturers would not compensate for the increase in the manufacturers' discount by increasing the price before the discount applied.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

According to section 8(1a) of the AMG, it is prohibited to manufacture or to market medicinal products that are incorrectly labelled with regard to their identity or origin (counterfeit medicinal products, counterfeit active substances). An infringement is penalised by a fine or imprisonment of up to 10 years (the AMG, section 95(1) No. 3a and (3)). In addition to respective rules laid down in the StGB, the VfA issued a position paper titled 'Counterfeit Medicinal Products' in January 2009. Meanwhile, the European Commission has passed the respective proposal within the Pharmaceutical Package amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of counterfeit medicines (falsified medicinal products) in relation to their identity, history or source. Although the number of counterfeit medicines placed on the market in Germany is very low (approximately 1 per cent), the relevance for pharmaceutical manufacturers is expected to be very high.

In September 2012, the respective Second Law on the alteration of provisions relating to medicinal products and other regulations was enacted by the German Federal Assembly and constitutes the aforementioned measures to prevent counterfeiting. All medicinal products available only by prescription (Rx products, except listed in a white-list; 'opt-out solution') and specific over-the-counter products (listed in a white-list, 'opt-in solution') are, over time, obliged to add a unique identifier and a tamper-proof feature on the outer package, allowing a complete tracing of the product within the distribution chain (ie, manufacturer, wholesalers and pharmacies).

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

For the time being, the HWG does not contain detailed rules on information for the general public on medicines available for prescription only. As mentioned, section 10 HWG prohibits advertisements regarding medicines available on prescription only, whereas the provision of information to a non-healthcare professional is allowed, given that such information is provided within correspondence of a non-promotional

nature and needed to answer a specific question about a particular medicine (the HWG, section 1(5)). However, the restrictive approach stipulated in section 10 of the HWG will be subject to legal amendments in the near future (caused by the Pharmaceutical Package and the ECJ judgment on 5 May 2011 C-316/09 regarding MSD Sharp & Dohme GmbH/Merckle GmbH), and the availability of high-quality information addressed to the general public regarding medicines available only on prescription will be liberalised.

29 Outline major developments to the regime relating to safety monitoring of medicines.

In Germany, the AMG sets out that the marketing authorisation holder shall keep detailed records of all cases of suspected adverse effects. Furthermore, the marketing authorisation holder shall record every case of serious suspected adverse effects and every case of serious suspected unexpected adverse effects. Such adverse effects must be reported to the competent higher federal authority no later than 15 days after it comes to his or her knowledge. The 15th amendment to the AMG, enacted by the German Federal Assembly in 2009, clarified that the documentation and notification obligations do not apply to investigational medicinal products (the AMG, section 63b(9)). Adverse effects occurring when conducting a clinical trial must be reported under the requirements of good clinical practice.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

Generally, there is no obligation to vaccinate in Germany; general practitioners are responsible only for vaccination awareness. According to section 20d paragraph 1 of the SGB V, the Federal Joint Committee has enacted the Immunisation Guideline dated 1 July 2008. It regulates the reimbursement of vaccinations based on the recommendations of the Standing Committee on Immunisation. In Annex 1 of this Guideline, all reimbursable inoculations are listed. The SHI does not, however, compensate those vaccinations that are needed to prevent tropical diseases prior to a holiday trip.

According to the WHO, the vaccination rate should reach 95 per cent for major preventable diseases. In Germany, this rate is achieved for newborns and children. However, a certain vaccination fatigue among adults can be observed, for various reasons. People associate childhood diseases with young patients and do not fear being taken ill by such diseases, even though childhood diseases are often more dangerous for adults. In addition, people lose track of what kind of vaccination is necessary, and essentially they fear side effects. This leads to the proposed adult vaccination rates not being achieved.

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

Healthcare is a state responsibility according to the Constitution of India (article 42, 'Provision for just and humane conditions of work and maternity relief' and article 47, 'Duty of the State to raise the level of nutrition and the standard of living and to improve public health').

Each state has its own healthcare delivery system in which both public and private (for-profit as well as non-profit) parties operate. While states are responsible for the functioning of their respective healthcare systems, certain responsibilities also fall to the central government, namely aspects of policymaking, planning, guiding, assisting, evaluating and coordinating the work of the various provincial health authorities, and providing funding to implement national programmes. The organisational structure of the healthcare system is as follows:

- at the national level, the organisation consists of the Union Ministry of Health and Family Welfare (MoHFW);
- at the state level, the organisation is under the state department of health and family welfare of each state. Each state department is headed by a minister and has a secretariat under the charge of the Secretary or Commissioner (Health and Family Welfare) belonging to the cadre of the Indian Administrative Service;
- at the regional level, each regional and zonal setup covers three to five districts and acts under authority delegated by the State Directorate of Health Services;
- the district-level structure of health services is a middle-level management organisation that provides a link between the state and the regional structures on one side, and the peripheral-level structures (such as primary health centres and sub centres) on the other;
- at the sub-divisional (administrative division) level, healthcare services are rendered through the office of the Assistant District Health and Family Welfare Officer; and
- at the community level, one community health centre has been established for every 80,000 to 1.2 million members of the population, and the centres provide basic specialty services in general medicine, paediatrics, surgery, obstetrics and gynaecology.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

In-patient (hospitalisation) financing consists of the following:

- patient's out-of-pocket expenses;
- health insurance (held by 3 per cent of the population, and made up of 50 per cent social insurance, 23 per cent private insurance and 17 per cent community health insurance);
- government funding for the central government health scheme (CGHS) and employees' state insurance (ESI) scheme; and
- the public-funded scheme, which consists of the national health insurance programme (RSBY) and the National Rural Health Mission (NRHM).

Outpatient financing consists of the following:

- patient's out-of-pocket expenses (70 per cent);
- health insurance (there is very minimal funding by insurance);
- government funding for the CGHS and ESI scheme; and
- the public-funded scheme (ie, the RSBY and the NRHM).

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

Pharmaceutical advertising is governed by the following legislation:

- the Drugs and Magic Remedies (Objectionable Advertisements) Act, 1954, which controls the advertisement of drugs in certain cases (including misleading advertisement);
- the Drugs and Cosmetics Rules, 1945, which regulate labelling and branding of pharmaceutical products, cosmetics and homeopathic medicines in India;
- the Medical Council of India (MCI) (Professional Conduct, Etiquette and Ethics) Regulations 2002 (MCI Regulations), which relate to ethical conduct that may affect the relationship of medical practitioners with the pharmaceutical industry;
- the Marketing Code, which is a voluntary code for the Indian pharmaceutical industry that was introduced on 2 June 2011 by the Department of Pharmaceuticals under the Ministry of Chemicals and Fertilisers, and which relates to the promotion of pharmaceutical products and the interaction of pharmaceutical companies with healthcare professionals; and
- the OPPI Code of Pharmaceutical Marketing Practices (OPPI Code). OPPI is a non-governmental scientific organisation that is an active Indian member of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). The OPPI Code provides guidelines for pharmaceutical marketing that are based on the IFPMA Code of Pharmaceutical Marketing Practices. Although not mandatory, the OPPI Code provides useful guiding principles that may be followed to ensure better marketing of pharmaceutical products.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

The main rules and principles that apply to advertising aimed at healthcare professionals are as follows:

- section 3 of the Drugs and Magic Remedies (Objectionable Advertisements) Act, 1954;
- sections 16 and 17 and rules 94 to 106 of the Drugs and Cosmetics Rules, 1945;
- section 6.8 of the MCI Code;
- section 1 (general points) of the Marketing Code; and
- section 5 of the OPPI Code, which provides the requirements regarding information content in pharmaceutical advertising.

5 What are the main rules and principles applying to advertising aimed at the general public?

There is no legislation that regulates direct marketing of medicinal products to the general public. The direct marketing of prescription drugs (Rx) defined under schedules H and X of the Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954 is prohibited in India. However, over-the-counter (OTC) medicinal products can be advertised by pharmaceutical companies. There is no statutory binding legislation that prevents advertisement of drugs that are not defined under schedule H or X. Although the phrase 'over-the-counter' has no legal recognition in India, all drugs that are not included in the list of 'prescription drugs' are considered to be non-prescription (or OTC)

drugs. Various OTC drugs are advertised in India, including digestives, antacids, anti-flatulents, cold drugs and analgesic balms, vitamins, tonics and health supplements, medicated skin treatments, analgesic and cold tablets, antiseptic creams and glucose powders.

The OPPI Code of Ethics for the Advertisement of OTC drugs in India provides guidelines for responsible advertising promoting the sale of medicines that may be purchased by the public without prescription and for which therapeutic claims are made. These voluntary guidelines provide good faith principles that advertisements of non-prescription systemic analgesics and painkillers shall carry a 'use only as directed' warning. This must be clearly visible, audible or legible (as appropriate, depending upon the advertising medium). In the case of an advertisement for vitamin preparations and tonics, such advert shall not infer that such products are a substitute for good nutrition or can replace a balanced diet.

The Pharmacy Council of India notified the regulation, namely Pharmacy Practice Regulation 2015, in the Official Gazette on 15 January 2015. Under the Pharmacy Practice Regulation, the definition of 'prescription' has been defined under section 2(j).

'Prescription' means a written or electronic direction from a registered medical practitioner or other properly licensed practitioners such as dentist, veterinarian, etc, to a pharmacist to compound and dispense a specific type and quantity of preparation or prefabricated drug to a patient.

Prescription is defined as written or electronic direction from a registered medical practitioner, which means the prescription can be written or in an electronic form.

There are abundant online portals that offer the service of delivering schedule H and schedule X medicines to the patient or consumer against the prescription uploaded on their server. The elaborated definitions of 'prescription' as provided are an alternate means to deliver schedule H and schedule X medicines to the patients or user.

However, there is a restriction on the advertisement of schedule H and schedule X medicines. The portals are allowed to deliver schedule H and schedule X medicines as per the requirement. Therefore, restrictions on the advertising of schedule H and schedule X on the internet still persist.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The most common infringement committed in relation to adhering to the advertisement standards defined under the OPPI Code and the Marketing Code are advertisements that are incomplete: that is, advertisements not listing the date of production of the advertisement, and advertisements not listing the marketer's name and address, in both first and reminder advertisements.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

The Drug Controller General of India (DCGI) has not approved any off-label use of drugs. Consequently, off-label use of a drug is illegal in India, and health professionals are obliged to obey the Professional Conduct, Etiquette and Ethics Regulations 2002 of the MCI. Accordingly, they are required not to evade legal restrictions such as those found under the Drugs and Cosmetics Act (Chapter 1.9).

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals?

Do different rules apply regarding physicians in the outpatient and inpatient sectors?

The MCI Regulations form the primary legislation that governs connections between healthcare professionals and pharmaceutical companies, as well as their relationship to patients.

The MCI Regulations apply to doctor-patient relationships regardless of whether patients are in-patients or outpatients; they lay down the duty of doctors to give their patients the best possible treatment available. However, in the case of in-patient treatment, doctors may be held liable for any errors, and can be prosecuted under the Consumer Protection Act, tort law or through criminal proceedings depending upon the degree of negligence and the standard of care provided by a doctor to a patient.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The main rules in this regard are as follows:

- section 6.8 of the code of conduct for doctors and professional associations of doctors in their relationship with the pharmaceutical and allied health-sector industry; and
- section 6.8.1 of the above code: in dealing with the pharmaceutical and allied health-sector industry, medical practitioners shall follow and adhere to the legal restrictions as defined in section 1.9 of the MCI Professional Conduct, Etiquette and Ethics Regulations 2002.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

The most common infringements committed by manufacturers with regards to their interactions with healthcare professionals are violations of the ethical code of conduct laid out by the MCI Regulations, including offering a healthcare professional luxury trips and parties to secure his or her participation in an organised convention or conference; and giving gifts or incentives to encourage a healthcare professional to promote the manufacturer's medicinal products.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

In India, there is no regulation that corresponds to the European Federation of Pharmaceutical Industries and Associations Code of Practice on Relationships between the Pharmaceutical Industry and Patient Organisations.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes, by the Competition Commission of India (CCI).

13 Is follow-on private antitrust litigation against manufacturers possible?

The CCI is the primary authority in charge of the enforcement of competition law in India. The CCI can start investigations either on its own initiative or based on information received, and consumers can institute legal proceedings to recover losses or damages caused by anticompetitive practices. The CCI will scrutinise the anticompetitive practice and issue its finding.

The Appellate Tribunal, COMPAC, under section 53N of the Competition Act 2002, can adjudicate on claims for compensation that may arise from the findings of the CCI.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

See www.gettingthedealthrough.com.

Compliance - medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Yes.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The Drugs and Cosmetics Act 1940, regulates the import, manufacture, distribution and sale of drugs and cosmetics in India.

17 Which authorities may grant marketing authorisation in your jurisdiction?

The Central Drug Standard and Control Organisation (CDSCO) is the national regulatory authority in India that evaluates the safety, efficacy and quality of drugs. The CDSCO is headed by the DCGI, which is an apex regulatory body under the MoHFW and is responsible for the approval of new drugs. The DCGI is advised by the Drug Technical Advisory Board and the Drug Consultative Committee. Licensing and classification of medical devices are handled by the Central Licensing Approval Authority (CLAA). The CLAA is also responsible for setting and enforcing safety standards; it appoints notified bodies to oversee and assess conformity, conduct post-market surveillance, and issue warnings and recall drugs in the event that there are any adverse effects. The CDSCO establishes safety, efficacy and quality standards for pharmaceuticals and medical devices. It publishes and updates the Indian Pharmacopoeia, which is a list of regulated pharmaceuticals and devices.

The CDSCO is divided into several zonal offices that conduct pre and post-licensing inspections, post-market surveillance and issue recalls when necessary. In addition to its regulatory functions, the CDSCO offers technical guidance, trains regulatory officials and analysts and monitors adverse events. The CDSCO works with the World Health Organization (WHO) to promote good manufacturing practice and international regulatory harmony.

18 What are the relevant procedures?

The regulatory approval process in India can be divided into two categories based on the definition of a drug: an approval process for a new drug and an approval process for a drug that has ceased to be a new drug. Approval for the manufacture and import of drugs is governed by the Drugs and Cosmetics Act of 1940 and the rules 1945. All applications for approval for 'new drugs' have to be obtained from the CDSCO. Once a drug ceases to be a 'new drug', the applicant can seek permission for a manufacturing licence from any of the more than 27 competent state regulatory authorities. The applicant is required to submit data as per Appendix I of Schedule Y, which is similar to the data required for any new chemical entity. All of the data from any Phase I to Phase III clinical trials are required for such new drug. However, if the drug is approved in other countries, the applicant is required to submit data based on the Indian population alone (ie, only from the Phase III trial).

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Under rule 28 of the Drug and Cosmetics Act 1940 and the 1945 rules, import licences are granted for three years. The applicant is required to seek a fresh import licence after the expiry of the existing licence, and such application should be made three months prior to the expiry of the existing import licence period. Marketing authorisations cease if a medicine is not put on the market within three years of its authorisation; as such, in the event that an importer or manufacturer fails to market a drug within three years, a fresh licence will be required.

20 Which medicines may be marketed without authorisation?

Manufacturing licences for drugs that cease to be new drugs, as per the definition of 'new drug' according to rule 122E of the Drug and Cosmetics Act, can be obtained directly from the state regulatory authority.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Directive 2001/83/EC states that an unlicensed drug may be made available in response to a bona fide unsolicited order by healthcare professionals for use by their individual patient under their direct personal responsibility. Rule 123 of the Drugs and Cosmetics Act, 1940 and the 1945 rules are directed to exemptions, and state that the drugs specified in Schedule K can be made available to the patients under certain circumstances.

Drugs can be supplied by a registered medical practitioner to his or her own patient, as can any drug specified in Schedule C supplied by a registered medical practitioner at the request of another such practitioner if it is specially prepared with reference to the patient's condition and for the use of such individual patient.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

The pricing of pharmaceutical products is regulated and falls under the Drug Prices Control Order (DPCO) 1995. In India, successive DPCOs have reflected a declining trend in the control basket. In 1970, all drugs were controlled, but such control has gradually been reduced (to 347 drugs in 1978, to 163 drugs in 1987 and finally to 73 drugs in 1994). The government set up the National Pharmaceutical Pricing Authority (NPPA) on 29 August 1997 (www.nppaindia.nic.in) as an independent body of experts that deals with the following matters:

- price fixing and revision, and other related matters such as updating the list of drugs included or excluded from price controlling on the basis of the established criteria and guidelines;
- monitoring the prices of uncontrolled drugs and formulations and overseeing the implementation of the provisions of the DPCO;
- monitoring the availability of drugs, identifying shortages and taking remedial steps to address such shortage;
- collecting and maintaining data on production, exports and imports, market share of individual companies, profitability of companies, etc, for bulk drugs and formulations;
- undertaking or sponsoring relevant studies in respect of pricing of drugs and pharmaceuticals;
- advising the government on revisions to the drug policy, as well as assisting the government in parliamentary matters relating to drug pricing; and
- monitoring and analysing price movements of non-scheduled medicines on a monthly basis. The prices of these formulations are fixed and determined by the manufacturers themselves depending on various factors (cost of production, market competition, the company's profitability, etc).

On 15 May 2013, the Department of Pharmaceuticals issued a DPCO that altered the price regulations and substantially increased the number of medicines covered by the price cap umbrella. The earlier DPCO of 1995 regulated only 74 bulk drugs, whereas the current DPCO will regulate the price of as many as 348 medicines. The new DPCO includes provisions for regulating the price of new drugs. A new drug class has been defined under rule 122E of the Drugs and Cosmetics Act, and can include patented medicines as well.

In *KS Gopinath* (2003), the Supreme Court directed the government to ensure that '[...] essential and life-saving drugs do not fall out of price control'. The DPCO 1995 controls the price both for bulk drugs and formulations that are scheduled drugs.

The DPCO 1995 does not regulate or fix the price of non-scheduled drugs; however, in cases where there is an annual increase of the retail price of 10 per cent or more, the NPPA can intervene. Manufacturers of non-scheduled drugs (eg, drugs not under direct price control) are not required to adhere to any price approvals issued by the NPPA regarding such drugs. However, in order for the NPPA to monitor the price of such drugs and take corrective measures where warranted, it is a requirement that manufacturers must inform the NPPA of the price of their drugs within 30 days of the commencement of any price increase. Further, in the case of non-scheduled drugs, the government may, as it deems necessary in the public interest, fix or revise the price of any non-scheduled bulk drug, and the manufacturer or importer of such bulk drug shall not sell said drug at a price that exceeds the fixed or revised price.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

Price negotiations for patented drugs have been on the agenda for some time. However, to date no guidelines appear to have been formulated by any specialised committee or by the Department of Pharmaceuticals to provide a formula for deriving the 'ceiling price' of patented drugs in the non-scheduled category.

In March 2013, the Department of Pharmaceuticals issued a draft policy on the pricing of patented drugs. A summary of the recommendations in this report are as follows:

- the government should expand the coverage of the healthcare and insurance scheme (at least for prescription medicines) to all citizens not covered under any other insurance or reimbursement scheme;

- there is no need to link price negotiations of a patented medicine with its marketing approval;
- a committee headed by the chair of the NPPA should be established for deciding the price of patented medicines;
- the reference prices of the patented medicines to be used for price negotiations in India will be the procurement prices of those medicines in the United Kingdom, Canada, France, Australia and New Zealand;
- there will be three categories of patented drugs as follows:
 - a brand new class of drugs that have no therapeutic equivalence in India: for such medicines, the originator company will submit the government procurement price list to the committee. The committee will take the per capita gross national income (with purchasing power parity) of the country of the originator company. The ratio of the per capita income of that particular country to the per capita income of India will be calculated. The price of the medicine in India will be worked out by dividing the price of the medicine in the originator country by this ratio, and the lowest price will be used for negotiations for further reductions;
 - drugs that have therapeutic equivalence in addition to improved therapeutic equivalence over existing drugs (improved efficacy) in India: the committee would use the reference pricing as explained above, but would ensure that the cost of treatment does not increase with respect to the cost of treatment with existing equivalent medicines; and
 - drugs that have comparable therapeutic efficacies to existing drugs should be given differential treatment while fixing prices; and
- for medicines introduced for the first time in India: the pricing committee for patented drugs will fix the price of new medicines taking various factors into consideration, such as the cost involved, risk factors and any other relevant factors.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

India's national health system covers the cost of medicines for patients registered under the CGHS or ESI schemes. The medicines are distributed at the hospital or dispensary level. However, if a medicine is not available at a distribution centre, the cost of such medicine is reimbursed.

Private insurance companies will reimburse expenses incurred for the treatment of diseases and conditions that are listed in their portfolios and for which a patient is hospitalised for at least 24 hours. In addition, medicines that are required by a patient for up to 30 days prior to hospitalisation and up to 60 days post-hospitalisation are reimbursed. However, medicines subsequently required by the patient must be purchased as an out-of-pocket expense. Further, private insurers do not reimburse the cost of medicines that are used for treating chronic diseases, such as blood pressure, diabetes, etc, which require regular medication for prolonged periods of time.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

As mentioned in question 22, the NPPA was set up on 29 August 1997 as an independent body of experts that is responsible for decisions regarding the pricing and reimbursability of medicinal products.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

No; manufacturers and distributors of medicinal products are not statutorily obliged to give a discount on pricing. However, the NPPA plays an important role in fixing the price of scheduled drugs.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Counterfeit medicines are medicines that are deliberately and fraudulently mislabelled with respect to their identity or source. Counterfeiting can apply to both branded and generic products, and counterfeit products include:

- products with the wrong ingredients or without active ingredients;
- products that are missing key ingredients;
- products with insufficient active ingredients;
- products that are improperly labelled, stored or handled; and
- products with fake packaging.

The term 'counterfeit medicine' is not defined in the Drug and Cosmetics Act, 1940. However, the terms 'misbranded drug', 'adulterated drug' and 'spurious drug' are defined under sections 17, 17A and 17B respectively of the Drugs and Cosmetics Act as types of 'counterfeit medicine'.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

The WHO Country Office for India, in collaboration with the Karnataka State Pharmacy Council, has established five drug information centres (in Haryana (Sirsa), Chhattisgarh (Raipur), Rajasthan (Jaipur), Assam (Dibrugarh) and Goa (Panaji)) to provide organised drug information to both healthcare professionals and consumers. Most drug information centres are attached to pharmacy colleges or hospitals where clinical pharmacy programmes are in place; a few are not attached to health facilities, but are often associated with state pharmacy councils. Drug information centres routinely respond to inquiries regarding:

- appropriate therapy for specific patients;
- adverse reactions to drugs;
- efficacy of drugs;
- drug interactions;
- intravenous additive incompatibilities;
- biopharmaceutic and pharmacokinetic parameters of drugs;
- dosing in cases of renal failure;

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- appropriate therapy for a disease state;
- identification of foreign drugs;
- information on investigational agents; and
- information on new drugs.

In addition, a reliable resource of information on medicines is the National Formulary of India (NFI). Although the NFI serves primarily as a guidance document for medical practitioners, pharmacists, nurses, medical and pharmacy students, and other healthcare professionals, it is also accessible to the general public. The first, second and third editions of the NFI were published by the MoHFW in 1960, 1966 and 1979 respectively. In the past three decades, there has been a massive expansion in the range of new drugs available and their formulations. To address the necessity of publishing an updated version of the NFI, the MoHFW, through Notification F.No.X.11035/2/06-DFQC dated 8 May 2008, has assigned this responsibility to the Indian Pharmacopoeia Commission (IPC). As a result, an updated NFI will be published by the IPC on behalf of the MoHFW.

29 Outline major developments to the regime relating to safety monitoring of medicines.

The Pharmacovigilance Programme of India (PvPI) was launched with the broad objective of safeguarding the health of the 1.27 billion people that form India's population. Adverse drug reactions (ADRs) are reported from all over the country to the National Coordination Centre (NCC) for the PvPI (NCC-PvPI), which also collaborates with the global ADR monitoring centre (which is based in Sweden and run by the WHO and Uppsala Monitoring Centre) to contribute to the global ADRs database. NCC-PvPI monitors ADRs in the Indian population and helps the CDSCO in making decisions regarding the safe use of medicines.

The CDSCO, which is under the aegis of the MoHFW, initiated the PvPI in July 2010, and the All India Institute of Medical Sciences (AIIMS) is the NCC for monitoring ADRs in India to safeguard the public's health. (AIIMS is one of 22 ADR monitoring centres that were set up under the PvPI). To ensure a more effective implementation of the programme, the NCC was moved from AIIMS to the IPC in April 2011.

The PvPI's mission is to safeguard public health by ensuring that the benefits of using medicines outweigh the risks associated with their use. Since considerable social and economic consequences arise from ADRs and a positive cost/benefit ratio of implementing appropriate risk management exists, there is a need to engage both healthcare professionals and the public at large in a well-structured programme to build synergies for monitoring ADRs in the country.

The PvPI collates and analyses data, and uses the inferences to recommend informed regulatory interventions, as well as communicating risks to healthcare professionals and the public. The broadened scope of pharmacovigilance regarding patient safety includes the detection of medicines of substandard quality as well as prescribing, dispensing and administration errors. Counterfeiting, antimicrobial resistance and the need for real-time surveillance of mass vaccinations are further pharmacovigilance challenges that need to be addressed.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

India's immunisation programme has undergone a number of significant changes in recent years. These include a new policy environment (NRHM), new vaccines (eg, hepatitis B and Japanese encephalitis), new procedures to solve old problems (eg, injection safety), and new technologies for vaccine delivery and cold chain security.

The immunisation programme forms part of the reproductive and child health programme under the NRHM, and the MoHFW is responsible for its implementation. The National Health Policy (2002) is directed towards achieving an acceptable, affordable and sustainable standard of health through an appropriate healthcare system. Provision of a universal immunisation programme for children against vaccine-preventable diseases is one of the major goals under the Policy. India developed a comprehensive Multi-Year Strategic Plan for Immunisation in 2005 with an addendum in 2010 to achieve the targets of improving access and utilisation of immunisation in the country.

The information contained in this chapter is accurate as of November 2015.

Ireland

Michael Finn and Robert O'Shea

Matheson

Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

Healthcare policy in Ireland is determined by the Department of Health. Public healthcare services are provided by the Health Service Executive (HSE). There is a two-tier health service in Ireland, comprising the public healthcare system and the private healthcare system. The HSE owns and runs public hospitals. Other hospitals, known as voluntary public hospitals, are owned by religious orders or similar institutions. There are also privately owned hospitals in Ireland.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The public healthcare system is generally funded by taxation and social welfare contributions. Voluntary hospitals also receive state funding. The private healthcare system is funded by private funds and private insurance. Private hospitals have agreements in place with private health insurers to fund the treatment of patients.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

Advertising of medicinal products is governed by the Medicinal Products (Control of Advertising) Regulations 2007 (the Advertising Regulations). General consumer legislation also applies to advertising medicinal products, including the Consumer Protection Act 2007 and European Communities (Misleading and Comparative Marketing Communications) Regulations 2007, and others.

In addition to legislation, there are also codes of practice that apply to advertising. There are two codes of practice published by the Irish Pharmaceutical Healthcare Association (IPHA). The IPHA Code of Practice for the Pharmaceutical Industry, Edition 8.1 (the IPHA Code) transposes the EFPIA Code on the Promotion of Prescription-only Medicines to, and Interactions with, Healthcare Professionals. The IPHA Code also provides practical guidance on implementing the provisions of the Advertising Regulations. IPHA has also published a Code of Standards of Advertising for the Consumer Healthcare Industry, Revision 5.1, which sets standards for the advertising of over-the-counter (OTC) medicines to consumers.

In addition to these industry codes, general consumer codes also apply. The Advertising Standards Authority of Ireland has published the Code of Standards for Advertising, Promotional and Direct Marketing in Ireland and the Broadcasting Authority of Ireland has also published the General Commercial Communications Code.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

Advertising of authorised medicinal products to healthcare professionals (HCPs) is permitted provided the advertisement includes the following information:

- essential information compatible with the Summary of Product Characteristics (SmPC);
- the name of the product and the list of the active ingredients;
- the classification of the product;
- one or more indications for use of the product;

- information regarding adverse reactions and contraindications;
- the dosage and method of use of the product; and
- details of the marketing authorisation (MA) and MA holder.

5 What are the main rules and principles applying to advertising aimed at the general public?

Irish law prohibits the advertisement of prescription-only medicinal products, unlicensed medicines and controlled drugs to the general public.

The following are not advertisements for the purposes of the Advertising Regulations:

- labels and package leaflets of medicinal products;
- correspondence, which may be accompanied by material of a non-promotional nature, needed to answer a specific question about a particular medicinal product;
- factual, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, provided they include no product claims;
- books, journals, periodicals and other publications that are imported into the state and that contain advertising that is not intended for or directed at persons resident in the state; and
- information relating to human health or diseases, provided there is no reference, even indirect, to medicinal products.

OTC products may be marketed to the general public, subject to conditions that include that the advertisement must not:

- give the impression that a medical consultation or operation is unnecessary;
- suggest that the effects of the medicine are guaranteed and not subject to adverse reactions;
- suggest that health could be enhanced by taking the product or could be affected by not taking it;
- refer to recommendations by scientists, professionals or celebrities;
- use exaggerated claims or superlatives; or
- use the word 'safe' without qualification.

Any advertisement must contain the name of the product and the common name of its active ingredient, any information necessary for the correct use of the product plus an express invitation to read the instructions for use.

Consumer protection laws also place restrictions on advertising and MA holders must ensure that marketing materials are not misleading nor aggressive. Unsolicited electronic communications must also be avoided.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

This information is not publicly available. According to the latest Health Products Regulatory Authority (HPRA) annual report, 152 advertisements were reviewed in 2015 for compliance and non-compliance was identified in 31 instances. In all cases of non-compliance identified, the HPRA supervised implementation of the necessary corrective or preventative actions by the MA holder.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

The promotion of a medicinal product must be consistent with the terms of the MA. However, at international congresses or symposia held in Ireland, promotional material that appears on exhibition stands or that is distributed to participants may refer to a medicinal product, or indication for a medicinal product, which is not the subject of an authorisation in Ireland but that is authorised in at least one EEA member state. This is subject to a number of conditions including that:

- the meeting is a truly international, scientific event with a significant proportion of the speakers and delegates from other countries;
- the promotional material must include a clearly visible and legible statement to the effect that the medicinal product is not authorised in Ireland or that it is authorised for different indications in Ireland; and
- any promotional material referring to prescribing information (indications, warnings, etc) authorised in other countries must include an explanatory statement that the licensing conditions differ internationally.

The IPHA Code also provides that promotional material for products not authorised in any EEA country at the time cannot be displayed or distributed to participants. However, scientific papers on the products can be provided.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

The Advertising Regulations provide a legal framework for the collaboration of the pharmaceutical industry with HCPs. In addition, the IPHA Code governs the collaboration of the pharmaceutical industry with HCPs. The rules do not differentiate between physicians in the outpatient and in-patient sectors.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

Gifts, pecuniary advantages and benefits in kind may not be given to HCPs.

However, companies are not precluded from providing reasonable educational support, grants or donating equipment for the betterment of patients where this is:

- in response to a written request from a HCP or institution;
- relevant to the practice of medicine or pharmacy;
- not linked to product promotion;
- paid to the institution rather than an individual; and
- reasonable, modest and in proportion to the scale of the institution.

Free samples may be given to HCPs subject to certain conditions including that:

- samples are provided on an exceptional basis and do not exceed four per year under the IPHA Code;
- any free samples are given in response to a written request;
- such samples are no larger than the smallest presentation of the product on the market and are marked 'free medical sample – not for sale' or with words of like effect; and
- the sample is accompanied by a copy of the SmPC.

Collaboration with HCPs can also involve engaging HCPs to provide services. This, too, is governed by the IPHA Code. HCPs may provide services such as speaking, advisory or research services provided:

- there is a legitimate need for such services and selection of consultants is related directly to this need;
- there is a written contract governing such services;
- no more consultants are retained than necessary;
- records of services are maintained;
- hiring of HCPs is not an inducement to prescribe, purchase, supply or sell a particular product; and
- compensation for such services is reasonable and reflects fair market value.

Companies may organise and sponsor conferences and events with HCPs provided these are held at appropriate venues that are conducive to the main purpose of the events. In addition, companies may sponsor meetings of HCPs provided expenditure does not extend beyond the general expenses of the meeting. Major meetings or series of meetings should not be sponsored by one company to the exclusion of other available and willing sponsors. If the meeting is being held in Ireland, a pharmaceutical company should not provide or offer any meals to the HCPs unless the value of each meal per recipient does not exceed €80 (including VAT and excluding any gratuity).

The IPHA Code also contains a set of industry rules relating to the disclosure of 'transfers of value' from pharmaceutical companies to HCPs and healthcare organisations (HCOs).

The disclosure rules oblige every member pharmaceutical company to document and publicly disclose all 'transfers of value' (subject to certain exceptions) it makes to HCPs or HCOs. These include items such as donations, grants, consultancy or speaking fees, and hospitality, sponsorship or funding for attendance at medical meetings, conferences or symposiums. Disclosure must be made on an annual basis within six months of the end of the reporting period. A reporting period is a full calendar year and the first reporting period was 2015.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

This information is not publicly available.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

The IPHA Code provides guidelines on the collaboration of the pharmaceutical industry with patient associations or organisations.

At a general level, the independence of a patient organisation must be guaranteed and, where there is joint cooperation, full transparency is required. Promotion of a company's products cannot be undertaken directly or indirectly by a patient organisation. Free samples may not be provided to patient organisations.

Funding of a patient organisation is acceptable, for example, where a donation is made without reference to the specific purpose; funding for a publication meeting, project or piece of research where a company has little or no involvement; for projects of joint interest; or providing or sponsoring speakers and making contributions for travel expenses. A number of principles apply, including:

- companies cannot seek to influence the text of materials they sponsor in a manner favourable to their own commercial interests;
- companies must publish a list of patient associations to which they provide financial support or significant indirect or non-financial support. This should include a description of the nature of support given; and
- companies must publish a list of patient associations they have engaged to provide significant contracted services. This should include a description of the nature of the services provided. They must also disclose the total amount paid per patient organisation.

Contracts between companies and patient organisations for the provision of services to companies are only allowed for the purpose of supporting healthcare research. Patient organisations can be engaged as experts and advisors for services such as advisory board meetings and speaker services. Certain criteria must be fulfilled, for example:

- there must be a written contract specifying the nature of the services and basis of payment;
- a legitimate need must be identified and documented in advance;
- engaging a patient organisation is not an inducement to recommend a particular product; and
- the compensation for the services is reasonable and does not exceed fair market value.

The IPHA Code also provides that no one company should fund a patient organisation to the exclusion of others. However, the organisation's independence must be recognised in terms of whom they wish to work with exclusively. A company must have permission to use a patient organisation's logo or proprietary material.

There are also restrictions on hospitality, for example, any hospitality provided should be reasonable and secondary to the main purpose of an event and directly linked to the event itself.

12 Are manufacturers' infringements of competition law pursued by national authorities?

The Irish national competition authority, the Competition and Consumer Protection Commission (CCPC), has statutory powers to investigate suspected breaches of competition law by pharmaceutical manufacturers on its own initiative or in response to complaints from third parties. We are not aware of the CCPC having pursued a competition law investigation of a pharmaceutical manufacturer to date.

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes, follow-on private antitrust litigation against pharmaceutical manufacturers is possible but no such action has proceeded to judgment before the Irish courts to date.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

The IPHA Code contains a set of disclosure rules that took effect in January 2015 and aim to bring greater transparency to the interaction of pharmaceutical companies with HCPs and HCOs. They oblige every member company to document and publicly disclose all 'transfers of value' (subject to certain exceptions) it makes to HCPs or HCOs.

The disclosures must be made on annual basis within six months of the end of the reporting period. As such, all transfers of value to HCPs and HCOs during 2016 must be disclosed by 30 June 2017. These disclosures may be made on the company's website or on a central platform. Importantly, the information disclosed must remain in the public domain for a minimum of three years after first disclosure.

The Code provides that all transfers of value should be documented. It is recommended that provisions consenting to disclosure should be incorporated into any new written contracts with HCPs and HCOs. Companies should also consider renegotiating existing contracts to include such consent provisions.

Under the Prevention of Corruption Acts 1906-2010, as amended, it is an offence for:

- an agent or any other person to corruptly accept, agree to accept, or agree to obtain a gift, consideration or advantage for him or herself or any other person, as an inducement, reward or on account of the agent doing any act, or making any omission, in relation to the agent's office or position, or his principal's affairs or business; or
- any person to corruptly give, agree to give or offer, a gift, consideration or advantage to an agent or any other person as an inducement to, or reward for, or otherwise on account of the agent doing any act, or making any omission in relation to his office or his principal's affairs or business.

'Agent' is defined broadly, but it can be assumed that, at a minimum, the agent must be separate from the principal. If the party taking payment for an act or omission in connection with his or her affairs or business is the principal, this should not amount to an offence of bribery under the Prevention of Corruption Acts. However, it should be cautioned that there is no Irish case law directly on this point.

'Corruptly' is defined in the Prevention of Corruption (Amendment) Act 2010 as including '[...] acting with an improper purpose personally or by influencing another person, whether by means of making a false or misleading statement, by means of withholding, concealing, altering or destroying a document or other information, or by any other means'.

Consequences for breach of anti-corruption laws include imprisonment, fines or both.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

The advertising of medical devices is not regulated as rigorously as the advertising of medicinal products. However, only medical devices that are CE marked may be marketed and promoted (subject to limited exceptions regarding trade shows or exhibitions). There are no specific regulations relating to the advertisement of medical devices. Instead, advertisements of medical devices must comply with the general laws on advertisements outlined in question 3.

In addition, the codes of ethics of the representative bodies of medical device manufacturers do not contain the same level of obligations and restrictions as those contained in the IPHA Code.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

Subject to some minor exceptions, all medicinal products must be authorised before being marketed in Ireland. The marketing of medicinal products in Ireland is governed by the Medicinal Products (Control of Placing on the Market) Regulations, 2007 as amended, which implement certain provisions of EU Directive 2001/83/EC on the Community Code relating to medicinal products for human use.

17 Which authorities may grant marketing authorisation in your jurisdiction?

An application for an MA must be made to the HPRA or the European Medicines Agency (EMA), where appropriate.

18 What are the relevant procedures?

An MA can be obtained using the following four procedures.

National procedure

An application for an MA is made directly to the HPRA. If the MA is granted it permits marketing of the medicinal product on the Irish market only.

Mutual recognition procedure (MRP)

The MRP is used when a medicinal product has been granted an MA in another EEA member state. Under the MRP, an application can be made to the HPRA to mutually recognise an MA granted in another EEA member state.

Decentralised procedure (DCP)

The DCP is used when a medicinal product does not yet have an MA in any EEA member state, and the applicant wants to market its product in two or more member states. A 'reference member state' is chosen by the applicant. The regulatory authority of the reference member state then examines the application and prepares a preliminary assessment report which is sent to the regulatory authority of the other 'concerned member states' where the applicant wants to market its product.

Centralised procedure

This procedure is triggered in respect of the marketing of certain types of medicinal products, including all medicinal products for human use derived from biotechnology and other high-technology processes, as well as all human medicines containing a new active substance intended for the treatment of acquired immune deficiency syndrome, cancer, diabetes or new degenerative diseases and for all designated orphan medicines intended for the treatment of rare diseases. An application under this procedure must be made directly to the EMA and the MA granted is valid in all EEA member states.

Update and trends

One of the main priorities of the Department of Health and the HSE in 2016 has been the reduction in the costs of medicines to the state. A new agreement between the HSE and the IPHA was reached in June 2016, which will save the state €775 million in the costs of medicines for the next four years.

Transparency of arrangements between pharmaceutical companies and healthcare professionals and organisations has become a prominent issue in recent years. The new IPHA code of practice took effect in January 2015, containing a set of industry rules relating to the disclosure of 'transfers of value' from pharmaceutical companies to healthcare professionals and healthcare organisations, and the first reporting period has passed.

Brexit is a major issue facing the life sciences industry in both Ireland and the UK. The Irish government made a decision in October 2016 to formally seek relocation of the EMA headquarters from London to Ireland.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Under the Medicinal Products (Control of Placing on the Market) Regulations 2007, as amended, an MA holder is required to notify the HPRA of the date that the product was actually marketed and to notify the HPRA no less than two months in advance of a cessation in marketing, either temporary or permanent, unless there are exceptional circumstances. The MA will cease to be valid if the medicinal product is either not marketed at all for a period of three consecutive years or is marketed but marketing ceases for a period of three consecutive years. This provision is known as the 'sunset clause'.

The HPRA may grant an exemption from the sunset clause in exceptional circumstances and for public health reasons. The MA holder would be required to justify why the sunset clause shall not apply and each case will be judged on an individual basis. The HPRA has published guidance which states that although the regulations do not specify the situations in which an exemption may be granted, some examples of where it would be appropriate to grant exemptions include for:

- critical medicinal products used only when needed, such as vaccines;
- medicinal products used in emergency situations in response to a public health crisis;
- medicinal products under litigation; and
- medicinal products where the authorisation for the use of the product is suspended.

For products listed on the interchangeable list (see question 22 below) the HPRA is obliged to remove a medicinal product from that list if it is satisfied that product has permanently ceased to be marketed in the state. Where the HPRA is satisfied that a product on the interchangeable list has temporarily ceased to be marketed in the state, it may, after having regard to how long it is expected that the cesser will last and the degree of disruption that the cesser causes or may cause patients who have been using the medicinal product, remove the medicinal product from the interchangeable list. There are similar provisions providing for the removal of medicinal products from the reimbursement list (see question 23) where the product has not or is no longer marketed in Ireland.

20 Which medicines may be marketed without authorisation?

There are a number of exemptions from the requirement to hold a MA set out in the Medicinal Products (Control of Placing on the Market) Regulations 2007. For example, patients may get access to unauthorised medicines by participation in an approved clinical trial or in an 'expanded access programme' or as part of named patient scheme. (See question 21.)

Other medicines such as herbal medicines or homeopathic medicines can avail of simplified licensing or authorisation procedures.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

The Medicinal Products (Control of Placing on the Market) Regulations 2007, as amended, transpose article 5(1) of Directive 2001/83/EC and

therefore recognise the possibility for relevant medical practitioners to access unauthorised medicines for patients under their care. This is known as the 'named patient scheme' and applies to individual patients as opposed to groups of patients. Under the named patient scheme, an unauthorised medicine is considered exempt from authorisation when it is supplied to the order or prescription of a relevant medical practitioner for use by his or her individual patients on his or her direct responsibility in order to fulfil the special needs of those patients.

It is subject to a number of conditions:

- the medicinal product must be supplied to a relevant medical practitioner or for use in a pharmacy under the supervision of a pharmacist;
- no advertisement or representation relating to the medicinal product may be published;
- the manufacture of the medicinal product must be carried out to ensure that the product meets the specifications of the relevant medical practitioner who requires it;
- written records as to the manufacture must be maintained and available to the HPRA on request;
- if the medicinal product is manufactured in Ireland, or imported into Ireland from a non-EEA state, the product must be manufactured or imported by the holder of a manufacturer's authorisation which relates specifically to the manufacture or import of that medicinal product; and
- the medicinal product must be distributed by the holder of a wholesaler's authorisation or by the person who has manufactured or imported the product.

Wholesalers and manufacturers based in Ireland are required to notify the HPRA when they are importing exempt medicines for the purposes of supply in Ireland. The wholesaler or manufacturer is required to have processes in place to capture and record any adverse reaction notified in relation to an exempt medicine and to report this to the HPRA. The HPRA does not issue approvals for use of exempt medicines, nor does it keep records of patients that are being treated with exempt medicines. However, it maintains a database of exempt medicinal products to enable it to institute appropriate risk mitigating measures (such as product recall) in the event of a notification of a quality defect (or other non-compliance issue).

Currently, there is no provision in Irish legislation for the approval of compassionate use programmes for specific groups of patients with an unmet medical need.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

The statutory powers covering the pricing of medicinal products are contained in the Health (Pricing and Supply of Medical Goods) Act, 2013 (the 2013 Act). Historically, the price of medicinal products was governed by framework agreements in place between pharmaceutical associations, the Department of Health and the HSE on the supply terms, conditions and prices of medicines. Since the introduction of the 2013 Act, the framework agreements are no longer the sole criterion for determining price, but remain a key factor to be considered.

The prices paid by the HSE for medicines supplied under Ireland's community drugs schemes are maintained by the HSE on an official Reimbursement List. The prices are set by the HSE by reference to criteria set out in the 2013 Act. Any company who wishes to sell a new medicine in Ireland must apply to the HSE to be included on the Reimbursement List.

The 2013 Act also introduced a system of generic substitution and reference pricing in Ireland, which operates as follows:

- the HPRA publishes and maintains a 'List of Interchangeable Medicines' which contains products grouped together according to their active substance, strength, pharmaceutical form and route of administration;
- the HSE sets one price, called the reference price, that it will pay for medicines in a group of interchangeable medicines. This is typically the price of the cheapest medicine in the group;
- pharmacists are obliged, in certain circumstances, to dispense the product which is the lowest cost to the HSE; and

- if a patient wants the more expensive medicine in the group, the patient must pay the difference between the reference price and the retail price.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

The HSE maintains a 'Reimbursement List' and must follow the processes set out in the 2013 Act to add products to the Reimbursement List and to set the reimbursement prices for those products. For products dispensed under the state-sponsored community drug schemes, the reimbursement price of items is set by the HSE by reference to the criteria set out in the 2013 Act. The framework pricing agreements (referred to in question 22) are one of the factors in setting the reimbursement price for products. The latest Framework Agreement was signed in July 2016 for a period of four years.

Where a supplier of a new medicinal product applies to the HSE to have a medicinal product added to the Reimbursement List, the HSE may add the product to the Reimbursement List at a price agreed with the supplier subject to the criteria in the 2013 Act.

When considering the price of a product that is already on the Reimbursement List, the HSE must take account of the criteria in the 2013 Act. Although this pricing procedure does not entail negotiation with the manufacturer per se, the manufacturer is entitled under the Act to make representations to the HSE in relation to the price changes.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

Any person who is ordinarily resident in Ireland is legally entitled to either free or subsidised approved prescribed medicines and certain medical and surgical aids and appliances. For products dispensed under the state-sponsored community drug schemes, the reimbursement price of items is set by the HSE by reference to the criteria set out in the 2013 Act. Pharmacy contractors provide community pharmacy services to the eligible population across the various community drug schemes operated in Ireland. In return, pharmacy contractors are paid a dispensing fee and are reimbursed for the price of the product.

Patients are required to make co-payments under certain government schemes. Whether or not a co-payment is required, and the level of the co-payment, depends on the scheme under which the medicinal product is dispensed.

Under the General Medical Services Scheme (the GMS scheme) a patient receives their medicine after paying a €2.50 fee per item prescription charge (up to a maximum charge of €25 per family per month). The GMS scheme is a means-tested scheme which applies to those who do not have sufficient means to pay for their medicine. There is an exception to these charges under the related Hi-Tech Scheme, which covers expensive medicines required for long-term care, the Health Amendment Act 1996 scheme, which covers Hepatitis C treatment as a result of contaminated blood and the Misuse of Drugs Regulations 1998, which covers Methadone. Under these schemes, no co-payment is required. Under the Drug Payment Scheme, the patient pays a maximum co-payment of €144 per month for all medicines supplied to

them and their family. This is governed by the Health Services (Drug Payment Scheme) Regulations 2012. Under the Long-Term Illness Scheme, the patient receives medicines for specific long-term medical conditions, such as diabetes and epilepsy, free of charge and no co-payment is required.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The HSE is the competent body for determining the price and reimbursability of medicines. HSE policy is determined by the Department of Health. In addition, the HSE use Health Technology Assessments to generate information about the clinical and cost-effectiveness of health technologies to determine the reimbursement status (or continued reimbursement status) of medicines. These are carried out by the Health Information Quality Authority.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

The framework agreements referred to in question 22 contain provisions for discounts to state-funded hospitals and agencies, subject to conditions. Discounts are available for orders above €634.57 in respect of products from a single manufacturer on the basis of monthly settlement of accounts. Discounts are not available where orders are placed with a distributor for products for which the distributor is not the nominated distributor of an individual supplier.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

The EU 'Pharmaceutical Package' is a series of measures proposed by the European Commission which includes legislative proposals:

- on modernising pharmacovigilance to improve the safety of medicines;
- on improving patient safety by reducing the infiltration of counterfeit medicines into the supply chain; and
- on improving patient access to high-quality health and medicines information.

Directive 2011/62/EU (the Falsified Medicines Directive) amends Directive 2001/83/EC to safeguard public health by protecting the pharmaceutical supply chain from infiltration by falsified or counterfeit medicines. The Irish regulations applicable to the marketing, manufacturing and wholesale distribution of medicinal products have been amended to take account of the Falsified Medicines Directive.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

There has been an increased focus on improving the public's access to information. Recent attempts by the European Commission to



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implement a directive and regulation dealing with the provision of information to the general public on prescription medicinal products were withdrawn in May 2014. At a national level, the IPHA launched a website (www.medicines.ie) in 2014, which provides information such as the SmPC and Patient Information Leaflet for the general public.

29 Outline major developments to the regime relating to safety monitoring of medicines.

In July 2012, new pharmacovigilance legislation came into effect across the EU, namely Regulation (EU) No. 1235/2010 and Directive 2010/84/EU. The regulation had a direct effect and the changes introduced by the directive were transposed into Irish law on 25 July 2012 by the Medicinal Products (Control of Placing on the Market) (Amendment) Regulations 2012, the Medicinal Products (Control of Manufacture) (Amendment) Regulations 2012 and the Medicinal Products (Control of Wholesale Distribution) (Amendment) Regulations 2012. The aim of the legislation was to improve the pharmacovigilance system in the EU making the reporting of adverse drug reactions easier and introducing special provisions for medicines that need additional monitoring. The legislation also aims to ensure that members of the public become better informed about the benefits and risks of taking medicines.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

The National Immunisation Office (the NIO), which is part of the HSE, is the body responsible for managing vaccine procurement and

distribution and developing training and communication materials for the public and health professionals. The NIO is entirely government funded.

Vaccines are provided for children from birth, through their school years as part of the childhood immunisation and schools immunisation programmes. In Ireland, all the recommended childhood vaccines given in the childhood immunisation and schools immunisation programmes are free. Vaccinations under the childhood immunisation programme are provided at the maternity hospital and GP practices. In most areas, the School Immunisation programme is carried out by the HSE School Immunisation teams. In a small number of areas, the school vaccinations are carried out in GP practices.

Parents must consent to vaccinations for children and young people up to the age of 16. Vaccination is not compulsory, but is strongly advised by the Department of Health.

In relation to adults, vaccinations are generally not provided free of charge in Ireland; however, some vaccines (eg, seasonal influenza and pneumococcal) are provided free of charge to high-risk groups subject to certain conditions.

The Health Protection Surveillance Centre collates data and reports on the uptake of vaccines provided through the childhood vaccination programmes. The most recent statistics published were for the end of the first quarter of 2016. The national immunisation uptake statistics at 12 months of age ranged from 90 to 92 per cent for nine of the 10 recommended vaccinations (the remaining vaccination had an uptake rate of 72 per cent). The National immunisation uptake statistics at 24 months of age ranged from 87 to 95 per cent.

Italy

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The Italian healthcare system (SSN) is a comprehensive system of structures and services aimed at granting all citizens equal access to healthcare treatment, and represents a direct expression of article 32 of the Constitution, under which ‘the Italian Republic safeguards health as a fundamental right of the individual and as a collective interest, and guarantees free medical care to the indigent’.

The main rules and principles of the SSN are laid down by Law No. 833/1978, which also established the SSN.

Regarding the specific services offered by the SSN, a Presidential Decree dated 29 November 2001 provides a list of the essential levels of assistance (LEAs) that must be granted to all citizens for free or, at most, subject to the payment of a prescription charge. The LEAs represent minimum performances equally granted throughout all of the Italian territory; regions can also guarantee additional – but no fewer – services if they so autonomously decide so.

The SSN consists of different territorial levels (central, regional and local), mostly operating on a decentralised basis.

At the central level, the Ministry of Health serves policy and coordination purposes, mainly by drawing up the national health plan (PSN), laying down the LEAs and issuing guidelines on technical issues of national importance.

At the regional level, the regions hold legislative and administrative powers that include implementing the PSN, adopting a regional healthcare plan, setting forth rules regarding the organisation of local health authorities (ASLs), and accrediting and arranging agreements with public and private health entities.

At the local level, the ASLs, which deliver the health services related to the LEAs, are divided into territorial areas managed by a general director appointed by the competent region.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

There are no differences between the outpatient and in-patient sectors in Italy.

The SSN is mostly financed through the tax system, with citizens being directly charged only in a few specific cases and for low amounts; as seen above, pursuant to article 32 of the Constitution, the state guarantees free medical treatment to all citizens. Therefore, no compulsory health insurance is required in Italy.

In particular, the SSN is financed as follows:

- taxation collected by the regions, specifically regional business tax and an additional personal income tax;
- prescription charges to patients, which also serve to discourage people from requesting unnecessary health services. Prescription charges are provided for the following: specialist services; first aid services; thermal treatments; and charges for the purchase of drugs, if a region so decides, citizens may be relieved from paying for prescription charges depending on their income, age, social condition, whether they are suffering from specific diseases or disabilities, or in other particular situations (eg, pregnancy, cancer prevention, HIV testing);
- incomes of public hospitals deriving from private intramural activities performed by employed physicians; and

- the state budget, which finances SSN’s needs where these are not already covered by other funding sources. Resources derive from VAT, excises on fuel and the National Health Fund.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

The advertising of medicinal products in Italy, both to the general public and to healthcare professionals (HCPs), is regulated by Legislative Decree No. 219/2006 (also referred to as the Code of Drugs) implementing Directive No. 2001/83/EC and Directive No. 2003/94/EC.

Articles 113 to 128 of Decree No. 219/2006 specifically address the rules and procedures related to the advertising of medicinal products.

Furthermore, guidelines issued on 10 February 2010 and then amended by new guidelines issued on 28 March 2013 by the Ministry of Health concerning the advertising of medical products through new media, as well as guidelines and directives issued by the Italian Medicine Agency (AIFA), must also be considered.

Finally, it should be noted that all advertising is subject to the general rules set forth by Legislative Decree No. 145/2007 on misleading and comparative advertising.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

Marketing activities can be directed only to HCPs authorised to prescribe or supply the relevant drug.

No prior authorisation is required; nevertheless, undertakings shall submit the marketing material to AIFA in advance. If within 10 days following the submission AIFA does not prohibit the use thereof, the material can be freely delivered to HCPs.

Adverts must always include a summary of the product’s characteristics, specify the classification for the purposes of distribution, and indicate the selling price as well as the conditions under which it can be reimbursed by the SSN. As an exception to the above, advertising can merely include the drug’s denomination and the name of the related active ingredient or ingredients, together with the name of the licence holder and of the co-promoter (if any) when, for instance, due to reasons of space more detailed information cannot be included.

Furthermore, all marketing statements must be accurate, up to date, supported by verifiable evidence, complete enough to allow the addressee to be properly informed on the characteristics of the product and its therapeutic effects, and present the product in an objective, non-exaggerated manner. The information must be consistent with the documentation issued to obtain the marketing authorisation and the relevant revisions thereof.

Insofar as the above-mentioned principles and further relevant specific provisions are complied with, the following kinds of marketing activities are allowed:

- delivery of verbal information;
- delivery of promotional material;
- delivery of free samples;
- invitations to scientific congresses and conventions;
- refresher courses;
- visits to company laboratories;
- investigators’ meetings; and
- scholarships and scientific consultancy.

5 What are the main rules and principles applying to advertising aimed at the general public?

Advertising to the general public is subject to stricter requirements than those aimed at HCPs.

First, marketing towards customers is allowed only insofar as the drugs are not subject to prescription or do not need the intervention of a doctor for diagnostic purposes (ie, over-the-counter drugs). Furthermore, it is forbidden to promote drugs that are available on medical prescription only; contain psychotropic or narcotic substances; or are, even partially, reimbursed by the SSN.

As a general rule, advertising aimed at the general public, when allowed, is subject to prior authorisation by the Ministry of Health, with the only exceptions being promotional messages included in newspapers or the periodical press that thoroughly reproduce the information contained in the patient information leaflet; or advertising consisting of a picture of the package with price tags added on. Specific authorisation must be sought for every single advert, even if the same content is released through different media (internet, on paper, etc). The Ministry of Health has 45 days to grant the authorisation: if 45 days elapse without any resolution, the authorisation is deemed as granted and will last for 24 months.

Detailed provisions are provided for regarding both the minimum content of advertisements and forbidden messages.

Minimum requirements

Advertisements of drugs aimed at the general public must always:

- have a plain commercial purpose;
- make it clear that the product is a drug; and
- include at least the drug's name and, if the product is not composed of multiple active principles, the relevant common denomination; information essential for the correct use of the drug; and a clearly written warning to carefully read the patient information leaflet or the external packaging, or both.

Forbidden content

Advertisements of drugs aimed at the general public cannot:

- contain any element that may persuade users to believe that:
 - consulting a physician or undergoing surgery is unnecessary, in particular by offering a diagnosis or suggesting a mail-order treatment;
 - the product entails no side effects, or that it is superior or equal to any other treatment or to another drug;
 - the drug can improve their regular state of health;
 - failure to use the drug, except for vaccinations, may entail detrimental effects on their regular state of health; or
 - the drug's safety or efficacy derive from it being a 'natural' substance;
 - be exclusively or mostly addressed to children;
- include advice from scientists, HCPs or famous people;
- assimilate the drug to a foodstuff, cosmetic product or any other consumer product;
- induce a wrong self-diagnosis;
- make improper, striking and misleading reference to their healing capacities; or
- make use of visual representations of alterations to the human body brought about by a disease, or visual representations of the effects of the drug on the human body, or part of it, in an improper, striking and misleading manner.

Furthermore, promotional messages whose commercial purpose is concealed by a plethora of other information are forbidden.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

Infringements concerning advertising rules are mostly related to promotional messages aimed at customers. Specifically, manufacturers often fail to comply with the rules on forbidden content, for example, by including misleading messages that may induce customers to believe that a drug has no side effects or that it is not necessary to seek a physician's advice. Another common infringement is not including a sufficiently clear warning to read the patient information leaflet or the external packaging, or both.

With specific reference to advertising aimed towards HCPs when manufacturers advertise products on their websites, a common infringement is a failure to publish a warning stating that information in such advertising is aimed towards HCPs only.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

This is not allowed under any circumstances. It is a fundamental principle that all advertising concerning a medicinal product – directed both to HCPs and to the general public – must comply with the product's instructions of use (IFUs). By definition, off-label use is the use of medicinal products for an unapproved indication not stated in the IFUs. As a consequence, since advertising can only refer to approved uses indicated in the IFUs, provision of information regarding off-label use is forbidden.

On a side note, it should be noted that, under the following very specific circumstances, physicians are nevertheless allowed to use drugs off-label:

- medicines can be used off-label and are reimbursed by the SSN if no valid therapeutic alternative exists; supporting data deriving from phase II clinical trials are present; or the drugs are inserted in a specific list drawn up by the AIFA (as per article 1.4 of Law Decree No. 536/1996, converted into Law No. 648/1996). In exceptional cases, medicines used off-label may be reimbursed by the SSN, even if a valid therapeutic alternative does exist, provided that AIFA deems that specific use is known and compliant with the researchers conducted on national and international levels (as per article 1.4 bis of Law Decree No. 536/1996, converted into Law No. 648/1996); or
- physicians, on their own responsibility, can use a medicine off-label – including a drug not present in the AIFA list referred to in the bullet point above – if the physician deems that the patient cannot be successfully treated with a different product, even if said product has been authorised with respect to the relevant disease; after having been duly informed, patients give their consent to such use; the off-label use is consistent with scientific papers credited by the international community; and supporting data deriving from phase II clinical trials are present. In this case, the SSN shall not reimburse the drug (as per article 3, paragraph 2 of Law Decree No. 23/1998, converted in Law No. 94/1998).

However, under no circumstances shall the SSN reimburse the use of off-label drugs if such use acquires a regular and widespread character.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

The relevant legislation is Legislative Decree No. 219/2006.

Further guidance is provided for by the Code of Professional Conduct issued by Farmindustria, the Italian pharmaceutical companies, trade association. While not legally binding – it is a voluntary document that pharmaceutical companies belonging to Farmindustria agree upon adhering to – the Code is also considered as a general guideline for companies that are not members of Farmindustria. As mentioned in question 2, there is no difference between the outpatient and in-patient sectors.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The main principle governing relationships between pharmaceutical companies and HCPs is that the former shall behave in a fair and transparent manner such as not to illicitly induce the latter to prescribe their products. Therefore, the relevant rules and regulations limit the possibility for pharmaceutical companies to grant benefits to HCPs.

With reference to gifts, it is forbidden to grant, offer or promise any goods or advantages, either monetary or in kind, unless they are of negligible value and refer to an HCP's activity.

As to congresses, very strict rules are set forth by the Farmindustria Code:

- they shall be inspired by ethical, scientific and cost-effective criteria;
- hospitality offered on occasion of such events shall be limited to travel, accommodation and payment of registration fees;

- pharmaceutical companies may only offer economy-class air travel to Italian HCPs invited to congresses in Italy or abroad;
- the category of hotel accommodation shall not exceed four stars;
- under no circumstances can scientific venues also serve touristic purposes. Therefore, it is forbidden to provide accommodation in the following: resorts, ships or castles that lie outside the city where a conference is being held; or farms, golf clubs, thermal baths or other venues whose main activity is dedicated to health or spa services;
- meals and drinks can be offered only up to a threshold of €60 for each professional per meal for all events in Italy; and
- the number of invitations to HCPs (save to speakers or moderators) cannot exceed two a year.

Congresses and scientific venues must be authorised by the AIFA beforehand. Applications must be delivered to the AIFA 60 days before the proposed commencement of the congress and must encompass the following information:

- the company's particulars;
- place and date of the congress;
- addressed professionals;
- the subject and programme of the conference, as well as its relation to the marketed drug; and
- professional and scientific information.

With specific reference to collaboration, pharmaceutical companies can avail themselves of physicians as scientific consultants and as moderators at conferences, provided that the following requirements are complied with:

- the parties shall stipulate a contract clearly identifying the relevant services;
- the physician shall disclose his or her relationship with the pharmaceutical company whenever he or she writes or speaks in public on the subject matter to which the contract refers;
- the company shall keep the documentation on the services offered by consultants for at least three years;
- fees paid by pharmaceutical companies shall meet cost-performance criteria and reflect the market value of such services; and
- the decision on such initiatives shall be reserved to the executive top management.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

The most common infringements concerning collaboration with HCPs derive from non-compliance with the rules on congresses set forth in question 9. Undertakings sometimes try to improperly impress physicians by setting up scientific venues not chosen according to cost-effective criteria or by offering them unlawful benefits, or both.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

This matter is governed by Chapter 4 of the Farmindustria Code of Conduct; as previously stated, the Code is not legally binding, but is a voluntary document that pharmaceutical companies belonging to Farmindustria agree upon adhering to, and is additionally considered as a general guideline for companies that are not actual members of Farmindustria.

As a general rule, pharmaceutical companies can grant either direct or indirect economic support to patient organisations. However, this is subject to very strict requirements:

- a preliminary agreement regulating the amount of financing and the related grounds shall be executed. For this purpose, pharmaceutical companies shall develop a standard internal procedure for the approval of such agreements;
- the use of the logo or other material belonging to the patient association (or both) by the pharmaceutical company shall be authorised in advance by the patient association;
- any form of sponsorship by pharmaceutical companies in relation to patient associations shall be transparent and have no promotional objectives;

- the pharmaceutical company cannot make a request to be the sole financer of a patient organisation; and
- pharmaceutical companies shall disclose, for at least the first quarter of each year, a list of the patient organisations it has financed during the previous year (including the monetary value of the financial support granted to each individual organisation) on their websites.

Furthermore, the execution of contracts concerning the services to be provided by patient organisations to companies is allowed. For example, patient organisations can be appointed as experts for services such as acting as speakers during conferences. Nevertheless, it is necessary that the contract be executed in writing and in advance, specify the nature of the services and state the basis for payment of those services. With reference to this final point, compensation for the services shall be reasonable and must not exceed the relevant fair market value. For the purposes of transparency, pharmaceutical companies shall disclose, on an annual basis, the list of patient organisations they have engaged to provide the mentioned services.

Considering that the above-mentioned rules are not statutory, but on the contrary are provided under the Farmindustria Code, the competent enforcing bodies are Farmindustria's own supervisory committee, single-judge tribunal and jury. Related powers and procedures are set forth in the last section of the Farmindustria Code.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes. The competent authority is the Italian Antitrust Authority (AGCM), which enforces articles 101 and 102 of the Treaty on the Functioning of the European Union (TFEU) on anticompetitive agreements and abuse of a dominant position. Appeals can be filed with the Regional Administrative Court against AGCM decisions, while the Council of State acts as judge of final instance.

In cases of anticompetitive behaviours affecting more than one member state, the competent authority is the European Commission.

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes, as was stated by the Italian Supreme Court in judgment No. 2207/2005.

Follow-on actions must be lodged with the ordinary courts and generally aim to seek compensation for damages. Bearing in mind that punitive damages cannot be awarded in Italy, private parties can request, for example, the difference between the price actually paid and the one they would have presumably paid had the restrictive agreement or abuse of dominant position not been carried out.

Pursuant to article 140-bis of Law Decree No. 206/2005 (Italian Consumers' Code), class actions are possible in the case of antitrust private enforcement.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

The EFPIA Disclosure Code has been implemented by the Farmindustria Deontological Code – Chapter 5, governing the transparency of transfers of value among pharmaceutical companies, healthcare professionals and healthcare organisations. Although Farmindustria Code is compulsory for those pharma companies that are members of Farmindustria only, as a matter of fact, almost all the companies operating in Italy are enrolled with Farmindustria. Chapter 5 is fully compliant with the EFPIA Disclosure Code, therefore each pharmaceutical company must, on an annual basis, document and disclose on the company website all transfers of value carried out directly or indirectly to healthcare professionals and organisations. The disclosure of this data shall come about on an individual basis and any eventual disclosure in aggregate form shall represent an exceptional circumstance.

An additional transparency requirement applicable to Italian pharma companies is set forth by article 48, paragraph 17, Legislative Decree Law No. 326/2003 and the implementing ministerial decree of the Ministry of Health dated 23 April 2004, according to which, by 30 April of each year, pharma companies are subject to the duty of disclosing to AIFA the cost supported in the preceding year for promotional activities (including samples, gadgets, advertising, promotional

Update and trends

After two years of the implementation in Italy of the Directive 2011/62/EU on falsified medicines by the Legislative Decree No. 17 dated 19 February 2014, which has also introduced the possibility to trade non-prescription drugs online, almost 400 existing pharmacies have been granted the authorisation to sell over-the-counter (OTC) drugs online as well and that number is expected to increase in the near future.

However, the implementation of the above measures has, in practice, given rise to the need of some clarification that has recently been provided by the Ministry of Health, according to which:

- pharmacies authorised to sell OTC drugs online are not entitled to make use of apps for smartphones or tablets, nor of the e-commerce marketplace, but can only proceed through their specific website that has been authorised by the Ministry;
- free delivery for orders over a specific amount are admitted, provided that: (i) such a condition is applicable to the sale of all the products available on the pharmacy's website and not only to the OTC drugs; and (ii) customers are informed in advance on the delivery charges; and
- pharmacies are entitled to sell online only those OTC drugs that they have already purchased and have in stock. They are forbidden to ask their wholesaler to deliver the OTC drugs to the customer directly.

material, etc) in order to assess a 5 per cent contribution to be paid to AIFA each year.

Italian companies are also subject to the enforcement of the Legislative Decree No. 231 of 8 June 2001, which has introduced an administrative liability of the companies in connection with criminal actions performed directly by their chief executive officers or employees in the interest of or to the advantage of the company.

Compliance - medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Despite being governed by a different set of rules (ie, Legislative Decree No. 46/1997, implementing Directive 93/42/EEC, in addition to further regulations and guidelines set out by the Ministry of Health on 28 March 2013), medical devices are regulated in a manner quite similar to drugs. Nevertheless, it mostly depends on the specific area and on the category of medical device (eg, whether high risk or low risk) under consideration.

With reference to advertising of medical devices towards HCPs, the rules are less rigorous since no prior communication to the AIFA is necessary. On the contrary, as concerns the general public, the limitations are very similar to those provided for medicinal products: it is forbidden to advertise medical devices that can be used upon medical prescription only or that require the assistance of professionals, or both; and advertisements, when allowed, must be duly authorised by the Ministry of Health, which assesses both the content of advertisements and the chosen marketing method. The evaluation process may take up to 45 days running from the date when an application is submitted. Should no formal resolution be issued within that time period, the authorisation is deemed granted. As an exception, mere accessories of medical devices are not subject to the above-mentioned rules insofar as they are chosen by the patient only on the basis of aesthetic factors and without considering any medical aspects (eg, frames for glasses).

Regarding cooperation, Assobiomedica (the Italian association of companies operating in the medical devices sector) has issued a Code of Ethics that provides for rules thereof. As per section 2.7, congresses and other similar events shall respect sobriety. As such, for example:

- it is forbidden to provide accommodation in five-star hotels;
- between 15 June and 30 September, events shall not be organised in seaside resorts, whereas between 15 December and 30 March and between 15 June and 15 September, mountain resorts are forbidden;
- flight tickets shall be economy class only; and
- meal costs shall be reasonable.

Furthermore, in the event that HCPs are entrusted with a paid task (eg, speaker duties), the medical device company shall receive proper authorisation thereof from the public body at which the HCP works.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

This matter is governed by the Code of Drugs, EC Regulation No. 726/2004, EC No. Regulation 1394/2007 and a Ministerial Decree dated 29 August 1997. The relevant law depends on the activity being considered.

17 Which authorities may grant marketing authorisation in your jurisdiction?

The competent Italian authority for granting marketing authorisations is the AIFA.

18 What are the relevant procedures?

Marketing authorisations can be granted pursuant to different procedures: national procedures, EU procedures (mutual recognition and decentralised procedures) and parallel import procedures.

Rules concerning national procedures are provided under article 8 of the Code of Drugs. The concerned undertaking must submit an application with the AIFA, providing it with all the required information and the results of any clinical trials. The AIFA, assisted by the Technical Scientific Commission (CTS) and by experts belonging to the National Institute of Health (ISS), reviews all the documentation and performs the necessary assessments. No later than 210 days from the date of receipt of the application, and if all the requirements are met, the AIFA shall grant the marketing authorisation (AIC) to the pharmaceutical company. Although the registration process complies with the same criteria provided for by the EU procedures, the AIC will only be valid in Italy.

In respect of EU procedures, the relevant rules are provided for under articles 41 to 49 of the Code of Drugs. Specifically, the mutual recognition procedure allows the extension of a marketing authorisation granted by a member state to one or more other countries of the European Union, whereas the decentralised procedure allows the granting of a single marketing authorisation that is simultaneously valid in all the countries belonging to the European Union for a medicinal product that has not yet been authorised in Europe.

With reference to the parallel import of drugs already licensed in Italy, the relevant rules are set forth by a Ministerial Decree dated 29 August 1997. The importer shall submit an application for authorisation to the AIFA, which will then make a decision within 45 days. The application must include:

- details of the importer and the relevant member state;
- the name of the drug to be imported;
- the drug's quantitative and qualitative composition;
- the drug's therapeutic purposes, contraindications and side effects;
- use of the product in terms of dosage, medication, etc; and
- a summary of the product's specification and a hand-out of the packaging, both translated into Italian.

It is possible to file an opposition with the AIFA, to be decided within 90 days, should a licence application be refused. Subsequently, the concerned party can lodge an appeal with the regional administrative courts within 60 days of receipt thereof.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Under article 38, paragraphs 5 to 8 of the Code of Drugs, any marketing authorisation lapses if the medicine is not actually marketed in Italy within three years following the grant of the authorisation. Furthermore, even if the drug is marketed for a period of time after the authorisation, any marketing authorisation lapses if the drug stops being marketed in Italy for a consecutive period exceeding three years.

In very exceptional circumstances and for public health reasons, the AIFA, by means of a justified measure, may prevent the above-mentioned lapse of the authorisation.

20 Which medicines may be marketed without authorisation?

No medicine lacking an authorisation can be marketed. Even in the case of homeopathic and equivalent generic products, marketing authorisations must be obtained, although in this case the authorisation is achieved through a simplified procedure.

As per article 7 of the Code of Drugs, the sole exception to the above are radiopharmaceuticals prepared at the time of use by people or by plants authorised to use such medicinal products, in an approved healthcare complex, and exclusively from authorised generators, kits or precursor radiopharmaceuticals in accordance with the manufacturer's instructions.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Article 5(1) of Directive 2001/83/EC was implemented into Italian law by article 5, paragraph 1 of the Code of Drugs.

Therapeutic use of unlicensed drugs is allowed only if a physician that has a patient under his or her care specifically so requests and if the following conditions are met: the required drug is deemed as absolutely necessary for the patient's treatment, and no equivalent licensed product is present on the Italian market. Applications must be addressed to the Ministry of Health, and must include:

- details of the healthcare centre;
- details of the custom office territorially competent for the importation;
- details of the foreign pharmaceutical company;
- details of the drug (name, active principle, dosage, etc);
- confirmation that the drug is duly authorised in the country of origin;
- confirmation that the drug cannot be replaced for the same therapeutic purpose by another drug licensed in Italy; and
- the volume required.

Furthermore, the physician must undertake that the drug will be used only with respect to a limited number of patients under his or her responsibility, and that the latter have given their informed consent to the therapy. Such therapy cannot last longer than 90 days for each patient. After the authorisation is granted, the drugs can be imported.

Moreover, unlicensed drugs can be used following the end of a clinical trial in order to continue to provide the trial drug - still unlicensed - to trial participants upon specific request of the physician and provided that trial drug has been - or will be - included in phase III clinical trials or, in the case of terminally ill patients, phase II clinical trials; and results of the required trials show efficacy and tolerability to the trial drugs. Such use is allowed both on participants in the clinical trials and on new patients. The above access falls within the scope of compassionate usage programmes governed by the Decree of the Ministry of Health, dated 8 May 2003.

Pricing and reimbursement of medicinal products**22 To what extent is the market price of a medicinal product governed by law or regulation?**

This depends on the refundability class of the concerned drug.

Under Law No. 326/2003, if a drug cost is reimbursed by the SSN, the price is set through negotiation between the AIFA and the marketing authorisation holder.

On the contrary, the price of drugs whose cost is charged to customers can be freely determined by the pharmaceutical company. Nevertheless, price adjustments are limited and can take place only once every two years.

Italian law does not envisage any differences to the above that depend on whether the outpatient or in-patient sector is involved.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

No; any negotiations over prices are carried out between the pharmaceutical companies and the AIFA alone.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

Medicines are divided into the following refundability classes:

- Class A, including medicines required for the treatment of serious, chronic and acute diseases and those necessary to guarantee the LEAs (see question 1), are reimbursed by the SSN, although prescription charges may be applied;
- Class H, which covers the same medicines as Class A, but under Class H they are only supplied in hospitals, and not in chemist's shops; and
- Class C medicines are used for the treatment of slight illnesses, and are thus not essential. These are fully chargeable to customers.

Italian law does not envisage any differences in the outpatient and in-patient sectors regarding the above.

Pursuant to Law 648/1996, provided that no therapeutic alternative exists and that the AIFA's CTS expresses a favourable opinion thereof, the SSN also reimburses innovative medicines marketed in a different country; medicines not yet authorised under clinical trials; and drugs used off-label that may be reimbursed, in exceptional cases, even if a valid therapeutic alternative does exist, provided that AIFA deems that specific use is known and compliant with the researchers conducted on a national and international levels. In any case, data pertaining to phase II clinical trials must be present. Drugs reimbursed as above are then inserted in a specific list drawn up by the AIFA.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The competent authority is the AIFA's price and reimbursement department.

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The application for reimbursement and pricing negotiations must be started jointly. Specifically, negotiations operate in three steps: submission of the dossier, discussion and final contract. Negotiations usually last 90 days, but this term length is not mandatory. The contracted price is valid for 24 months and is subject to tacit renewal unless the parties decide to renegotiate the terms.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

The relevant rules do not provide for such an obligation.

However, chemist's shops are allowed to give discounts on all medicines that are directly paid for by customers, provided that the latter are so informed in advance and there is no discrimination among customers. However, promotional sales (eg, three-for-two deals) are forbidden.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Under articles 147 and 148 of the Code of Drugs, unlawful distribution of medicines can entail both criminal and pecuniary sanctions.

Furthermore, IMPACT Italia, a task force involving the AIFA, the ISS, the Carabinieri NAS, the Ministry of Health, representatives from other administrations and private stakeholders, is dedicated to tackling counterfeiting and the illegal distribution of medicines.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

On 13 November 2013, the AIFA launched a medicines database (available at <https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci>). The database contains information on all licensed drugs available in Italy and is freely accessible to the general public.

29 Outline major developments to the regime relating to safety monitoring of medicines.

Italian rules concerning pharmacovigilance are contained in the Code of Drugs, and the competent authority is the AIFA.

The European legislation on pharmacovigilance was recently amended by Regulation No. 1235/2010 and Directive No. 2010/84/EU, which are currently implemented in Italy through Ministerial Decree dated 30 April 2015.

The introduced changes aim at increasing the efficiency, speed and transparency of pharmacovigilance operations through rules that will:

- strengthen the systems for pharmacovigilance;
- streamline activities between member states;
- increase the participation of patients and HCPs;
- improve the communication systems of decisions taken and the reasons thereof; and
- increase transparency.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

In Italy, the following vaccinations are compulsory: diphtheria, tetanus, poliomyelitis and hepatitis B. Further vaccinations, although not compulsory, are strongly encouraged (eg, for measles, papilloma and parotitis). All of these vaccinations are supplied by the SSN.

Vaccinations are scheduled according to the age of the person concerned (mostly in children) and are administered by HCPs.

As for adult population, some vaccinations are compulsory for specific categories of people or workers:

- meningitis, typhus, measles, mumps and rubella for the military personnel at the moment of enrolment (Decree of the Ministry of Defence dated 19 February 1997); and
- tuberculosis, only for sanitary personnel, medicine students, trainee nurses and whoever, with a negative tuberculin test, operates in healthcare environments or high-risk drug-resistant environments.

Vaccination rates in Italy for DTP3, HepB3, Hib3, MCV, Pol3 and Rubella1 all exceed 90 per cent.

Japan

Junichi Kondo, Yoshikazu Iwase and Hiroko Kasama

Anderson Mōri & Tomotsune

Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

In Japan, two systems coexist: the national health insurance system (NHIS) and private health insurance, the latter being taken out voluntarily by individuals.

The NHIS, a public healthcare system that covers the entire country, was established in 1961. Under the NHIS, everyone in the country is, in principle, entitled to all types of medical care services (including medical treatments and drugs) provided by medical institutions. Patients (insured) pay a portion of the medical fees to medical institutions on each visit (see question 2). Being a public healthcare system, the NHIS allows every patient to freely choose, without any restrictions, the medical institution that will provide the medical treatment. It is worth noting that medical fees in Japan are almost the same across all medical institutions that provide the same kind of medical services.

In addition to the NHIS, private health insurance provided by insurance companies is also available. It is taken out voluntarily by individuals to cover the portion of the medical fees they bear under the NHIS (see question 2). Private health insurance is typically important in cases of prolonged hospitalisation or particularly expensive medical treatments, such as surgical operations.

In Japan, medical costs have been rapidly increasing primarily due to the steep rise in the ageing population, which could potentially contribute to a future collapse of the NHIS. To partly address this issue, a new healthcare system designed for those aged 75 and over, called the 'healthcare system for the latter-stage elderly', was established on 1 April 2008.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The NHIS is financed by insurance payments made by the general public and public funds from the national and local governments. In addition, patients (insured) bear a portion of the costs of medical care as follows:

- 10 per cent (or 30 per cent for those with income above a certain level) for those aged 75 and over;
- 20 per cent (or 30 per cent for those with income above a certain level) for those aged 70 to 74. This percentage has been tentatively reduced to 10 per cent by a government welfare policy, but those who reach the age of 70 after 1 April 2014 shall bear the 20 per cent portion;
- 30 per cent for those aged six to 69; and
- 20 per cent for those aged five and below.

Under the NHIS, there is no distinction between the outpatient and in-patient sectors. However, private health insurance is financed by the insurance premiums paid by the insured, and the coverage of such insurance (ie, whether both outpatient and in-patient services are covered) depends on the type of insurance obtained by the insured.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

The Pharmaceutical Affairs Act (PAA) governs the advertising of medicinal products to the general public and healthcare professionals.

In addition to the PAA, the 'Notice of Fair Advertisement Criteria for Medical Products' (Advertisement Criteria) was issued by the chair of the Pharmaceutical Affairs Bureau of the Ministry of Health, Labour and Welfare (MHLW) on 9 October 1980 to set out certain guidelines in respect of advertising medical products.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

The rules and principles provided in the PAA and the Advertisement Criteria do not make any distinction between advertising aimed at healthcare professionals and advertising aimed at the general public, except for the following: the use of expressions in advertisements aimed at the general public that imply a certain disease may be cured without any medical treatment by a doctor is strictly prohibited.

This means that, other than the above point, the specific rules and principles applicable to advertising aimed at the general public (see question 5) also apply to advertising aimed at healthcare professionals. Please note, however, that a certain portion of such applicable rules and principles varies depending on the nature of the medicinal products, namely, prescription drugs or non-prescription drugs including over-the-counter (OTC) drugs. Non-prescription drugs may be advertised to the general public while, in respect of prescription drugs, advertising aimed at the general public is prohibited.

5 What are the main rules and principles applying to advertising aimed at the general public?

Article 66 of the PAA prohibits, inter alia, false or exaggerated advertisements and advertisements implying abortion or using obscene writings or images. Further, article 67 of the PAA provides that advertisements of drugs for certain diseases stipulated in article 64 of the relevant cabinet order may be restricted by ministerial ordinance. The Enforcement Order of the PAA and the MHLW ordinance restrict advertising of drugs for cancer, sarcoma and leukaemia by only allowing advertisements of such ailments to be aimed primarily at medical professionals. Furthermore, article 68 of the PAA prohibits advertisement of medical products prior to marketing approval. Under the PAA, a violation of article 66 or article 68 is subject to imprisonment for up to two years or a fine of up to ¥2 million (or both), and a violation of article 67 and the related MHLW ordinance is subject to imprisonment for up to one year or a fine of up to ¥1 million (or both).

- In addition to the PAA, the Advertisement Criteria:
- set forth the purpose of the Advertisement Criteria (ie, to prevent false or exaggerated advertisements and to rectify inappropriate advertisements);
 - oblige the advertiser to communicate correct information; and
 - provide for detailed guidelines regarding the advertisement of medical products in respect of the following matters:
 - restrictions on the use of product names;
 - restrictions on expressions relating to manufacturing methods;
 - restrictions on expressions relating to efficacy and safety;
 - prohibitions against advertisements that may lead to abuse;
 - prohibitions against advertisements of prescription drugs aimed at the general public;
 - restrictions on expressions used in advertisements aimed at the general public (where such advertisement implies that certain diseases may be cured without medical treatment by doctors);

- cautionary notes for addiction-forming drugs;
- notice of precautions, if necessary;
- prohibitions against dyslogistic advertisement of other companies' products;
- prohibitions against endorsements by healthcare professionals;
- restrictions on advertisements for prize promotions;
- prohibitions against intimidating advertisements, especially by emails;
- guidelines on advertising of medical products on television or radio shows;
- prohibitions against emphasising the use of medical products for cosmetic or food purposes; and
- prohibitions against advertisement that injures the integrity or credibility of medical products.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

One of the most common infringements committed by manufacturers with regard to the advertisement rules and principles is the advertising of nutritional fortification products that declare efficacy not shown in the relevant marketing approval (these are considered to violate the Advertisement Criteria regarding restrictions on expressions relating to efficacy and safety; see question 5).

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

Provision of information regarding off-label use is not prohibited as long as it is only aimed at healthcare professionals.

It should be noted that in Japan, off-label use is allowed at the discretion of the doctor, despite the official position of the MHLW being that drug manufacturers should obtain marketing approval for such use.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

To ensure fair competition, the Act against Unjustifiable Premiums and Misleading Representations prohibits, inter alia, the inducement of customers by means of unjustifiable premiums to ensure fair competition. Based on this Act, the Restrictions on Premium Offers in the Ethical Drugs Industry, Medical Devices Industry, and Hygienic Inspection Laboratory Industry (Restrictions on Premium Offers) and the Fair Competition Code concerning Restriction on Premium Offers in the Ethical Drugs Industry (Fair Competition Code), the latter being a form of self-regulation by the industry, have been promulgated. These rules govern the collaboration of the pharmaceutical industry with healthcare professionals.

In addition, the National Public Service Ethics Act (NPSEA) also governs such collaboration to some extent as most important healthcare professionals are national public officers in Japan. There is no difference between the outpatient and in-patient sectors.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The Restrictions on Premium Offers provide that the pharmaceutical industry shall not offer, as a means of unjustifiably inducing transactions involving ethical drugs, medical devices or hygienic inspection, any premiums to medical institutions and other similar institutions beyond that which is necessary for the use of ethical drugs, medical devices or hygienic inspection, or reasonable in light of normal business practice.

The Fair Competition Code also provides that the pharmaceutical industry shall not offer premiums to medical institutions and other similar institutions as a means of unjustifiably inducing transactions involving ethical drugs.

Under the NPSEA, healthcare professionals who are national public officers of a certain rank are obliged to report and disclose certain gifts of money, articles, entertainment or other benefits that they receive from business operators. Pursuant to the NPSEA, the National Public Service Ethics Code has been promulgated to, inter alia, prohibit such officers from receiving certain gifts from those who have any interests in the performance of their duties.

In addition to the above rules and principles, the Promotion Code for Ethical Drugs (the Promotion Code) has also been promulgated by the Japan Pharmaceutical Manufacturers Association (JPMA), a voluntary organisation of drug makers. The Promotion Code provides that JPMA members should abide by the PAA, the Act on the Prohibition of Private Monopolisation and Maintenance of Fair Trade (the Antimonopoly Act), the Fair Competition Code and other applicable laws and regulations.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

The provision of excessive entertainment by manufacturers is the most common infringement. However, it is often difficult to clearly determine to what extent entertainment is considered acceptable as far as professional behaviour goes, and to what extent it may be considered beyond the bounds of socially accepted norms.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

There are currently no rules or principles applying to the collaboration of the pharmaceutical industry with patient organisations. Such collaboration is, therefore, not common in Japan. We do note, however, that the JPMA provides symposia, workshops, educational campaigns and other support to patient organisations.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes. Such infringements are pursued by the Japanese Fair Trade Commission (JFTC) and the Consumer Affairs Agency. Insofar as infringements of the Act against Unjustifiable Premiums and Misleading Representations are concerned, the Fair Trade Council of the Ethical Pharmaceutical Drugs Marketing Industry (FTC of the EPDMI) is an organisation officially authorised by the JFTC and the Director-General of the Consumer Affairs Agency to conduct self-regulation regarding restrictions on the provision of unjustifiable premiums. In practice, as long as a manufacturer is a member of the FTC of the EPDMI, it exercises preliminary supervision over such manufacturer regarding the provision of unjustifiable premiums on the basis of such membership.

13 Is follow-on private antitrust litigation against manufacturers possible?

For certain violations by manufacturers of the Antimonopoly Act, private litigation seeking injunctions or claiming for damages are allowed under the Antimonopoly Act and the Civil Code. Note, however, that these litigations are private and based on tort liability, not through the antimonopoly procedure. In addition, as to litigation seeking injunctions, while this is theoretically possible, no actual case has been filed to date.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

To prevent corrupt acts, the Penal Code broadly restricts public officers from receiving or requesting bribes and citizens from offering bribes to public officers. With regard to pharmaceutical products, the Act against Unjustifiable Premiums and Misleading Representations prohibits the inducement of customers by means of unjustifiable premiums; and also the Fair Competition Code prohibits the above conduct more specifically (see question 8). In addition to these rules, the Transparency Guideline that stipulates the relevant disclosures of payments for healthcare professionals (such as research and development costs and scholarship funds) has been promulgated by the JPMA. The member companies of the JPMA (73 companies as of 1 April 2016) have created their own transparency guidelines based on the above Guideline and made them public. Although the Transparency Guideline and individual guidelines are not legally binding, or have any penal consequences, they ensure the transparency and accountability of pharmaceutical manufacturers.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Yes. The advertising of medical devices is regulated as rigorously as the advertising of medicinal products (see questions 3 to 5). Except for article 67 of the PAA, which only applies to medicinal products for designated special diseases, the pertinent provisions on advertising under the PAA also apply to the advertising of medical devices.

In the same manner, the collaboration of manufacturers of medical devices with healthcare professionals is also regulated as rigorously as the collaboration in respect of medicinal products (see questions 8 and 9).

As regards collaboration with patient organisations, see question 11.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The PAA (together with the orders, regulations, notices and guidelines issued pursuant thereto) sets out the regulatory framework for granting marketing authorisations and placing medicines on the market.

17 Which authorities may grant marketing authorisation in your jurisdiction?

As a general rule, any person intending to market a medicinal product must obtain approval for marketing such a product. The Minister of the MHLW (the Minister) has the authority to grant the approval for marketing medicinal products, although the prefectural governors may exercise such authority in certain circumstances (such as approval for cold medicines). This occurs after review and examination in respect of the approval for marketing medicinal products, performed by the Pharmaceuticals and Medical Devices Agency (PMDA), except where such review and examination has been undertaken by the relevant prefectural governor.

To obtain approval for marketing medicinal products, generally speaking, there are two steps involved:

- the manufacturing establishment of the medicinal products must obtain a licence for the manufacture of such products; and
- the person intending to market a medicinal product must obtain a licence for marketing such a product.

18 What are the relevant procedures?

In brief, the procedure for obtaining the approval for marketing medicinal products (as mentioned in question 17) is as follows.

Clinical trials must be performed to collect data that is necessary for the application. In essence, clinical trials performed before the application consist of phase I (for a small number of healthy adults); phase II (for a small number of patients); and phase III (for a large number of patients).

After clinical trials, any person intending to market a medicinal product must file an application with the PMDA for approval to market such a product. The PMDA then reviews and examines such application, and reports the results of such review to the Minister. The Minister then decides whether to grant the approval to market the products based on the report of the PMDA.

As regards licences for manufacturing or marketing, applications must be filed for the issuance of such licences with the Minister or prefectural governors (as the case may be).

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Under article 74-2(3)(vi) of the PAA, the Minister may cancel any approval issued in respect of medicinal products, or order partial changes to any such approval if the relevant medicinal products have not been manufactured or marketed for three consecutive years without justifiable reasons. In practice, when the relevant medicinal products have not been manufactured or marketed for three consecutive years, the Minister would urge the companies to voluntarily withdraw

the approval, and these companies tend to comply with the Minister's request for withdrawal of approval.

For commercial supply to occur, in addition to a marketing approval, ethical drugs must be listed on the National Health Insurance Drug Price Standard (NHI Drug Price Standard), which is provided by the Minister in accordance with the Health Insurance Act. The listed drugs need to be commercially provided within three months after their listing on the NHI Drug Price Standard. If the manufacturer fails to abide by this timeline, it will receive an administrative inquiry and advice or direction from the MHLW regarding the reason for not providing the products. However, this does not mean that the marketing licence or approval is cancelled or invalidated.

20 Which medicines may be marketed without authorisation?

The following medicinal products may be marketed without the authorisation described in questions 17 and 18:

- medicinal products with standards specified and designated by the Minister (it should be noted that medicinal products recognised in the Japanese Pharmacopoeia can be included in such medicinal products designated by the Minister); and
- in vitro diagnostic reagents specified and designated by the Minister (in lieu of authorisation, such diagnostic reagents should have been certified to be marketable by the registered certification body).

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

In Japan, there is no generally available system or programme equivalent to a named patient programme. However, there are three actual cases in which pre-approved drugs were provided under the supervision of the government authority from a humanitarian point of view as these drugs were for the treatment of life-threatening diseases for which there were no alternative therapeutic measures. Tropical disease drugs and AIDS curative drugs are being provided free of cost to a study group by the MHLW. For the treatment of leprosy, pre-approved curative drugs were obtained by the government and provided at national sanatoria (leprosy was covered by off-label use after 2008 when thalidomide was approved for other diseases).

A report of a working group at the MHLW issued in 2007 stated that:

- the current approval system should be maintained continuously;
- nevertheless, the necessity of a compassionate use system is recognised for serious diseases with no effective therapeutic measures; and
- compassionate use should be introduced as long as it does not interfere with the current approval system.

At present, the system is under discussion, although the government takes a relatively conservative position on it.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

Medical examinations and treatments covered by the NHIS are known as 'health insurance treatment'. The cost of health insurance treatment, which consists of compensation for medical services given by medical institutions, the price of medical drugs and medical materials, is determined entirely by the National Health Insurance Act and related regulations. As previously mentioned, patients (insured) pay 10, 20 or 30 per cent (depending on, inter alia, age; see question 2) of the price of health insurance treatment to medical institutions on each visit. There is no distinction between the outpatient and in-patient sectors.

The (official) price of a medicinal product is determined by the NHI Drug Price Standard (see question 19). The NHI Drug Price Standard governs the price of medicinal products, which is paid by the NHIS (and individual patients who pay the said percentage of the price) to medical institutions and pharmacies. The NHI Drug Price Standard does not regulate the market price between manufacturers and wholesalers, and between wholesalers and medical institutions or pharmacies. Usually, manufacturers provide their medical products to medical institutions and pharmacies at a price lower than the price in the NHI Drug Price Standard. The NHI Drug Price Standard is reviewed periodically (currently every two years) in keeping with the diminishing market price.

Update and trends

Introduction of the Preceding Review and Examination System

In April 2015, the government tentatively enforced the Preceding Review and Examination System. This system aims to accelerate the development and practical use of innovative medical drugs, medical devices and regeneration medical products. Certain medical products that meet four requirements (ie, novelty, seriousness of the patient, high effectivity and proper structure for development and registration in Japan) can obtain authorisation for six months under this system. As of 27 October 2015, six medical drugs are designated (in addition, two for medical devices and three for regeneration medical products as of 10 February 2016).

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

The price of medicines and medical treatments are determined by the NHIS (see question 25), and medicines and medical treatments are provided to the patients at such listed price.

Pharmaceutical manufacturers do not negotiate the price of their products with public healthcare providers (such as medical institutions and pharmacies). Usually, pharmaceutical manufacturers distribute their products to medical institutions through pharmaceutical wholesalers. The negotiation for a wholesale price (including rebate and allowance) is conducted between pharmaceutical manufacturers and pharmaceutical wholesalers in consideration of the price determined by the NHIS.

Pharmaceutical manufacturers not only sell their products to wholesalers, but also send their own medical representatives to medical institutions to provide information about their products and to collect feedback from physicians and pharmacists. However, manufacturers should not negotiate the prices of their products, because if the manufacturers negotiate the retail price with medical institutions, they might be held liable for unfair resale price maintenance, which is prohibited under the Antimonopoly Act.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

The prices of medicines and medical treatments covered by the NHIS are determined by the NHI Drug Price Standard and Central Social Insurance Medical Council. Patients are required to pay only a portion of the price (10, 20 or 30 per cent, depending on, inter alia, age; see question 2) to medical institutions on each visit, as long as the patient shows his or her insurance card. In that sense, it is not a reimbursement system, but the patients are only required to pay a portion of the price. There is no limit to the health insurance treatment under the NHIS. In addition, if payment exceeds a certain level in the same month at the same medical institution due to extensive hospitalisation or advanced and complicated treatment, patients are reimbursed for all or 99 per cent of the amount exceeding that level (the reimbursement is calculated based on the patient's household income). There is no distinction between the outpatient and in-patient sectors.

If patients use medical services not covered by the NHIS, they shall bear the entire cost of such medical services. Medical services not covered by the NHIS include the use of unapproved medical drugs, off-label use of approved medical drugs, ordinary orthodontics, cosmetic surgery, and normal pregnancy and parturition (because normal pregnancy and parturition are not deemed to be injuries or diseases).

For reference, off-label use of approved medical drugs may be covered by the NHIS under exceptional circumstances.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The competent body for decisions regarding the price of medicinal products is the Minister. The Minister provides the NHI Drug Price Standard, which determines the price of new medicinal products paid by the NHIS to medical institutions and pharmacies by reference to, in principle, the price of existing similar medicinal products. As the actual market price of medicinal products sold from the manufacturing companies or distributors to medical institutions or pharmacies usually differs from the price paid by the NHIS, the Minister conducts research

into such actual market price. Based on the outcome of such research, the Minister revises the NHI Drug Price Standard once every two years, in principle. In relation to generic drugs, the price is set at around 60 to 70 per cent of the corresponding original drug price when the generic version is first approved. If other generic versions have already been approved, the price is set to the lowest among the other generic versions available in the market.

The competent body for decisions regarding reimbursement (ie, whether the products are covered by the NHIS) is the Health Insurance Claims Review & Reimbursement Service (HICRRS). The review committee of the HICRRS examines whether individual use of the medicinal products is covered by the NHIS from its medical perspective. In this regard, off-label use of approved medicinal products is, in principle, not covered by the NHIS. However, there are some exceptions, and the review committee publicly announces specific cases where certain off-label use is covered by the NHIS. It should be noted that the HICRRS states that each review is conducted on a case-by-case basis and, therefore, the announced cases should not be used as precedents.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

There is no such statutory obligation to give a discount under Japanese law.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

If, for instance, (i) the active ingredients of any counterfeit medicines are patented, (ii) the product names of any counterfeit medicines are identical or similar to any registered trademark, or (iii) the product names of any counterfeit medicines are identical or similar to any well-known marks, the manufacture and distribution of such counterfeit medicines would be prohibited by the Patent Act (for (i)), the Trademark Act (for (ii)) and the Unfair Competition Prevention Act (for (iii)).

The owner of the patent, registered trademark or well-known mark is entitled to seek an injunction against the manufacture and distribution of the counterfeit medicines, destruction of the counterfeit medicines possessed by the counterfeiter, and damages caused by the illegal manufacture and distribution of the counterfeit medicines. In addition, violations of these acts are subject to criminal penalties. For instance, under the Patent Act, the infringer of a patent right is subject to imprisonment of up to 10 years or a fine of up to ¥10 million, or both (imposable on individual offenders, ie, employees) and a fine of up to ¥300 million (imposable on the employer company).

In addition, the manufacture and marketing of unapproved medicines is prohibited by the PAA. Any violation of the PAA in this regard is subject to administrative penalties (suspension of business) and criminal penalties (imprisonment or fine).

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

The PMDA provides an online database of the package inserts of medicines (both prescription-only and OTC medicines). In addition, the PMDA also discloses online the minutes of the deliberations on the approval of applied medicines online. Accordingly, the general public may access the PMDA website and obtain information regarding any medicines.

Further, under the general procedure for information disclosure, the general public may request the MHLW to disclose any documents and materials submitted in connection with the application for the approval of medicines. However, the major part of the disclosed documents is usually redacted for the protection of the trade secrets of the applicants, and the request usually takes several months to be acted upon. For the foregoing reasons, this alternative may not be a very effective way for the general public to access important information about medicines. The amended PAA stipulates that manufacturers should draft package inserts based on the latest knowledge available and notify them to the Minister. Immediately after the notification, the manufacturers must also announce the information concerning the package inserts through the PMDA website.

29 Outline major developments to the regime relating to safety monitoring of medicines.

Post-marketing surveillance (PMS) is required pursuant to the PAA to ensure the effectiveness and safety of approved medicines. It was first introduced in 1967, whereby marketing approval holders were required to report any adverse reactions for two years after obtaining marketing approval. Since then, several changes have been made to the system. The current PMS consists of three systems: the adverse reaction and infection reporting system, the re-examination system and the re-evaluation system.

As regards the adverse reaction and infection reporting system, where marketing approval holders have knowledge of any adverse reaction or infection relating to the approved medicines, they must generally notify the MHLW within 15 days or 30 days (depending on the severity thereof).

With respect to the re-examination system, new medicines must be re-examined after approval, with the effectiveness and safety of an approved medicine being re-examined in view of the data collected during the re-examination period, which lasts for eight years, in principle, after approval. If a problem is discovered during the re-examination, the marketing approval may be cancelled.

Regarding the re-evaluation system, marketing licence holders are required to perform a re-evaluation of the approved medicines in order to monitor the effectiveness and safety thereof upon instruction from the MHLW. Similar to the re-examination system, if a problem is discovered as a result of the re-evaluation, the marketing approval may be cancelled.

The means of implementation of PMS is stipulated under the Good Post-Marketing Study Practice Ordinance and Good Vigilance Practice Ordinance.

For reference, with respect to the re-examination system, since the data submitted at the time of the application for the approval of new medicines is not available to generic drug companies to support their applications for approval during the re-examination period, the re-examination system effectively works as a data exclusivity system in Japan.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

Japan's modern government vaccination programme started after World War II. The programme was initially compulsory, and avoiding vaccinations without justifiable reason was subject to penalties. However, as infectious diseases decreased over time, vaccinations came to be viewed as less important, while their side effects were increasingly considered as social problems. As a result, in 1994, the legal obligation to have any vaccination was abandoned, and the Preventive Vaccination Act (the Act) now only requires individuals to make efforts to have vaccinations that are designated by the Act and relevant rules and orders.

The Japanese vaccination system is administered by the MHLW. (However, the register of vaccinations administered is maintained by

local governments, which are generally required to keep such records for five years.) In 2013, the Act was reviewed and amended (the 2013 Amendment) in response to the swine flu pandemic in 2011. Two of the main purposes of the 2013 Amendment are to give flexibility to the government vaccination programme by allowing the Minister of the MHLW to formulate a Preventative Vaccination Basic Plan and to review it every five years; and to resolve the 'vaccination gap' problem, where the number of vaccines supported by the Japanese government is lower than in other developed countries by adding haemophilus influenza type b, pneumococcal and HPV to the government vaccination programme.

The government vaccination programmes

The diseases targeted by the government vaccination programmes are classified into two groups: Category A and Category B.

Category A diseases are defined as 'diseases which should be included in the vaccination programme in order to prevent their occurrence and transmission, taking into consideration (i) their capability of being transmitted from one person to another; and (ii) their severity or potential severity', and include the following diseases: diphtheria, pertussis, polio, tetanus, measles, rubella, Japanese encephalitis, BCG, haemophilus influenza type b, pneumococcal, HPV and smallpox.

Category B diseases are defined as 'diseases which should be included in the vaccination programme in order to prevent individual pathogenesis or severe symptoms, as this will prevent the transmission of such diseases', and include influenza.

The government vaccination programme involves two types of vaccinations: routine vaccination and temporary vaccination. In addition, there is also voluntary vaccination, which exists outside of the government vaccination programmes in terms of funding.

Routine vaccination

Routine vaccination is carried out on a routine basis against predetermined individuals who may be affected by the relevant Category A or Category B disease (excluding smallpox). The individuals that are subject to routine vaccination and the date or period for being vaccinated are preliminarily determined by the governors of the local government. If such governors recommend individuals to receive a routine vaccination, such individuals or their guardians should make reasonable efforts to have the vaccination administered. However, it is not mandatory to receive a routine vaccination.

Temporary vaccination

If the governors of the local governments find that there is an urgent necessity for vaccinations to prevent the transmission of a Category A or Category B disease, they may recommend designated individuals to receive temporary vaccinations at a designated time or period. If such a recommendation is made, the designated individuals or their guardians should make reasonable efforts to have the vaccination administered. However, it is not mandatory to receive a temporary vaccination.

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Voluntary vaccination

Individuals can voluntarily receive vaccinations for diseases that are not listed as Category A and Category B diseases, provided they must bear all expenses. Further, vaccinations for Category A and Category B diseases that are received outside the designated date or period are considered to be voluntary vaccinations and the recipients of such vaccinations must bear all expenses.

Costs for vaccinations

Most of the costs for routine and temporary vaccinations are covered by public financial support, and some local governments even provide them for free. However, the costs for voluntary vaccinations must be fully borne by recipients.

Under the Act, it is provided that if any damage to health is caused by routine or temporary vaccinations, the governors of local governments shall provide relief measures. With respect to voluntary vaccinations, individuals may receive relief through the relief system provided by the PMDA for injuries to health caused by pharmaceutical products with adverse effects.

Reporting obligations

All medical agencies that provide routine and temporary vaccinations, individuals that receive vaccinations and their guardians shall report any damage to health caused by routine or temporary vaccinations (or both) to the MHLW.

If the MHLW receives such a report, it may ask the PMDA to investigate the case. Based on the investigation results of the PMDA, the MHLW, in close cooperation with the National Institute of Infectious Diseases, will organise all information concerning the adverse effects of the vaccination, report such information to each local government and recommend necessary measures to be taken to prevent the adverse effects.

WHO targets for vaccination

As of 1 August 2013, the WHO recommends routine vaccinations against the following diseases: BCG, hepatitis B, polio, DTP, haemophilus influenza type b, pneumococcal, rotavirus, measles, rubella and HPV.

The 2013 Amendment to the Act added haemophilus influenza type b, pneumococcal and HPV to the list of Category A diseases as of April 2013, and, as a result, the government vaccination programmes now cover all the routine vaccinations recommended by the WHO, except for hepatitis B and rotavirus vaccinations.

Lithuania

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The Lithuanian health system consists of governance institutions (the government, ministries and municipalities, as well as other specialist governance and control bodies), providers of healthcare services, and health system resources and services.

The Ministry of Health (MoH) is at the centre of formation and implementation of national health and pharmaceuticals policy. It regulates the sector and its funding, allocates capital investments and is in charge of health insurance policy. The State Patients Fund (SPF) and its five subordinate territorial branches manage the Compulsory Health Insurance Fund (CHIF) and implement the national health insurance system.

Healthcare is delivered by both public and private bodies licensed for particular care by the State Healthcare Accreditation Agency. Private bodies that have signed agreements with territorial branches of the SPF for compensation of healthcare service costs and all public bodies are statutorily considered to be a part of the Lithuanian health system.

According to the Law on the Health System, the national healthcare institutions are organised and controlled at national and municipal levels. The healthcare system is structured into three levels: primary, secondary and tertiary. Primary care is delivered by a general practitioner (GP) who performs a gatekeeping function to the secondary or tertiary level, which delivers highly specialised services and are divided into in-patient and outpatient care. Patients may freely choose the primary care institution, the GP, the secondary and, to a certain extent, tertiary level institutions and specialists. In the late 1990s, Lithuania moved away from a system funded predominantly from local and state budgets to a mixed system, predominantly funded by the National Health Insurance Fund under the Ministry of Health of Lithuania (NHIF), which also manages the CHIF that regulates financial flows and purchasing, through the national health insurance scheme and based on compulsory participation. The current compulsory health insurance system means that residents of Lithuania are obliged to obtain health insurance coverage (ie, pay compulsory health insurance contributions). With respect to the insured, the state guarantees healthcare services compensated by the CHIF. The compulsory health insurance is a guarantee for all insured that when needed, their healthcare expenses will be compensated from CHIF, irrespective of the contributions paid by the specific insured individual.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The Lithuanian healthcare funding system is mixed. Most of the health services are publicly funded (national or municipal budgets, CHIF) but for certain services (direct patient payments, private health insurance) privately financed delivery also exists. For publicly funded health services a combination of payment methods exists. Primary care is financed predominantly through capitation, with a smaller share from free-for-service and performance-related payments. The outpatient sector is basically financed through case payments from CHIF, and through fee-for-service for diagnostic tests. In-patient care is financed mainly through case payment (diagnosis-related groups (DRGs) were introduced in 2012) and historical budgets. Public health is mainly financed through historical budgets.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

The Law on Pharmacy provides the definition of medicine and medicinal products and regulates advertising and promotion of medicinal products, as well as the Regulations on Medicinal Products Advertising, approved by the Order of the MoH. Also, there is an industry code of ethics – the Code for Pharmaceutical Marketing (the Code of Ethics) at the will and upon common agreement of IFPA (local EFPIA) and VGA (Medicines Manufacturers Association, in principle, manufacturers of generics), which also provides rules on advertising medicinal products. However, this Code of Ethics it is a self-regulation document, not a legal act.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

According to the Law on Pharmacy the advertising of both prescription and non-prescription medicinal products is allowed only in special publications intended for healthcare professionals (HCP) or pharmaceutical specialists and in special websites that are intended for HCPs and not accessible to general public. The main principles for the advertising of medicinal products are as follows: only registered medicinal products may be advertised in Lithuania; advertising may not be misleading and must be objective. The use of free samples is allowed in order to market products only to HCPs that are able to prescribe medicinal products. These samples must be identical with the smallest presentation on the market of the medicinal product of the same name, form as well as strength and have to be marked as ‘Not for sale’. It is prohibited to leave free samples of medicinal products for HCPs, distribute them among HCPs and the general public, or use them for healthcare purposes. Advertisers of medicinal products may distribute the information about the product in promotional events, but the hospitality during the event must be reasonable and cannot extend to others than the participating HCP or pharmaceutical specialists. It is prohibited to pay for the travelling, accommodation and other expenses for the participants mentioned above.

Different rules apply to the professional and scientific congresses, as the payment of travelling, accommodation, catering and/or registration expenses of healthcare professionals and/or pharmaceutical specialists is authorised, nevertheless, the hospitality of such event must be secondary to the main purpose of the meeting.

Special procedures apply with respect to free samples for their importation, storage, distribution, etc.

Inducements to HCPs by remuneration, whether in money, or in kind, are prohibited.

5 What are the main rules and principles applying to advertising aimed at the general public?

Only non-prescription medicinal products are allowed to be advertised to the general public, while advertising of prescription medicinal products and reimbursable pharmaceuticals aimed at the general public is prohibited. Additionally, no advertising is allowed for non-registered medicinal products. The advertisements at the general public should include the name of the particular medicinal product and the generic name of its main substance, pharmaceutical form and strength, as

well as the information that is necessary for the correct use of the drug (dosage, route of administration, indications, etc). The Regulations on Medicinal Products Advertising indicates references that should be included into the advertisements, such as 'Please carefully read the leaflet and use the pharmaceutical as it is indicated. Misuse of the medicinal product may have a harmful effect on your health'. These references should also be included in advertisements that are spread by electronic communication means, as well as in advertisements on radio and television.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

When analysing the rules of advertisement, established in the Law on Pharmacy, manufacturers are usually infringing advertising rules by providing information about the product that is misleading or not objective, persistently offering residents to buy medicinal products, indicating alleged price reductions or using other means that are contrary to good morals or public order. Also, there are cases when manufacturers breached the prohibition of advertising prescription-only pharmaceuticals.

As far as the Regulations of Medicinal Products Advertising are concerned, the most common infringements with regard to advertising are using the word 'new' (or its synonyms) for medicinal products that received marketing authorisation more than a year ago, as well as not providing all mandatory information about the products (ie, when the information about the dosage or indication is missing, when there are no references mentioned in the answer above).

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

Part 3 of article 48 of the Law on Pharmacy indicates that only pharmaceutical information can be provided about unregistered medicinal product and it must be clearly stated that particular medicinal product is off-label. The advertising for non-registered medicinal products is prohibited (part 1 of article 49 of the Law on Pharmacy).

The legal act regulating the legality of off-label use in Lithuania is the Order of 8 March 2002, No. 112 (with latest amendments) of the Minister of Health On Issuance of Prescriptions and Dispensing (Selling) Reimbursable Medicinal Products to Residents and it is only mentioned that off-label use of medicinal products can be prescribed after the consultative doctors' panel has decided to prescribe this product for a particular case when the indications, pharmacological properties, dosage and route of administration are not indicated in the pharmaceutical's summary but are supported by scientific evidence to demonstrate safety and efficacy.

Rules on the Acquisition of Medicinal Products on a Named-Patient Basis adopted by the Order of the Minister of Health regulate use of unauthorised medicinal products, however, only to the scope that these products are used: (i) under a specific named patient (singular case) basis and (ii) only in case they are registered at least in one European Economic Area (EEA) state. Information about this product can be provided only for interested parties.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sector?

The collaboration of the pharmaceutical industry with HCPs is governed by the Law on Pharmacy and also by the self-regulatory mechanism (Code of Ethics). In some cases, the Law on Charity and Sponsorship may be applied. The rules are identical and apply to all physicians regardless of the sector they work in.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The main rules and principles applying to the collaboration of the pharmaceutical industry with HCPs are established mainly in the Law on Pharmacy, which are as follows:

- healthcare or pharmaceuticals professionals providing healthcare and pharmaceutical services have no right to advertise medicinal products;

- these professionals may be given advertisement of prescription-only medicines (POM) products in accordance with particular advertising rules;
- visits of medicinal representative of the company are allowed only outside of working hours and not at the time that is dedicated for consultation or treatment of the patients;
- special rules are applied to promotional events; and
- special rules are applied to scientific and professional events.

The Law on Pharmacy states that hospitality of both promotional and scientific events should be reasonable and strictly limited to the main purpose of the event. Paying for the travelling, accommodation and other expenses for the participants of promotional events is prohibited, while paying for these expenses for participants of professional events is allowed. The Code of Ethics stipulates disclosure requirements, therefore the companies have to disclose all transfers of value that were provided to HCPs and healthcare organisations. It is prohibited to supply, offer or promise gifts or pecuniary advantage (in cash or benefit in kind) to a HCP.

The Pharmaceutical Marketing Ethics Commission, which is responsible for supervising the Code of Ethics, advises pharmaceutical companies about whether particular venues are suitable for the events.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

There are only a few examples of infringements committed by manufacturers on this matter and it breaches article 17 of the Code of Ethics, which is the prohibition of gifts or pecuniary advantage. In one particular case, the pharmaceutical company committed an infringement of article 17 of the Code as it supplied pharmacy specialists with educational leaflets about the medicinal product with a calendar on the other side of the leaflet. The Pharmaceutical Marketing Commission found that the calendar was not directly connected with the practice of HCPs, nor was it useful for the care of patients; therefore, it was regarded as a gift.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

The Annex C of the Code of Ethics provides the main rules and principles that apply to the collaboration of the pharmaceutical industry with patient organisation (PO). As it was mentioned before, the Code of Ethics is self-regulatory supervised by the Pharmaceutical Marketing Ethics Commission. The main principles are as follows:

- the independence of PO, in terms of their political judgement, policies and activities, has to be assured;
- all partnerships between PO and the pharmaceutical industry has to be based on mutual respect;
- the pharmaceutical industry must not request, nor must PO undertake, the promotion of a particular prescription-only medicine;
- the objectives and scope of any partnership has to be transparent. Financial and significant non-financial support provided by the pharmaceutical industry must always be clearly acknowledged; and
- the pharmaceutical industry welcomes broad funding of patient organisations from multiple sources.

The main rules established in the Code of Ethics are as follows:

- promotion of POM to the general public is prohibited;
- written agreements are mandatory when pharmaceutical industry companies provide financial or non-financial support to a PO;
- each pharmaceutical company must make a publicly available list of POs that receive their financial or significant non-financial support; and
- information must be provided annually to the Pharmaceutical Marketing Ethics Committee.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes, the manufacturers' infringements are pursued by national authorities. The national authority responsible for the protection and enforcement of competition law is the Competition Council (the Council).

The Council investigates competition restrictions both on its own initiative and on the basis of notifications and complaints. The Council also investigates cases of unfair competition, but only if the allegedly unfair actions are damaging the interests of the majority of entities or consumers.

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes, private antitrust actions may be brought against manufacturers. Private antitrust litigation is possible for breaches of both national and EU legislation. In accordance with article 47 of the Law on Competition, a person whose legitimate interests were violated by actions infringing articles 101 or 102 of the Treaty on the Functioning of the European Union (TFEU), or provisions of the Law on Competition, has a right to file a claim to the Vilnius Regional Court concerning the termination of illegal actions and compensation of incurred damage. Also, in accordance with article 33 of the Law on Competition, if the undertakings and other persons who believe that their rights protected by the Law were violated they have a right to appeal to the Vilnius Regional Administrative Court against the Competition Council's resolutions, which prevent any further investigation of the violation or which complete the examination of the notification of concentration.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

Criminal liability arises for corruption-related crimes under regulation of the Criminal Code. Active and passive corruption is prohibited, therefore, both the giver and the recipient of a bribe in the public or private sector can be held liable for violations of anti-bribery provisions in the Criminal Code. Legal persons are also liable for corruption-related violations. Bribery through intermediaries and trading in influence are also prohibited by the Criminal Code.

Regarding the transparency rules, pharmaceutical companies, together with the European Federation of Pharmaceutical Industries and Associations, adopted the Code of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations (the Disclosure Code). In Lithuania, 40 companies united by the Innovative Pharmaceutical Industry Association and the Pharmaceutical Manufacturers' Association follow the rules of the Disclosure Code and disclose the information on their inputs into the improvements of HCPs' competence and qualifications, information on the involvement of practising HCPs in medical innovation-related clinical trials and other information by disclosing transfers of value to HCPs or healthcare organisations.

Compliance - medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

The promotion and advertising of medical devices is not specifically regulated, therefore, the standards for this sector are not as rigorous as in the pharmaceuticals sector. The reason for different standards could be the fact that there are only few manufacturers of medical devices in Lithuania or maybe because medical devices are mostly bought through centralised tenders, therefore, historically, there was no need of stricter regulation.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The Law on Pharmacy and the order of the Ministry of Health (MoH) adopted on 10 July 2007, No. V-596 regarding the rules of marketing authorisation of medicinal products and related matters.

17 Which authorities may grant marketing authorisation in your jurisdiction?

A national medicinal product marketing authorisation is granted by the authorised institution – the State Medicine Control Agency under the MoH.

18 What are the relevant procedures?

A person seeking to obtain marketing authorisation of a medicinal product only in the Republic of Lithuania while such medicinal product has not been granted marketing authorisation in any other EEA member state must submit an application for granting the medicinal product marketing authorisation to the State Medicines Control Agency in accordance with the national procedure.

The person willing to obtain marketing authorisation simultaneously in several EEA member states for a medicinal product not granted marketing authorisation in EEA states, including the Republic of Lithuania, must submit an application to the State Medicines Control Agency for granting of the marketing authorisation in accordance with the decentralised procedure, while also submitting the dossier submitted to the competent authorities of the other member states.

The person seeking marketing authorisation of a medicinal product in any EEA member state, including the Republic of Lithuania, must submit an application to the State Medicines Control Agency to be granted marketing authorisation for a medicinal product in accordance with the mutual recognition procedure and supplemented with the dossier identical to the one whereon the medicinal product was granted a marketing authorisation by the first member state with all the subsequent supplements.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

According to the paragraph 6 of article 14 of the Law on Pharmacy, if the medicinal product is not marketed within three years, or if the medicinal product has been marketed before but has not been in the market for three consecutive years, the marketing authorisation becomes invalid.

20 Which medicines may be marketed without authorisation?

Article 8 of the Law on Pharmacy provides three exceptions when non-registered medicinal products may be supplied to the Lithuanian market and used for healthcare according to the procedure established by the Minister of Health:

- the necessary medicinal products if they have been granted marketing authorisation in any EEA state;
- bearer prescription medicinal products where the doctor prescribing them for the use of a single patient assumes direct and personal responsibility; and
- when the Minister of Health provisionally grants an authorisation to place on the market medicinal products that are necessary when pathogenic or chemical factors, toxins or ionising radiation posing a health hazard are suspected or established, also in case of a natural disaster.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

The Rules on Acquisition of Medicinal Products on Named-Patient Basis (the Rules) adopted by the Order of the Minister of Health regulate the use of named-patient medicines in which article 5(1) of Directive 2001/83/EC has been transposed. The medicinal product on a named-patient basis must be authorised in at least one EEA country or in the manufacturer country.

Even though currently there are no special regulations for compassionate use programmes (CUP) in Lithuanian jurisdiction, in practice, CUPs are quite widely used by various pharmaceutical companies. The legality of such practices has not been challenged, because article 20 of the Law on Health System allows for HCP to use all scientifically substantiated, but not yet registered medicines, when authorised medicines are unsatisfactory.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

In general, the selling price of pharmaceuticals in the whole distribution chain is not statutorily set in Lithuania. Wholesale and retail prices are set by wholesalers (distributors) of the pharmaceuticals and retailers (pharmacies) respectively. However, certain highest price thresholds, which cannot be exceeded while selling pharmaceuticals in the distribution chain (wholesaler, retailer or final customer/patient), are statutorily set: the Minister of Health approves the base, the highest retail prices and highest wholesale and retail mark-ups of reimbursable pharmaceuticals, and the highest wholesale and retail mark-ups of non-reimbursable pharmaceuticals.

Wholesale mark-ups for reimbursable pharmaceuticals ranges from 5.5 per cent to 14 per cent and are capped at €14.48 per unit depending on the ex-factory price, whereas wholesale mark-ups for non-reimbursable pharmaceuticals range from 5 per cent to 18 per cent and are capped at €14.48 per unit depending on the ex-factory price. This involves a combination of linear and regressive schemes.

The pharmacy mark-up for reimbursable pharmaceuticals range from 4 per cent to 22 per cent and are capped at €5.79, whereas the pharmacy mark-up for non-reimbursable pharmaceuticals range from 15 per cent to 30 per cent and are capped at €17.38. This involves a combination of linear and regressive schemes. Reduced VAT of 5 per cent applies to all reimbursable pharmaceuticals.

Base and the highest retail prices of reimbursable pharmaceuticals are approved only for those products that International Non-proprietary Names (INN) has entered in the List of Diseases and Reimbursable Medicinal Preparations for their Treatment (the so-called A-list) and List of Reimbursable Medicinal Products (the so-called B-List) approved by the Minister of Health, and in respect whereof an application has been received for entering them in the Price-List of Reimbursable Medicinal Products.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

There is no obligation to negotiate prices, although it is a condition for an innovative medicinal product to be included on the A-list when the pharma-economic value or therapeutic value of the medicinal product does not meet the criteria. Then manufacturers are negotiating the price of their products not with healthcare providers, but with the state. When the manufacturer and the Negotiation Committee (consisting of representatives from NHIF and MoH) agree the price, the budget management agreement is concluded. These agreements are controlled by the NHIF and arranged through the Negotiation Committee.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

In the outpatient sector, three main criteria are evaluated for the cost of medicines to be reimbursed:

- the medicinal benefits provided by the pharmaceutical (effectiveness, safety and severity of the diseases treated, taking into account the data from published clinical trials);
- the results of pharma-economic evaluation; and
- the impact of reimbursement of that pharmaceutical on the budget of the NHIF.

If the medicinal product meets these criteria, it is included on the A-list, then the product is reimbursed and the SPF pays the pharmacies according to the doctor's prescription.

The medicinal product must be prescription-only and the indications, according to which the medicinal product was proposed for reimbursement, must be registered. The government only reimburses the base price of the medicinal product and only for certain compensation levels of such base price (either 100 per cent, 90 per cent, 80 per cent or 50 per cent). The base price is calculated using a certain formula and, in principle, is part of the lowest retail price of the medicinal product within a specific group of medicines. Accordingly, patients buying reimbursable medicinal products have to make a co-payment, since, in general, the selling price of a medicinal product in the whole distribution chain is not statutorily fixed in Lithuania.

According to the order of 5 April 2002, No. 159 (with latest amendments) of the Minister of Health On Inclusion of Diseases, Drugs and Medical Aid Means to Reimbursement Lists, off-label use cannot be reimbursed.

Outpatient services are reimbursed on a per-case basis and are free for diagnostic tests. A case is defined as an episode consisting of up to three visits to a specialist related to the same illness and is called a consultation. Almost all recurrent costs of outpatient institutions, including the majority of laboratory tests, are covered by the price of the consultation.

Long-term and nursing hospitals are reimbursed on a bed-day basis. Patients may be treated in these hospitals for up to 120 days and later should be transferred to homes for the elderly, where a co-payment for services may be applied. Medical rehabilitation is paid according to reference prices. Since 2010, the lists of reference prices per bed-day, outpatient visit and rehabilitation at home for adults and children are applied.

When in-patient sector is concerned, either SPF procures medicinal products through the Central Procurement Organisation (in this case, it is still required that the medicinal products would be included into the reimbursement list) or the hospitals individually procure through hospital tenders. In-patient services are fully reimbursed, ie, the patient does not need to pay any co-payments for pharmaceuticals when in hospital. The hospital independently purchases pharmaceuticals needed for in-patient treatment through public procurement.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The MoH has the most important role because it decides on the strategic planning and on whether a product will be reimbursed and at what price. Regarding the pricing and reimbursability in the outpatient sector, applications for reimbursing medicinal products are being submitted to the Pharmacy Department under the Ministry of Health. The Pharmacy Department transfers the application to the Pharmaceutical Reimbursement Commission (Commission), consisting of nine members:

- three representatives from the MoH;
- one representative from the Ministry of Social Security and Labour;
- one representative from the Ministry of Finance;
- two representatives of NGOs or associations; and
- two representatives from academic institutions.

The Commission adopts a recommendation to the MoH whether or not to reimburse the pharmaceutical, which is transferred to the Council of Compulsory Health Insurance (the Council). The Council also adopts a recommendation for the MoH. For the final step of the reimbursement procedure the Minister of Health makes the reimbursement decision and if it is positive, the order to amend the List of Reimbursable Medicinal Products is issued. In the in-patient sector, when medicinal products are procured through the Central Procurement Organisation or individually through hospital tenders, competent bodies for making decisions are the particular hospitals concerned and the MoH, which is responsible for the planning and strategies of healthcare policies. The SPF, in this case, only distributes the funds.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

Manufacturers or distributors of medicinal products are obliged to give a discount if the product does not meet criteria for price in order to be included on the reimbursable product list (the above-mentioned A-list). The product's declared price cannot be higher than 95 per cent of the EU average in order for its application to be accepted and may only decrease later on (during negotiations or further assessment of the product regarding inclusion on the A-list when it is necessary to gain a certain amount of scores on the product's pharmacoeconomic value). When the product is included on the A-list and there are more of the same INN products, it is also necessary to reduce a price of the product if it costs more than 40 per cent more than others.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Counterfeiting and illegally distributing medicines are prohibited by the Criminal Code and the Code of Administrative Offences.

According to the Code of Administrative Offences, manufacturing, import from third countries, export or distribution of falsified medicinal products might render an administrative fine from €179 up to €1,158 and the confiscation of illegal products.

According to the Criminal Code, manufacturers (both legal and natural persons) that are found to counterfeit and illegally distribute medicinal products where there is a potential risk for one's health or life, may receive an administrative fine, face criminal charges and receive a fine, or be sentenced to up to two years of imprisonment.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

Recently, a new social advertising campaign called 'Use medicines wisely' was launched, aimed at encouraging the rational use of medicines and to promote awareness of services covered by the CHIF. This campaign seeks to inform people about correct usage of POM, importance of following their doctors' recommendations and explains about possible less expensive medicines with the same active substance. Another important aim of this social advertisement is to promote HCPs to prescribe medicinal products more responsibly and avoid unnecessary medicine prescription, as well as, remind the patients about importance of rational usage of medicines and possible health disorders if patients do not follow professionals' recommendations.

29 Outline major developments to the regime relating to safety monitoring of medicines

As of 1 January 2013, new amendments of the Law on Pharmacy entered into force and the requirements for pharmacovigilance were renewed. One of the greatest developments relating to the safe monitoring of medicines is that the definition of 'adverse reaction' was extended and now covers a noxious and unintended response to a medicinal product, which may arise from use of the product within or outside the terms of the marketing authorisation, or from occupational exposure,

including off-label use, overdose, misuse, abuse and medication errors. Moreover, HCPs or pharmacy specialists are now obliged to inform the State Medicines Control Agency about the adverse reaction when it was caused by incorrect use of the medicine, for instance, through a wrong dose or route of administration. The new amendments of the Law allow pharmaceutical employees to inform the SMCA about adverse reaction when it was caused by the occupational exposure. Finally, the new amendments enable patients to inform the SMCA about adverse reactions they have experienced themselves or reactions that have been experienced by their relatives. It is possible to inform the SMCA about adverse reactions by free fax, email, post, or via the SMCA website.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans

No obligatory immunisation is administered in Lithuania. In accordance with the Law on the Prevention and Control of Human Communicable Disease, immunoprophylaxis may be administered to the persons only with their consent, with the exception of the cases provided for in other legal acts. Immunisation may only be administered in the presence of a medical doctor (paediatrician or GP).

There is no national immunisation register in Lithuania, however, reports regarding immunisation are to be provided to the MoH annually. The National Immunisation Programme has been approved by the MoH. Immunisation against communicable diseases is performed in pursuance of the Lithuanian Immunisation Schedule. Vaccinations given according to the Schedule (currently, to protect against 11 diseases and infections) are covered by the NHIF.

In 2014, vaccination coverage for all infections was more than 90 per cent; consequently, the target of the National Immunisation Programme 'to maintain the coverage among children across the country at levels no less than 90 per cent' was successfully achieved by the effectiveness criteria. Accordingly, a target of achieving 90 per cent DTP3 vaccination coverage set by the Global Vaccine Action Plan (GVAP) of WHO member states was met. However, in recent years a visible downward trend in overall vaccination coverage has been observed. This might have been influenced by anti-vaccine movements that have been gaining momentum in the country combined with non-evidence-based information being disseminated through the mass media.



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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The Mexican healthcare system comprises public (social security institutions) and private insurers, out-of-pocket payments and informal arrangements.

The major public segments of the Mexican healthcare system are:

- the Mexican Institute of Social Security (IMSS). This represents social security for the self-employed and employees in private companies;
- the Institute of Social Security for State Workers (ISSSTE); and
- the Seguro Popular. This is a programme created in 2004 as part of a strategic reform to the General Health Law. It provides a public insurance scheme for those not covered by social security and other formal arrangements. The Seguro Popular was created to cover people with lower incomes. The federal government pays 70 per cent of the annual family premium, states provide 20 per cent and patients provide 10 per cent.

Other social security institutes for particular sectors, for example, for members of the military and for Mexican petroleum workers (PEMEX Medical Services).

Private health insurance generally covers professional, executive and higher levels of the private sector. Enrolment in private health insurance has increased considerably over the past few years.

The public health sector normally faces financial problems and implements measures to limit costs, for example, by pressing for price reductions in public bids and encouraging competition.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The way of financing healthcare institutions relies on whether they belong to the public or private sectors rather than whether they belong to outpatient or in-patient sectors.

Public sector

They are mostly financed through contributions from public and private sector workers. Employers and employees both pay a sort of tax solely used to provide healthcare services. There are special rules for those who are unable to pay but are still eligible to benefit from the healthcare system. In the case of the Seguro Popular, as mentioned above, the federal government pays 70 per cent of the annual family premium, states provide 20 per cent and patients provide 10 per cent.

Private sector

According to official figures, up to 50 per cent of annual health spending in Mexico comes from out-of-pocket expenses, related to private doctors and insurance and drug acquisitions.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

The primary legislation for the advertising of medicinal products is the General Health Law (HL), and its Regulations concerning advertising (HLR concerning to advertising). These norms are supplemented

by guidelines published by the Regulatory Agency, the Federal Commission for Protection against Sanitary Risks (COFEPRIS). This agency is part of the Ministry of Health and controls the advertising of medicinal products.

Industry Codes of Practices complement this regulation. The Council of Ethics and Transparency of the Pharmaceutical Industry (CETIFARMA) has issued the following self-regulatory instruments (the Codes):

- the Code of Ethics and Transparency of the Pharmaceutical Industry (Code of Ethics & Transparency);
- the Code of Good Practices of Promotion (Code of GPP); and
- the Code of Good Practices of Interaction of the Pharmaceutical Industry with Patient Organisations (Code of GPI).

The latest versions of these Codes have been in force since 1 April 2013. Affiliate members of the National Chamber of the Pharmaceutical Industry (CANIFARMA) are required to follow these codes. CETIFARMA supervises members' and adherents' compliance.

There are also opinions issued by the Advertising Council, which include representatives from the Ministry of Health, the academic and scientific communities, the business sector, the media and consumer groups.

Additionally, other general legislation may be relevant for the advertising of medicinal products, particularly, the Federal Law for the Protection of Consumers and the Industrial Property Law.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

According to article 42 of the HLR concerning advertising, advertisements directed at healthcare professionals can only be published in specialised media, and they must be based on the recommended information for the corresponding medicinal product, which must contain the following data:

- the distinctive denomination, if this is the case;
- the generic denomination;
- pharmaceutical form and formulation;
- therapeutic indications;
- pharmacokinetics and pharmacodynamics;
- side-effects;
- general precautions;
- restrictions of use during pregnancy and breastfeeding;
- secondary and adverse reactions;
- medical interactions;
- alterations in results from lab tests;
- precautions related to carcinogenic, mutagenic, teratogenic and fertility effects;
- the dose and tract of administration;
- manifestations and handling of overdose or accidental ingestion;
- presentation or presentations; storage recommendations; protection notices; the name and domicile of the laboratory; and
- the marketing authorisation number.

Article 42 also mentions that in case some of the above-mentioned data does not exist, the circumstance must be expressly mentioned.

The Code of GPP states that the relationships between pharmaceutical industry personnel and healthcare professionals should encourage

the development of a medical practice committed to patients' well-being, based on truthful and accurate information and tested and up-to-date scientific evidence in order to contribute to the appropriate use of approved medicines.

5 What are the main rules and principles applying to advertising aimed at the general public?

Pursuant to article 310 of the HL, only non-prescription medicines can be advertised to the general public, and the objective of said advertisements is to inform the public about the characteristics of the products, its therapeutic properties and the form of use. The advertising is subject to approval by COFEPRIS.

Pursuant to article 43 of the HLR concerning to advertising, any visual or audio advertisement must bear the following message: 'Consult your physician.' Advertisements should mention applicable precautions, and when the use of the medicine represents any danger in the event of an existing pathology.

The Code of GPP requires that members' promotional activities directed towards consumers must be undertaken with the aim of generating a new culture in regard to rational and appropriate consumption of medicines, encouraging the guidance of healthcare professionals authorised to prescribe.

In February 2014, COFEPRIS issued detailed guidelines regarding the approval of ads for non-prescription medicinal products.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

Probably the most renowned recent infringements have been committed by manufacturers of health or dietary supplements and 'miracle' products, which launched aggressive infomercial campaigns with exaggerated claims about the benefits of such products. In this regard, the HLR on advertising allows COFEPRIS to order both manufacturers and media outlets to cease advertising activities. Infringements can lead to high fines and closure of business.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

According to article 42 of the HLR concerning advertising, prescribing information about products to healthcare professionals is subject to approval before publication. This information is approved while granting marketing authorisation for the corresponding product. Any publication should have the marketing authorisation number of this product.

The Code of GPP sets forth that information of medicinal products must be grounded on scientific evaluation and related empirical evidence, which must be kept at the disposal of healthcare professionals, if required. It must not induce confusion by means of distortion, unjustified pressure, omission or any other means.

This Code also states that, when scientific information is provided and is not part of the prescribing information duly approved or authorised in the marketing authorisation of a product, it should be strictly limited to a scientific audience, avoiding the promotion, directly, indirectly or through a third party, of any unauthorised directions of use.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the in-patient and outpatient sectors?

There are several bodies of law that refer in general terms to the relationship between the pharmaceutical industry and the healthcare professionals, including the HL, the HLR concerning advertising and the HL Regulations concerning sanitary control of activities, establishments, products and services. The Code of GPP sets forth guidelines for promotional activities. Public institutions usually have their own particular guidelines. These regulations apply to both physicians in the in-patient and outpatient sectors.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

Scientific and educational events

The Code of GPP states that congresses, lectures, symposia, meetings and other similar scientific or educational events sponsored, financed

or supported by pharmaceutical companies or any other third party must have, as a main purpose: scientific exchange; medical education; or information about medicines.

Whenever support for continuing education or independent educational programmes is being provided, the education of healthcare professionals should be encouraged, primarily, to improve their knowledge of patient care. In each case, programmes must comply with the guidelines of the applicable laws; they must have a strict scientific content sustained, if required, on clinical evidence; and, most importantly, they must be accredited and certified by the corresponding academic authorities.

Support in general will not be offered, under any circumstance, in order to have any kind of influence on the decision-making process involved in prescribing medicines or buying, including, excluding or modifying official product catalogues.

Samples

According to the Code of GPP, samples are provided directly, in fair amounts and without cost to healthcare professionals, so that they may get to know the products or in order to initiate a treatment.

According to article 49 of the HLR concerning to advertising, providing samples of products for free does not require approval, provided that they meet the requirements of the approved medicinal product. These samples should be contained in a package with lesser number of units than the approved product.

The Code of GPP establishes guidelines for sampling. It prohibits members to offer or supply samples with the aim of seeking or rewarding prescription practices. The Code also forbids any trade of samples.

Members are required to have full and up-to-date control of their samples, including their manufacture, storage, delivery to regional coordinators or others, and provision to medical representatives and physicians.

We always recommend our clients have strict control on product samples since there have been cases of the re-sale of said samples.

Gifts and donations

The Code of GPP essentially states that companies must act responsibly regarding sponsorships and donations. No gifts of significant commercial value may be offered to healthcare professionals, or incentives of any kind, as an inducement to use, prescribe, purchase or recommend a specific product or influence the results of a clinical study.

No gifts, bonuses, pecuniary advantages, benefits in kind, or any sort of incentive may be offered or promised to healthcare professionals, administrative staff or government employees involved in the cycle of prescription, purchase, distribution, dispensing and administration of medicines, except in the case of inexpensive promotional aids related to the practice of medicine or pharmaceutical activities.

The Code delineates an inexpensive promotional aid as that one that does not exceed the equivalent of 10 times the minimum wage (around US\$50).

Concerning healthcare professionals in government institutions, article 47 of the Federal Law of Responsibilities for Government Officers expressly forbids these officers from requesting, accepting or receiving any gifts or donations from persons whose commercial or industrial activities are directly linked, regulated or supervised by government officers.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

According to the 2013/14 annual report of CETIFARMA, in that period they received 10 complaints. CETIFARMA issued decision in six of those complaints. Concerning the remaining four complaints, one was withdrawn and the other three were dismissed. In this report, however, CETIFARMA does not provide any details of the complaints, such as grounds, parties or decisions. CETIFARMA states that complaints have increased 30 per cent in comparison with the previous period, as there were 32 complaints.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

The Code of GPP establishes that collaboration between the pharmaceutical industry and patient organisations must have a written agreement in place that will include, at least:

- the activities to be undertaken, cost, source and destination of funding; and
- direct and indirect support and any other relevant non-financial aid.

In these agreements, members have to follow their applicable guidelines, codes of ethics and conduct, their transparent practices and the deontological instruments approved by CETIFARMA and CANIFARMA.

The Code requires members to set forth criteria and procedures for the approval and implementation of these kinds of collaborations.

Any other kind of sponsorship provided by social, governmental or private sector organisations should not be excluded.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Whereas Mexico does have a Federal Antitrust Law and an active Antitrust Commission (ECCF) (www.cfc.gob.mx), there have been a number of investigations initiated against manufacturers of pharmaceutical products.

A notable exception is a 2011 investigation that reviewed public tender proceedings before the IMSS after evidence was found of collusion between manufacturers in order to set prices. A fine was imposed. The ECCF has broad jurisdiction to investigate future cases of infringements to the Federal Antitrust Law.

13 Is follow-on private antitrust litigation against manufacturers possible?

The Federal Antitrust Law allows for private entities to request investigations, as well as to provide all kinds of elements and evidence related to a certain investigation in process.

Further, once the preliminary determination of antitrust practices has been declared and published in the Mexican Government Official Gazette, anyone related or affected by the decision has the opportunity to provide arguments and evidence.

Follow-on private litigation against manufacturers is possible, but has not been as widespread as in other jurisdictions, such as the United States.

It is worth mentioning that on 20 July 2016, the ECCF announced that it will conduct a study regarding competition concerns over pharmaceutical products with lapsed patents. This is the first time such a study has been undertaken in Mexico.

The ECCF emphasised that this analysis should not be considered in any way as a prejudgment of potential misconduct. It pointed out that this assessment aims to provide Mexican Regulatory Agencies with recommendations on how to encourage competition and correct inefficiencies.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

On 18 July 2016, several decrees were enacted in accordance with a Constitutional Amendment for Anti-corruption Matters in Mexico. These decrees were aimed at implementing, amending and supplementing various laws and acts, which together comprise the new National Anti-Corruption System.

The main mandatory anti-corruption rules and provisions currently in place applicable to private parties, whether individuals or corporations (including pharmaceutical manufacturers), are contained in: (i) the Mexican Federal Constitution; (ii) the Federal Anticorruption Law for Government Procurement; (iii) the Federal Criminal Code; and (iv) the international anti-corruption conventions to which Mexico is a party (the United Nations Convention Against Corruption, the Inter-American Convention Against Corruption and the Convention on Combating Bribery of Foreign Public Officials in International Business Transactions).

As of 19 July 2017, the General Act of Administrative Responsibilities (GAAR) will enter into force in Mexico, repealing the

Federal Anticorruption Law for Government Procurement. The GAAR sanctions, among other corrupt activities, the actions of private parties related to administrative liabilities when interacting with public officials, such as bribery, illegal participation on administrative procedures, influence peddling, collusion and undue contracting of former public officials. Some of the main administrative liabilities considered under the GAAR include the disqualification from public acquisitions for no less than three months and no more than 10 years, and the suspension of activities for no less than three months and no more than three years.

Conversely, regarding the mandatory transparency rules, the Code of Ethics and Transparency of the Pharmaceutical Industry issued by CETIFARMA, is a fundamental principle guiding to pharmaceutical manufacturers to prevent unfair competition, greater transparency and an effective accountability, for the purpose of pharmaceutical manufacturers to practise and promote ethical and social responsibility conducts.

The latest version of this Code has been in force since 1 April 2013. Affiliate members of CANIFARMA are required to follow this code, and CETIFARMA supervises members' and adherents' compliance.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

General speaking, it would be fair to say that regulation regarding medical devices is lighter than that for drugs and other substances. Advertising concerning medical devices is regulated in articles 52–56 of the HLR regarding to advertising. Standards of the Code of GPP for medicines apply to medical devices.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The primary legislation for medical products is:

- the HL;
- the Health Law Regulations;
- the Official Mexican Norms (NOMs); and
- Mexican Pharmacopoeia.

17 Which authorities may grant marketing authorisation in your jurisdiction?

The regulatory authority in charge of the granting of marketing authorisations is the Federal Commission for Protection against Sanitary Risk (COFEPRIS) (www.cofepris.gob.mx), which is an administrative agency of the Ministry of Health. The granting of authorisations for innovator drugs is also reviewed by the New Molecules Committee of COFEPRIS, which includes physicians from the National Academy of Medicine.

18 What are the relevant procedures?

The relevant procedures are commented as follows.

New molecules

Essentially, applicants for marketing authorisations must prove safety and efficacy of their products through standard clinical trials, according to the rules set out by the General Health Law, its regulations and NOMs of good manufacturing of medicines and active ingredients.

Concurrently, they have to request approval of their products as new molecules by the New Molecules Committee of COFEPRIS. A new molecule is (article 2, section XV Health Law Regulations):

- an active ingredient or drug not approved worldwide (new molecular entity);
- an active ingredient or drug already available in other countries but with limited clinical experience or disputed information, without approval in Mexico;
- a drug that is a non-marketed combination of two or more active ingredients; and
- an active ingredient or drug already available in the market, but to be marketed for a new therapeutic indication.

R&D companies can benefit from a special procedure for drugs to be approved for the first time in Mexico, if they have been previously approved by:

- the European Medicines Agency;
- the US Drug and Food Administration;
- Health Canada;
- the Swiss Agency for Therapeutic Products (Swissmedic); and
- the Therapeutic Goods Administration in Australia.

In 2012, COFEPRIS published new rules to set out this procedure. This is essentially based on the dossier filed with the foreign regulatory agency, to reduce approval time frames by up to 60 working days. Industry participants have welcomed and used these new rules.

Generics

Applicants for marketing authorisations have to prove basically that their products are bioequivalent to the innovator product. They have to provide information concerning dissolution profiles or bioavailability studies regarding the reference product. COFEPRIS periodically issues a list of reference medicinal products.

Recently, the NOM setting the test to prove that a generic drug is interchangeable with a reference drug was updated (NOM-177-SSA1-2013). Legally, COFEPRIS should not grant marketing authorisation for generics breaching exclusivity rights.

There is a linkage system between COFEPRIS and the Mexican Institute of Industrial Property (IMPI), which aims to prevent the granting of marketing authorisations in violation of exclusive rights. According to the IP Regulations, every six months the IMPI must publish a gazette that includes patents covering allopathic medicines (*Linkage Gazette*). The initial IMPI position was that only patents relating to a compound were relevant to linkage review (excluding formulation and use of patents). In 2012, for the first time the IMPI included formulation patents in the *Linkage Gazette*, in accordance with a 2010 ruling of the Mexican Supreme Court (Jurisprudence No. 2a./J./2010, *Federal Judicial Gazette*, No. XXXI, page 135).

Under the linkage regulations, at the filing of the application, the applicant must prove that it is the owner or licensee of the patent of the active ingredient of the product (recorded with the IMPI), or state under oath that their application does not violate the list of products published in the *Linkage Gazette* and observes patent law.

Biologics (biotech products)

The Mexican jurisdiction recognises already that biotech products deserve special treatment as a result of their distinct characteristics, such as their complex structures, their size in comparison with chemically synthesised drugs and, particularly, their susceptibility to variation during manufacturing. The regulatory scheme distinguishes from other biologics those products that have been manufactured by molecular biotechnology and provides a robust regulatory process to approve them.

The standards to approve biotech products are essentially the same as for other drugs in Mexico: they must be safe and effective and have appropriate quality. The biotech products, however, must comply with a number of additional dossier requirements, in view of their distinct characteristics. Applicants have to prove quality, safety and efficacy requirements under the General Health Law, its regulations and applicable NOMs, particularly, those for biotech products (NOM-257-SSA1-2014), for good manufacturing practices for medicinal products (NOM-059-SSA1-2015) and for active ingredients (NOM-164-SSA1-2015).

Biocomparables (follow-ons)

Applicants must submit clinical tests and, when appropriate invitro tests, to prove safety, efficacy and quality of this product comparable (similar) to those of the reference biologic.

The pre-clinical and clinical test used by an applicant for a biocomparable must use the corresponding reference biologic to perform comparative and physico-chemical studies. For this, the applicant must have to submit essentially:

- in vitro studies;
- a report of comparative test of pharmacokinetic, if determined by the Ministry of Health, to show pharmacokinetic comparability on key parameters between both the follow-on and the reference biologic;
- pharmacodynamics test reports; and

- comparative efficacy and safety clinical test to show similarity between both the follow-on and the reference biologic.

Although industry participants welcomed amendments to approve biologics, specific rules to approve follow-ons have caused debate. In Mexican domestic law there is currently no indication of a data-protection period for biologics. The recognition of data package exclusivity rights for biologics has been achieved through litigation.

Additionally, on 5 October 2015, Mexico and its 11 new partners finalised negotiations of the most ambitious free trade agreement ever, the Transpacific Partnership Agreement (TPP) (see 'Update and trends'). The recent execution of the TPP will improve recognition of the data package exclusivity rights, as there are parameters for granting a minimum five-year protection term for biologics.

Orphan drugs

They were recently introduced into the General Health Law and the Mexican Pharmacopeia. In practice, they are approved by a particular procedure, following rules for new molecules when applicable and appropriate. Specific rules are still pending. The draft of NOM requirements for granting marketing authorisations includes orphan drugs.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Before 2010 all marketing authorisations were issued without any sort of time limit, and therefore were not subject to expiry.

Since 2010 a reform to the law and regulations has established a five-year term on marketing authorisations. Even though proof of use is not a requirement for renewal, technical reports on pharmacovigilance are. Therefore, renewal of an authorisation for a drug that is not on the market would be denied.

20 Which medicines may be marketed without authorisation?

According to article 376 of the General Health Law, all medicines require a marketing authorisation. Health supplements and herbal remedies are excluded.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Yes. Article 102 of the HL establishes that COFEPRIS can authorise the use of drugs or materials that have not been previously authorised for clinical trials' purposes.

In addition, according to article 103 of the same law, a physician can authorise therapeutic or diagnostic resources that are still in the research phase when the potential to save lives, restore health or diminish suffering exists, as long as there is written consent, and an authorisation is provided by the Ministry of Health.

A special marketing authorisation for the distribution of an unauthorised medicinal product may also be granted if a medicine meets most of the criteria, but the requirements on effectiveness and the risk or benefit ratio are merely suspected and cannot be confirmed, since the number of patients involved in the clinical trial of the product is insufficient owing to the rarity of the disease.

Compliance with the requirements is assessed at least once a year. At the manufacturer's request the time limit of such provisional marketing authorisation may be extended by a maximum of one year.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

Mexican laws do not establish specific provisions concerning medicinal product pricing for either the outpatient or in-patient sectors. However, several mechanisms are in place, which leads to a certain degree of control of such prices in practice.

Price control in the private sector is based on a scheme of self-regulated maximum retail price (MRP) only covering patented products, overseen by the Ministry of Economy. Pharmaceutical companies' participation is voluntary. Under the price control each product's MRP must not exceed an international reference price, estimated as the average price in six major markets, plus a market factor. There are no established sanctions for violations of the MRP.

Update and trends

Advertising

Several amendments to the Industry Codes of Practices by CETIFARMA were approved in 2013. As a consequence of compliance practices, the rules governing pharmaceutical advertisements have been continuously strengthened by both industry associations and regulatory authorities.

Marketing authorisations

The NOMs for good manufacturing practices for medicinal products (NOM-059-SSA1-2015) and for active ingredients (NOM-164-SSA1-2015) has been updated to bring them into line with the standards of the Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme. These updated norms are currently in force.

The Trans-Pacific Partnership

On 5 October 2015, Mexico and its 11 new partners finalised the negotiations of the most ambitious free trade agreement ever. The member states of the agreement govern approximately 40 per cent of global trade and so this agreement has significant ramifications for many of the world's businesses buying and selling goods and services abroad.

In addition to establishing rules around free trade and access to market between member nations, the agreement also elevates and standardises intellectual property protection and includes important commitments in the labour, environmental and regulatory legal frameworks.

The agreement come into effect after the country-by-country ratification and implementation processes, but according to the hierarchy of international treaties approved by the Mexican Senate, certainly, the TPP will have a positive impact on the entire intellectual property structure in Mexico. It is no secret that the framework for IP protection in Mexico has required urgent review for a long time as more than 20 years have passed without any important amendments in Mexican law. It is expected the TPP is ratified by the Mexican Senate between the end of 2016 and the beginning of 2017.

First antitrust analysis of pharmaceutical products with lapsed patents

On 20 July 2016, the ECCF announced that it will conduct a study regarding competition concerns over pharmaceutical products with lapsed patents. This is the first time such a study has been undertaken in Mexico.

The press release stated that the Commission chose to conduct this market assessment due to the relevance of these products to the national economy and public health.

The ECCF noted that, according to 2015 national statistics, the pharmaceutical industry represented 2.7 per cent of gross national income, and 2015 government purchases of pharmaceutical products reached more than 50 billion pesos (about US\$2.6 billion).

The Commission will first analyse the rationale behind the fact that, according to the announcement, there are approximately 350 products listed in the National Formulary with sole suppliers, although about 63 per cent of these products have lapsed patents.

The ECCF emphasised that this analysis should not be considered in any way as a pre-judgment of potential misconduct. It pointed out that this assessment aims to provide Mexican Regulatory Agencies with recommendations on how to encourage competition and correct inefficiencies.

OLIVARES believes that the ECCF official communication in this regard contains several flaws and confuses concepts in order to justify the study. For example, the Commission provides data concerning out-of-pocket expenses of the private sector to explain its reasoning for reviewing public acquisitions of medical products; however, these are separate realms governed by various factors and rules and are not necessarily related.

Partners and associates of our law firm, through the various industry associations in which we participate, will follow up with the ECCF on this study, which demands further analysis with respect to the intersection of regulations over healthcare products, patent rights and competition.

Concerning to public acquisition of innovator drugs covered by patent rights, their price is negotiated in bulk between the patent or licence holder and a government commission for price negotiation. The negotiation proceedings end with a single yearly price for all public sales.

Off-patent drugs are purchased through public tender proceedings, where a reference price is set, based on previous purchasing experiences (ie, a maximum amount that can be paid for a specific drug), and the lowest bidder is assigned the tender.

Since the government is the main purchaser of drugs, pricing for publicly acquired drugs helps regulate prices in the private sector.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

Yes. As mentioned above, prices for patented drugs are negotiated with a government commission and set for every public acquisition. When patent rights have expired (or in some cases when there is more than one participant in the market), drugs are acquired through public tender proceedings based on previous purchasing prices.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

Commonly, public insurers dispense to patients medicinal products prescribed by their healthcare professionals. Products are prescribed and dispensed from a basic medicinal products list, which public insurers essentially base on the *National Formulary* issued by the Ministry of Health. Public insurers acquire those listed products mostly through public tender processes.

Public healthcare institutions, scientific organisations and pharmaceutical providers may request a drug to be listed in the *National Formulary*. Essentially, the principal conditions for listing eligibility are that the drug has marketing authorisation, has met all safety and efficacy tests (clinical trials) and is cost-effective (pharma-economic tests).

The IMSS is the largest public sector buyer of drugs. Public institutions may have their own formulary, such as in the case of the IMSS, whose formulary contains fewer drugs than the National Formulary.

Additionally, in the case of the ISSSTE, a prescribed medicinal product can be dispensed in a private drug store registered with this public insurer, provided that this is not available within ISSSTE facilities and under certain conditions. The ISSSTE reimburses the cost of that product to the drug store according to previous agreements.

In 2014, the National Formulary has included some orphan drugs and the Mexican Supreme Court ordered the IMSS to request the Ministry of Health to evaluate the inclusion of orphan drugs in the Formulary before considering its purchasing.

In addition, the Seguro Popular manages a National Fund for Natural Disasters, which covers a list of high-cost treatments, including certain orphan drugs. The number of treatments included has increased over time.

In September 2015, a circuit court ordered the IMSS to provide a patient with a drug that was not listed in any formulary. This precedent is not binding for other cases; however, it may provide a basis for a debate in this regard.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

While the Ministry of Economy is empowered to raise observations in the scheme of self-regulated maximum retail price, the Commission for Drug Price Negotiations, which is made up of several public offices, including the Ministries of Economy and Health, negotiate with the patent holder or licensee to establish a single price of a patented drug for all sales to the public sector.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

There is no obligation in Mexican law for this specific point, but sales to public institutions are generally done at much lower prices than sales in the private market.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

COFEPRIS has broad jurisdiction to seize counterfeit or illegal medicines. The manufacturing and sales of counterfeiting or falsified medicines is classified as a crime by the HL. In addition, COFEPRIS commonly enters into collaboration agreements with the Federal District Attorney's office and the Customs Office in order to investigate and prevent counterfeit and illegal medicines.

Private companies have also run successful collaboration campaigns with COFEPRIS to counter these actions, including funding investigations and providing full packages of information to the authority.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

As a general rule, laboratories are forbidden from any form of advertisement to the general public concerning prescription-only medicines. The public policy in place in this regard is that the public's access to information on these medicines must be limited to avoid self-prescription (since sale of drugs without a prescription is a common practice in Mexican pharmacies).

Concerning information on prescription-only medicines, which is online and is addressed to healthcare professionals, the Code of GPP states that this practice must be duly approved by the corresponding authorities. It must clearly identify the sponsoring pharmaceutical company and be disclosed on scientific websites. Companies must adopt the proper measures to ensure the promotion of prescription medicines on their websites will only be accessible to healthcare professionals.

29 Outline major developments to the regime relating to safety monitoring of medicines.

The NOM for pharmacovigilance (NOM-220-SSA1-2012) has been fairly recently updated, establishing that marketing authorisation holders basically must:

- report to the health authorities any adverse event, or suspected adverse reaction, that they are aware of and which may have been caused by their products manufactured or marketed in Mexico;
- have standard operating procedures;
- receive any report of suspected adverse reactions from any possible source;
- record, validate and identify any reports of misuse or abuse reported by health professionals or patients;

- record and monitor any information related to any product used during lactation and pregnancy;
- investigate serious and unexpected cases;
- estimate the frequency of suspected adverse reactions and investigate the possible risk factors with intensive pharmacovigilance studies (at the request of the health authorities);
- ensure the confidentiality of the identity of patients and reporters; and
- holders of marketing authorisations must submit reports periodically.

The NOM for good manufacturing practices of medicinal products (NOM-059-SSA1-2015) has been fairly recently updated, requiring a programme to recall products that do not meet quality standards to be implemented in an appropriate and efficient manner. This programme should essentially include those activities planned for recalling products in a rapid and effective manner, storage, and a list of authorities to be notified according to the distribution of the product. Marketing authorisation holders must report to COFEPRIS any product recall decision, providing details of these products, causes and a store centre. This NOM is currently under a new updating process in order to adjust this with those standards of the Pharmaceutical Inspection Convention or Pharmaceutical Inspection Co-operation Scheme.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

Within the Ministry of Health there is a National Committee for Vaccination, which implements and elaborates the public policies for vaccination and the prevention of diseases in Mexico. There is no obligation for an individual to be vaccinated unless it is an emergency situation requiring vaccination. The obligation to vaccinate the population is on the government through the different federal, local or municipal health entities, which should provide the population with the required vaccines free of charge in order to obtain universal coverage.

Official Norm NOM-036-SSA2-2012 establishes the standards and goals for vaccination of the population, listing the required vaccines and identifying the characteristics of the subjects of the vaccination. Control of vaccination through the National Health Card and the safety, efficacy and quality of the vaccines and biologics are also warranted in this official regulation. There is a principle of free and universal coverage for the listed vaccines in this Official Regulation.


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Muñiz IP

Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The General Law of Health (Law No. 26842) establishes the main framework of the Peruvian healthcare system as follows:

- the state has primary responsibility for public health. Responsibility for individual health is shared among the individual, society and the state;
- healthcare provision is in the public interest, regardless of the person or institution that provides that care. As such, the state is responsible for promoting conditions to ensure adequate coverage of health services to the population under socially acceptable terms regarding safety, timeliness and quality;
- the state is responsible for providing public healthcare services in accordance with the principles of equity;
- the state promotes universal and progressive insurance cover for citizens to protect the contingencies that may affect their health, and guarantees free choice of insurance systems, a system that is subject to a state-imposed mandate that no one is left unprotected;
- state funding is preferably allocated to public health actions, and to subsidise all or part of the medical care for low-income individuals who do not have coverage under another health-benefit system, whether public or private; and
- the standard of the population's health is a matter of public policy, and the healthcare system regulates health issues and the protection of the environment for health and medical care to allow for the recovery rehabilitation of people's health.

The health system in Peru consists of both a public and a private sector.

There are four types of national insurance within the public sector: the Seguro Integral de Salud scheme (SIS), which is mandated by the Ministry of Health (MINSa), national insurance services rendered by EsSalud, the Armed Forces (FFAA) and National Police (PNP). Coverage for EsSalud and the Armed Forces is achieved through employment contributions by working families and individuals.

In addition, MINSa mandates certain public hospitals that offer healthcare services, regardless of insurance coverage. At these public hospitals, the government provides healthcare to the uninsured population in exchange for a variable fee at the sole discretion of the individual hospitals or organisations, or through SIS.

2 How is the healthcare system, financed in the outpatient and in-patient sectors?

Healthcare is mostly financed through contributions from both public and private sector workers. Employers and employees both pay a tax to grant individuals access to public healthcare services.

Compliance - pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

The following legislation governs advertising of medicinal products:

- the Law on Suppression of Unfair Competition (Legislative Decree No. 1044);
- the General Law of Health (Law No. 26842);

- the Law on Pharmaceutical Products, Medical Devices and Sanitary Products (Law No. 29459);
- the Regulations for the Registration, Control and Sanitary Surveillance of Pharmaceutical Products, Medical Devices and Sanitary Products (Supreme Decree No. 016-2011-SA) and amendments;
- the Regulations on Pharmaceutical Establishments (Supreme Decree No. 014-2011-SA) and amendments; and
- the Administrative Directive which regulates the activities of medical sales representatives or other actors of pharmaceutical companies in the Health Facilities (Ministerial Resolution No. 413-2015/MINSa).

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

Law No. 29459 contains a chapter dealing with promotion and advertising. This chapter states that the promotion and advertising of pharmaceutical products and medical devices to be sold only by prescription must be exclusively targeted at those professionals who prescribe and dispense; as an exception, advertisements used to introduce products into the market can be advertised in the mass media.

The other main rules regarding advertising are stated in Supreme Decree No. 016-2011-SA and in Ministerial Resolution No. 413-2015/MINSa:

- the promotion and advertising of pharmaceutical products or medical devices to be sold only by prescription shall contain the technical information sheet in the corresponding technical report. Such information must be provided in a legible, visible, truthful and accurate manner, and must be complete and updated;
- for advertising of pharmaceutical products or medical devices to be sold only by prescription, disseminating clinical or pharmacological information shall be documented and updated in their sanitary registration; and
- samples of pharmaceutical products authorised for sale by medical prescription may only be distributed to prescribing practitioners (physicians, dentists and obstetricians).

5 What are the main rules and principles applying to advertising aimed at the general public?

Law No. 29459 establishes the following main rules:

- advertising through means that are available to the general public is related only to over-the-counter products;
- the Law further states that such advertising must contain the name of the product, dose, concentration or dosage, as applicable;
- if such advertising refers to the therapeutic indications or pharmacological actions of the product, it must necessarily also mention the main warnings and precautions regarding the product; and
- advertisements should not contain any exaggerations or other inaccuracies regarding a product's properties that are likely to mislead consumers or encourage self-medication and irresponsible use.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The most common infringement committed by distributors is advertising prescription-only medication to the general public.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

Advertising pharmaceuticals without their registration in the sanitary register is forbidden. Advertising for off-label use is also forbidden.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

The following regulations refer to collaboration between the pharmaceutical industry and healthcare professionals in both the outpatient and in-patient sectors (eg, physicians, dentists, pharmacists and obstetricians):

- the General Law of Health;
- Law No. 29459;
- Supreme Decree No. 016-2011-SA and its amendments;
- Supreme Decree No. 014-2011-SA and its amendments;
- the Regulations on Clinical Trials in Peru (Supreme Decree No. 017-2006-SA) and its amendments; and
- Ministerial Resolution No. 413-2015/MINSA Administrative Directive which regulates the activities of medical sales representatives or other actors of pharmaceutical companies in the health facilities.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The main rules and principles concerning the relationship between the pharmaceutical industry and healthcare professionals can be found in the legislation mentioned in question 8.

Physicians, dentists and obstetricians are authorised to receive medical samples (General Law of Health, article 26 and Supreme Decree No. 0162011-SA, article 196).

Peruvian regulations point out that medical sales representatives should not encourage unethical practices of prescribing or dispensing pharmaceuticals or medical devices, through courses, awards, trips or others. In addition, those that work for public hospitals are considered to be government officers, therefore, they are not allowed to receive donations or direct payments from pharmaceutical companies.

Professional bodies and private associations such as the National Association of Pharmaceutical Manufacturers (Alafarpe) have codes of conduct or ethics to which they expect their members to adhere. Members of Alafarpe also subscribe to the International Federation of Pharmaceutical Manufacturers Associations' Code of Practice (IFPMA Code).

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

Some manufacturers tend to provide information about off-label use to healthcare professionals in order to give extra benefits to their products, which is a practice not allowed in Peruvian regulations. It is mandatory that the advertising of pharmaceutical products under prescription shall be documented and updated in its sanitary registration (SD N° 016-2011-SA Art. 191°).

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

Peruvian legislation does not contain rules about the collaboration of the pharmaceutical industry with patient organisations.

As mentioned in question 9, members of Alafarpe sign and adhere to the IFPMA Code, one of the principles of which is the 'promotion and support of ethical practices'. The code contains a specific chapter on interactions with patient organisations and states:

- all interactions with patient organisations must be ethical, and the independence of patient organisations must be respected;
- when working with patient organisations, companies must ensure that the involvement of the company and the nature of that involvement are clear from the outset. No company may require that it be the sole funder of the patient organisation or any of its programmes;

- companies that provide financial support or in-kind contributions to patient organisations must have in place written documentation setting out the nature of such support, including the purpose of any activity and its funding; and
- companies may provide financial support for patient organisation meetings provided that the primary purpose of the meeting is professional, educational and scientific in nature, or otherwise supports the mission of the patient organisation. When companies hold meetings for patient organisations they must ensure that the venue and location are appropriate and conducive to informational communication. In addition, any meals or refreshments provided by a company must be modest as judged by local standards.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes. According to the Repression of Anticompetitive Conducts Law (Legislative Decree No. 1034), competition law is applicable to all natural or legal persons, whether public or private (and whether state or non-state), that supply or purchase goods or services. The law is enforced by the Commission for the Defence of Competition at the National Institute for the Defence of Competition and Protection of Intellectual Property (INDECOPI).

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes. According to Legislative Decree No. 1034 (article 49), any person who has suffered damages from anticompetitive conducts (as declared by INDECOPI) is able to claim compensation before the judiciary.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

In our legislation, there are no specific anti-corruption and transparency rules applicable to pharmaceutical manufacturers. The law is general and applicable to all industries and fields. Our anti-corruption legislation is contained in the Criminal Code, specifically under the following provisions:

- illegal collusion (article 384);
- bribery (articles 393–398); and
- incompatible negotiation (article 399).

Compliance - medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

The regulation of advertising of medical devices is the same that regulates pharmaceuticals products.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

Law No. 29459 and Supreme Decree No. 016-2011-SA and amendments thereof set forth the conditions for granting sanitary registrations (marketing authorisations) of a pharmaceuticals, medical devices and sanitary products, and for placing them on the market.

17 Which authorities may grant marketing authorisation in your jurisdiction?

The Medicines, Medical Supplies and Drug Administration (DIGEMID) (a sector agency within the Ministry of Health), as the national authority of pharmaceutical products, medical devices and sanitary products, is in charge at a national level for registering, re-registering, modifying, refusing, suspending or cancelling the sanitary registrations and marketing authorisations of products listed in Law No. 29459 and its Regulations, as well as for the sanitary control and surveillance thereof.

18 What are the relevant procedures?

There are two relevant procedures.

Biosimilar products

Registration of biological products may be applied on grounds of similarity. Interested parties must comply with requirements established for biological products as set forth in article 104 of Supreme Decree No. 016-2011-SA, except for points 13 and 14 of article 104, which shall be replaced by pre-clinical and clinical studies showing how the similar biological product compares with the reference biological product as to efficacy and safety.

Documents must be submitted to prove comparability of the quality of the similar biological product with the quality of the reference biological product. Any difference in quality features of similar biological products with respect to reference products must be justified, as well as its implications on product's safety and efficacy.

The degree of similarity in terms of quality between the reference biological product and the similar product determines the extension of any pre-clinical and clinical studies.

The specific aspects of the quality requirements, pre-clinical and clinical studies of biological products claiming biological similarity are indicated in SD N° 011-2016-SA and SD N° 013-2016-SA taking into consideration scientific progress and the recommendations of the WHO.

Data protection (Regulation of Legislative Decree No. 1072, protection of test data and other undisclosed information related to pharmaceuticals)

Data protection shall be granted by the health authority to an applicant when they have not previously obtained a sanitary registration in Peru for a new chemical entity, and the generation of such test data or other data on safety and efficacy not disclosed has led to considerable efforts on the part of the applicant.

Data protection must be requested in the dossier for obtaining sanitary registration.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

No. Licences will not become invalid if products are not commercialised.

It should be noted, however, that the effective term of the sanitary registration of all products comprised within the scope of the applicable regulations is five years, counted as from the date of granting. An application for re-registration may be submitted as from the year immediately preceding the expiry of the sanitary registration.

20 Which medicines may be marketed without authorisation?

According to article 8 of Law No. 29459, all pharmaceuticals require a marketing authorisation. Article 6 of the Law establishes the classification of pharmaceutical as follows:

- medicines;
- herbal medicines;
- diet products and sweeteners; and
- biological products.

DIGEMID provisionally authorises the import, manufacturing and use of pharmaceutical products, medical devices and sanitary products without granting sanitary registration or under conditions not established in the sanitary registration in the following cases, which must be duly substantiated:

- for use in situations when urgency or an emergency situation has been declared;
- solely for research purposes;
- for training purposes;
- for disease prevention and for treatment of a specific individual (see question 21); and
- in public health situations where the need and unavailability of the product on the national market is demonstrated.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

There are two kinds of named patient programmes.

Prevention and individual treatment (Supreme Decree No. 016-2011-SA)

DIGEMID authorises the import and use of pharmaceutical products, medical devices or sanitary products in cases where the product or device is not registered in Peru or, despite being registered, is not sold, without the prior presentation of an appropriate medical justification issued by a prescribing doctor and a report indicating the characteristics of the product or device.

The interested party must submit the following:

- an application that acts as a sworn statement;
- a medical justification issued by a prescribing doctor, and a report indicating the characteristics of the product or device; and
- a list of the pharmaceutical ingredient (expressed in dose unit or concentration), manufacturer and country of authorisation.

Compassionate use (SD No. 017-2006-SA)

Compassionate use is understood to be the use in-patients, as an exception and without a clinical trial, of an investigational product even with health registration for indications or for use under conditions other than those authorised, when the physician administering the treatment considers it to be essential. Such use will be at the patient's exclusive expense.

In order to use an investigational product, even with a health registration, under compassionate use conditions, the written informed consent of the patient (or his or her legal representative), a clinical report by the physician who intends to administer the treatment justifying the need for such therapy, the approval of the director of the institute where the treatment will be provided, and the authorisation of the General Direction of Medications, Supplies and Drugs, shall be required in each specific case.

The physician administering the therapy shall communicate to the General Direction of Medications, Supplies and Drugs the outcome of the therapy within an established time frame, as well as any suspected adverse reactions to the drugs as a result of that therapy, without prejudice to the communication of any adverse reactions to the pertinent territorial decentralised agency.

Pricing and reimbursement of medicinal products**22 To what extent is the market price of a medicinal product governed by law or regulation?**

Peruvian laws do not establish specific provisions concerning medicinal product pricing for either the outpatient or in-patient sectors. Rather, a free market pricing system is in place in Peru.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

No; there is no such negotiation with public healthcare providers. Sales to public health institutions are made through selection processes (public bids), and the offer prices are not negotiable.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

In both the outpatient and in-patient sectors, reimbursement of costs applies only to insured patients.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

Since there is no price regulation for medicinal products according to Peru's legislation, no such competent body exists.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

No. Since prices are not regulated, manufacturers and distributors are free to set prices and to give discounts.

Update and trends

The free trade agreement (FTA) Peru signed with the US, which has been in force since February 2009, has brought new challenges and opportunities to the pharmaceutical sector, mainly with regard to intellectual property, competition and sanitary regulation matters.

Important regulatory changes are still taking place regarding the above; therefore, the pharmaceutical industry should take advantage of the opportunity to deploy its resources in the manner most efficient to face the competition from generic drugs and copies of originator medicines that are plentiful on the market.

Andean Decision 486 regulates pharmaceutical patents in the Andean Community. The Decision does not contemplate any additional term to make up for unjustified delays by the Patent Office; since no linkage exists between sanitary registration and patents being in force, the Ministry of Public Health is trying to have compulsory licences imposed on HIV and oncology medicines.

Regarding competition and advertising of pharmaceutical products, no control exists over the merger of pharmaceutical companies.

In addition, no prior control exists over advertising because such advertising is only audited after the advertisement has been disclosed.

Investors in the Peruvian pharmaceutical sector must bear in mind the following sanitary regulation matters.

Test data protection for pharmaceutical products

A Special Law for Test Data has been in force since February 2009. At the time of writing, DIGEMID awarded test data protection to more than 45 active ingredients that meet the definition of new chemical element and all other requirements established in the Law for Test Data and in health legislation. As of November 2016, 28 active ingredients have current data protection.

All legislative changes regarding intellectual property and health matters have resulted from the commitments undertaken by Peru under the above-mentioned FTA between Peru and the US.

Two further agreements also regulate the protection of test data: the FTA signed with the European Free Trade Association countries (Iceland, Liechtenstein, Norway and Switzerland), and the trade agreement signed between the EU and its member states, on the one side, and Colombia and Peru, on the other.

It is noteworthy that the Trans-Pacific Partnership, recently signed, will provide a five-year data protection agreement for biologicals too.

Equivalence studies

The implementation of bioequivalence and bioavailability procedures for certain products to obtain sanitary registration means that it will be possible for Peru to place products on the market that can be interchanged with the original products after studies have been filed with and reviewed by the regulatory authority (in other words, quality generic products). The Sanitary Authority is in charge of implementing the local regulations and is responsible for ensuring effective compliance with these rules.

Biological products

For the first time, Peru is devising special regulations for biological products, which will directly benefit patients.

Unlike chemical drugs (or chemical synthesis), biological drugs cannot have generic products because of their nature, because they are produced from genetically modified living cells.

As no regulations existed for biological products, many biological (or biosimilar) products entered into the market without the requirement of any information to prove that they are safe and effective, or comparative, if applicable. In many cases, these products have not been allowed entry into the US or EU markets, because they are not supported by clinical studies, or have not met the minimum guarantees required by the US and EU regulatory frameworks.

Alafarpe has implemented a precautionary measure under which it is mandatory for DIGEMID, in a provisional and preventive manner, to abstain from registering in the health registries similar or biosimilar medicines that do not comply with the quality, safety and efficacy criteria and recommendations of the WHO and scientific progress. On September 2015, the final resolution that confirms the precautionary measure, has been issued.

Finally, two regulations about biologicals and biosimilars were published in February 2016 (SD N° 011-2016-SA and SD N° 013-2016-SA). These regulations require that the holders of biologicals inform the competent authority if the products are biosimilars or not. There are specific timelines the holders must meet or the sanitary registrations will be cancelled.

Education

Pharmacists and lawyers are receiving specialised training in courses and postgraduate programmes on intellectual property and pharmaceutical law at Cayetano Heredia University, which is the most recognised educational institution in Peru for life sciences.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

The legal rules available to fight drug counterfeiting and illegal distribution are contained in the Criminal Code, specifically in articles 294-A and 294-B:

- whoever forges, contaminates or adulterates pharmaceutical products, medical devices or health products, or tampers with their expiry date, will be punished with imprisonment for a term not shorter than four years or longer than 10 years, plus a fine amounting to between 180 to 365 days' profit;
- whoever knowingly imports, markets, stores, transports or distributes pharmaceutical products, medical devices or health products under the above-mentioned conditions will be subject to the same punishment; and
- whoever sells, imports or markets pharmaceutical products, medical devices or health products after their expiry date, or whoever stores, transports or distributes said products for marketing purposes after their expiry date, will be punished with imprisonment for a term not shorter than four years or longer than eight years, plus a fine amounting to between 180 to 365 days' profit.

Aggravating circumstances are stated in article 294C:

- when serious injuries or death are caused that could have been prevented by the agent, the term of imprisonment will not be shorter than eight years or longer than 15 years;
- if the agent is the technical director, or his or her designee, of a pharmaceutical establishment or health facility, then he or she will also be disqualified from holding public office, as outlined in paragraphs 1, 2 and 4 of article 36; and

- likewise, the supply of counterfeit pharmaceutical products can be fought through administrative channels.

Under Andean Decision 486 and Legislative Decree No. 1075, the owner of a registered trademark or patent in Peru may take action against those who use fake pharmaceutical products that violate their trademarks or patents.

The owner may apply for an injunction to force the infringing party to cease its marketing activities and also to force the cessation, and seizure or confiscation of, fake products. They may also ask that the infringer be punished with a fine.

The administrative authorities that deal with such cases are the Distinctive Signs Commission (for trademarks) and the Committee of Inventions and New Technologies (for patents).

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

The Ministry of Health conducts public campaigns in order to counteract self-medication, which is a common practice in Peru. In addition, the supervision of pharmacies has been intensified, as a result of which self-medication by antibiotics has been significantly reduced.

Furthermore, the Ministry of Health promotes the use of generic drugs through public awareness-raising campaigns that highlight the significant savings they offer to patients by outlining that generic drugs have the same quality of pharmaceuticals as those found in originator medicines. This issue continues to be a topic of discussion.

29 Outline major developments to the regime relating to safety monitoring of medicines.

Supreme Decree No. 013-2014-SA defines the members and objectives of the Peruvian pharmaceutical and technical surveillance system. The Regulation is a sign that Peru's pharmacovigilance system is currently under review, and that the monitoring and evaluation of the safety of pharmaceutical products and medical devices will improve in the near future.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

The Vaccine General Law (Law No. 28010) regulates the purchase by the Ministry of Health of vaccines, syringes and cold chain equipment

used in vaccination schemes using funds allocated for this purpose in the budget. Under the Vaccine General Law, the Ministry of Health is responsible for establishing the immunisation schedule.

Additionally, the state has established a national immunisation scheme that includes an exhaustive list of mandatory vaccines. It also has the authority to expand the use of new vaccines for specific diseases, provided such use complies with the purpose of protecting public health. Immunisation under the national immunisation scheme is compulsory for the entire country, and all public, private and mixed institutions within the health sector are involved in administering it.

The state guarantees free vaccines and their administration at regular intervals, in addition to supplementary immunisation activities that are part of the national immunisation schedule. Each immunisation is registered in a patient's clinical history and vaccination card.



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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The manner in which healthcare in Portugal is organised has been subject to many changes in the past few years. Organic changes have taken place regarding which state entities are responsible for centralising purchases for state hospitals. Public tenders to select suppliers for the Portuguese National Health System (NHS) have been launched through electronic platforms, and there have also been some changes regarding the entity that organises such public tenders. These changes have created some difficulties for pharmaceutical industry players that sell to NHS hospitals. Furthermore, public expenditure cuts have affected the prices of medicinal products that are reimbursed by the NHS, and have driven the government to propose the creation of a further tax applicable to pharmaceutical industry sales.

The extraordinary charge on the pharmaceutical industry (designated as ‘a special charge on the pharmaceutical industry’) was created by the 2015 State Budget, approved by Law 82-B/2014 of 31 December, which entered into force on 1 January 2015 with the aim of ensuring the sustainability of the NHS, in terms of its expenditure on medicinal products, which applies to entities that are carrying out the first sale of a medicinal product for human use in the Portuguese territory, both where such entities are holders of marketing authorisations or registrations, or are their representatives, intermediaries, wholesale distributors or suppliers holding exceptional use authorisations or other exceptional authorisations for use of medicinal products, remained in force for 2016 and now again for 2017. The extraordinary charge is applicable to the amount of the quarterly sales of the following medicinal products:

- medicinal products that are reimbursed by the NHS;
- medicinal products that are subject to a restricted medical prescription;
- medicinal products that are sold through exceptional or special use authorisations (eg, named patient authorisations);
- medicinal products that are medicinal gases, or human blood or plasma-derived products;
- packaged medicinal products aimed for use in hospitals; and
- orphan medicinal products.

The amount of the extraordinary charge varies between:

- 2.5 per cent for reimbursed medicinal products included in homogeneous groups or not included in homogeneous groups for which a marketing authorisation has been granted at least for 15 years and with a price inferior to €10; medicinal gases and derivatives from human blood or human plasma; and orphan medicinal products;
- 10.4 per cent for reimbursed medicinal products not covered by the 2.5 per cent rate; and
- 14.3 per cent for medicinal products subject to a restricted medical prescription, as well as those that have an exceptional use authorisation or exceptional authorisation or are intended for hospital consumption.

The sales amount to be considered regarding medicinal products that are reimbursed by the NHS will correspond to the portion of the sale price to the public that is reimbursed by the NHS after deducting VAT and another charge on the marketing of medicinal products (called a ‘tax on the sale of commercialised medicines’).

This regime provides an exemption of payment of the extraordinary charge by all entities that, individually and unreservedly, adhere to the agreement between the Portuguese state, represented by the Finance and Health Ministries and the Portuguese Pharmaceutical Industry Association (Apifarma), which sets the goals for maximum amounts of public expenditure with medicinal products and of charge according to the sales volume of the pharmaceutical industry companies in order to attain such goals. The entities that adhere to the mentioned agreement shall declare it to Infarmed (the Portuguese National Agency for Medicines), and are exempted from the payment of the extraordinary charge; however, they will be nevertheless subject to another charge under specific terms of the mentioned agreement.

The extraordinary charge shall be paid through a declaration with an official template (which was approved by Ministerial Order 77-A/2015 of 16 March) and the non-compliance of this obligation results in the compulsory collection of the charge by the tax authorities.

Organisation of healthcare

The Portuguese Constitution establishes the right of all Portuguese citizens to benefit from public healthcare, which is provided through a healthcare system that should cover the whole population and that should be universal. Citizens of other member states of the EU may be entitled to public healthcare in accordance with the applicable EU rules. Foreign citizens that are resident in Portugal may also benefit from public healthcare provision in the case of a reciprocal agreement with the foreign national’s state.

The main principles and rules governing public healthcare and the structure of the healthcare system are established in the 1990 Health Law (Law 48/90, 24 August 1990).

Hospitals, healthcare centres for outpatients and other entities included in the NHS comprise the healthcare providers in Portugal. The NHS depends on and is financed by the state and the public budget. Private entities and professionals may also render healthcare services to NHS patients pursuant to agreements with the entities representing the Health Ministry.

All of the services and institutions of the NHS fall under the supervision of the Ministry of Health, which is ultimately responsible for the healthcare sector and defining the government’s national healthcare policy.

Successive governments have continued to organise and reorganise the NHS through the years, mainly since 2002, specifically regarding the nature and functioning of the hospitals integrated in the NHS and the creation and extinction of public bodies and entities.

In 2002, rules were approved respecting health public-private partnerships (Decree Law 185/2002, 20 August 2002) and the rules clarifying the legal framework applicable to each type of hospital integrated in the NHS (Law 27/2002, 8 November 2002).

Hospitals may have different legal forms. Some remain public hospitals, but the majority are now public corporate entities, which are regulated by public law rules but have a certain degree of autonomy with regards to their management. The quality of healthcare services and equipment, generally speaking, is not at stake. The main discussion point regarding the NHS has been the excessive cost for the public budget.

Presently, Portugal is divided into five health regions with healthcare centres serving the outpatients of each region, and approximately 52 public hospitals.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The financing of the healthcare system is governed by the Constitution, which states that the right to benefit from public healthcare is ensured through a universal healthcare system, taking into account the social and economic conditions of all citizens, which tends to be cost-free for patients.

The NHS is financed by the state budget. Fees can be charged to certain outpatients, based on a co-payment scheme, but they only represent a small part of the cost of the service. In compliance with the reform programme, in January 2012, a new legal framework came into force regarding patients' moderating fees (Decree-Law No 113/2011, 29 November 2011). There are exemptions, for example, for pregnant women, children up to 12 years of age, patients with an incapacity level equal to or higher than 60 per cent and patients in a situation of financial insufficiency. Patients with an average monthly income lower than €628.83 are exempt from patient moderating fees. In April 2015, the exemption was expanded in order to cover minors.

The NHS's debt to pharmaceutical companies amounted to €821 million in August 2016, with an average payment period of 385 days in 2016.

At the end of 2013, the Ministry of Health implemented for the evaluation of medical care. The purpose is to evaluate the NHS's human resources. If further human resources are required, they should be hired through employment agreements instead of services agreements with providers of medical services. All results are currently published on the website of the Portuguese Health Regulation Authority (ERS), where they may be obtained according to rating indicators. In 2016, 160 hospitals were evaluated under SINAS according to various parameters, namely clinical excellence, patient security, facilities adequacy and comfort, focus on the patient and patient satisfaction. Seventy-nine per cent of hospitals were evaluated and 66 per cent obtained the first level, which means that they all met quality standards.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

The rules regarding advertising of medicinal products are contained in the Code of Medicinal Products approved by Decree-Law 176/2006 (30 August 2006) (Code of Medicinal Products), which was amended by Decree-Law 128/2013 (5 September 2013), imposing further notification obligations to Infarmed both on the payee and on the receiver with respect to any type of sponsorship, benefit or value in money, goods or right that may have a monetary value. The Code also transposes Directive 2001/83/EC on the Community code relating to medicinal products for human use (as amended) into national law. The Advertising Code approved by Decree-Law 330/90 of 23 October governs advertising in general, including all the aspects regarding the advertising of medicinal products not specifically set out in the Code of Medicinal Products. Regarding medical devices, Decree-Law 145/2009 of 17 June 2009 should also be considered, since it established the respective legal framework.

Most recently, Decree-Law 238/2015 of 14 October 2015 was published in order to regulate health advertising practices, by interventions of public or private nature. The Decree-Law covers advertising that aims to promote all acts carried out in order to protect or maintain health or to prevent and treat diseases, including the offer of diagnosis, as well as any other treatments or therapies and non-conventional therapies. This Decree-Law forbids any health advertising practices that:

- may mislead the patient regarding the characteristics of a certain act or service;
- may induce the patient into the acquisition of an act or service;
- contain false demonstrations and guarantees of cure or inexistence of side effects;
- may be misleading regarding the nature, attributes and rights of the intervention in favour of which the advertising act is being carried out;
- induce the patient into taking a decision regarding a transaction that he or she otherwise would not have taken and that involve an activity likely to create confusion between acts or services, brands and commercial names of a direct or indirect competitor or to create a conviction of quality through the misuse of a brand or

distinguishing marks or by claiming attributes not associated with such brands or marks;

- describe the act or service as 'free', 'free of charge' or 'with discount' or 'with promotion' if the patient has to pay a higher amount than the expected amount to respond to such advertising act; or
- propose the acquisition of acts or services at a certain price, with the intention to promote a different act or service, and afterwards refuse to offer the patient the act or service initially advertised.

Furthermore, the Decree-Law also prohibits any health advertising practices that limit or may limit significantly the freedom of choice or the behaviour of a patient concerning a certain act or service, may induce unnecessary or harmful consumption or any practices carried out through contests, draws or similar activities that promote health acts or services through the offering of prizes or other kind of awards. Any breach of the provisions established by this Decree-Law is sanctioned with a fine of €250 up to €3,740.98 for natural persons and €1,000 up to €44,891.81 for legal persons. The Decree-Law entered into force on 1 November 2015.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

The Code of Medicinal Products establishes that all advertising to healthcare professionals must include the following:

- the name of the medicinal product;
- essential information compatible with the summary of the product characteristics (SPC);
- the supply classification of the medicinal product (namely, if the supply depends on medical prescription); and
- if the medicinal product's cost is reimbursed by the state.

Adverts to health professionals that consist of a mere reminder should be composed only of the name of the medicinal product.

Prescription-only medicines may only be advertised to healthcare professionals. Furthermore, only products that have a valid marketing authorisation or registration in Portugal may be advertised within the Portuguese territory.

Infarmed is responsible for the manufacturing and marketing authorisation of medicinal products. All activities regarding the life cycle of medicinal products are subject to its regulation and supervision, including the advertising of medicinal products. Advertising to healthcare professionals is subject to the rules contained in Infarmed Regulation 44/CD/2008, which states those cases where, taking into account the advertising medium, a reduced version of the essential information compatible with the SPC may be included.

In 2013, the Code of Medicinal Products was subject to two major changes. In February 2013, it was amended by Decree-Law No. 20/2013 (14 February 2013), transposing Directive 2010/84/EU (15 December 2010) as regards pharmacovigilance. Subsequently, the Code was further amended in September 2013 by Decree-Law No. 128/2013 (5 September 2013), transposing Directive 2009/35/EC (23 April 2009) on the colouring substances that may be added to medicinal products, as well as Directive 2011/62/EU (8 June 2011) as regards the prevention of the entry into the legal supply chain of falsified medicinal products and Directive 2012/26/EU (25 October 2012) as regards pharmacovigilance. Other substantial amendments introduced into the Code include those regarding the advertising of medicinal products.

According to the above-mentioned new legal provisions, entities covered by the Code of Medicinal Products must submit a report at the Infarmed transparency platform within 30 days of any offer, sponsorship, grant, or any other amount, good or right assessable in cash terms, granted to any entity (regardless of its form or nature), individual, association or representative of a certain-patient group or medical company, association or corporation that is scientifically oriented or conducting clinical studies.

The payment and receipt of salaries or regular and periodic payments, in cash or in kind, owing to an employment contract or fees paid for services provided by independent workers are not subject to the duty of notification. Furthermore, the recipients of these benefits, which include not only the previously mentioned associations or corporations but also any entity or individual (namely healthcare professionals), must notify Infarmed and register such benefit on Infarmed's website. Since 7 October 2014, these rules only apply to transfers of a

value exceeding €60 (prior to 7 October 2014, these rules applied to transfers of a value exceeding €25). Infarmed further clarified that any hospital, service or medical society that organises a certain congress must be identified as the beneficiary of the event, and not the healthcare professionals individually considered. The main rule in this respect is aimed at preventing any type of prescription incentives; therefore, the holders of the marketing authorisation or of the registration of medicinal products, as well as companies responsible for the promotion of medicinal products and wholesale distributors, are not allowed to directly or indirectly give or promise to healthcare professionals or their patients prizes, offers, bonuses or pecuniary benefits or benefits in kind unless they are insignificant and relevant for medical or pharmaceutical practice.

5 What are the main rules and principles applying to advertising aimed at the general public?

Only medicinal products with a valid marketing authorisation or registration in Portugal that are classified as not subject to medical prescription can be advertised to the general public.

Furthermore, such medicinal products must not contain psychotropic or narcotic substances or benefit from state subsidy.

Pursuant to the Code of Medicinal Products, vaccination campaigns or campaigns promoting generic medicines carried out by the industry and approved by Infarmed may be advertised to the general public is also prohibited.

The use of comparative messages in advertisements to the general public is not allowed and the direct supply of medicinal products to the general public.

Advertisements to the general public must contain the following information:

- the name of the medicine and international non-proprietary name or brand name;
- the essential information for the rational use of the product, including therapeutic and special precautions; and
- a warning to the patient to peruse the information in the outer packaging and in the package leaflet, and to contact a doctor or a pharmacist if symptoms persist.

Decree-Law No. 20/2013 (14 February 2013) also amended the provisions regarding advertising of medicinal products to the general public. According to this modification, the prohibition to directly or indirectly give or promise prizes, offers, bonuses or pecuniary benefits or benefits in kind to health professionals is also applicable to the general public.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The most common infringements committed by manufacturers regarding advertisement rules arise from the misinterpretation of the advertising rules regarding comparative advertising. Since 2012, an increasing number of infringement procedures have been started by Infarmed. Until the second quarter of 2016, Infarmed evaluated 999 advertising materials, of which 650 concerned medicinal products and 349 concerned health products. During 2016, Infarmed maintained the monitoring of advertising materials submitted through the Medicinal Products Advertising System and improved the management platform for reporting, which improved the transparency of its functioning. Furthermore, Infarmed continues to ensure the compliance of market players with the principles applicable to the promotion of the rational use of medicinal products, medical devices and cosmetic and body hygiene products.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

The inclusion of information regarding off-label use in advertisements is not permitted, as advertisements to health professionals must contain essential information compatible with the SPC. It is not forbidden, however, to provide information regarding off-label use at a scientific event organised for healthcare professionals pursuant to the Code of Medicinal Products. Furthermore, it is permitted to provide information regarding off-label use of a product in answer to a specific question addressed by a health professional to the company holding the marketing authorisation of such product in Portugal.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

The legislation that applies to the collaboration of the pharmaceutical industry with healthcare professionals is the Code of Medicinal Products (articles 157 to 162), which regulates:

- the activities of medical sales representatives;
- offers and grants;
- consulting services;
- advertising at and transparency of scientific, training or promotional events for health professionals;
- hospitality costs; and
- free samples.

These rules were subject to substantial changes in 2013 with a view to ensuring greater transparency regarding sponsorships and grants in amounts exceeding €60 (since 7 October 2014) given by the pharmaceutical industry to any public or privately held entity or to any individual.

The Code of Ethics regarding the promotional practices of the pharmaceutical industry in collaboration with healthcare professionals approved by Apifarma regulates these matters in detail. The same rules apply to physicians in both the outpatient and in-patient sectors.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

Holders of marketing authorisations for medicinal products must create and maintain a scientific service responsible for maintaining information about, and advertising regarding, all medicinal products.

Medical sales representatives must have adequate training and scientific knowledge to provide accurate and complete information regarding medicinal products.

Providing or promising gifts, pecuniary advantages or benefits in kind to health professionals is forbidden, unless they are inexpensive and relevant to the practice of medicine or pharmacy activities. An object will be considered inexpensive if its value does not exceed €60.

The sponsorship of events, seminars, congresses or any scientific or promotional event or action, either directly or indirectly, by a manufacturer, holder of a marketing authorisation or distributor of medicinal products, must be mentioned in the documentation related to such events and must be notified to Infarmed within 30 days of the event. Training or informative events and sales promotions may only be addressed to healthcare professionals. There are also hospitality rules that limit the number of days events can run and the selection of the location of events.

Free samples are allowed within certain limits – 12 samples per product, per year to each healthcare professional – and healthcare professionals must request the samples in writing. Each sample shall be no larger than the smallest presentation and accompanied by a copy of the SPC.

Apifarma's Code of Ethics covers all the matters relating to the promotional practices of the pharmaceutical industry in collaboration with healthcare professionals, clarifying certain rules by providing further details and guidelines to companies regarding the practices that are allowed.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

The most common infringements committed by manufacturers and distributors arise from misinterpretation of the rules applicable to promotional events and to advertising in publications addressed only to healthcare professionals. These infringements are considered as violating the very broad and undefined rules stating that advertising 'shall encourage the rational use of the medicinal product by presenting it objectively and without exaggerating its properties'.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

The main principles applying to the collaboration of the pharmaceutical industry with patient organisations are found in Apifarma's Code of Ethics. The Code establishes guidelines that state that pharmaceutical companies that intend to render financial support directly or indirectly to patients' associations must enter into an agreement signed by both parties, following a template attached to the Code. Each company must establish an internal procedure regarding the approval of these agreements.

The use by a pharmaceutical company of a logo or other material protected by copyright belonging to a patients' association must be duly authorised. Furthermore, companies should not influence the contents of associations' materials, although they are allowed to suggest material or scientific corrections. A patients' association may not be sponsored exclusively by one company.

According to the Code, companies may organise or sponsor events for patients' associations as long as any hospitality costs are kept within adequate and reasonable limits.

12 Are manufacturers' infringements of competition law pursued by national authorities?

The Portuguese Competition Authority pursues infringements of competition law by manufacturers.

The Portuguese Competition Law (Law 19/2012, 8 May 2012) applies to anticompetitive practices or agreements and mergers that occur in the national territory or that have effects within the national territory.

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes; private antitrust litigation against manufacturers in the case of an infringement of the competition rules that causes damage to third parties is possible.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

The main mandatory anti-corruption rules applicable to pharmaceutical manufacturers, as in general to all entities, are the rules on bribery and active corruption set forth in articles 363 and 374 of the Portuguese Penal Code approved by Decree-Law 48/95 of 15 March 2016, as amended. Any person who commits bribery; those that convince, or try to convince an individual, through an offer or a promise of a material or otherwise benefit by issuing a false statement, a report or provide information that is not provided, being such criminal offense sanctioned with up to two years of imprisonment or 240 days of fine. Committing active corruption on those who directly or indirectly grant or promise to a civil servant, or to a third party with the knowledge of the civil servant, a material benefit or otherwise, to carry out an act or omission against the duties of the civil servant, which is a criminal offence sanctioned with one to five years of imprisonment. The civil servant may be sanctioned for active corruption.

Compliance - medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Medical devices are regulated by Decree-Law 145/2009 (17 June 2009), which establishes the rules regarding investigation, manufacturing, commercialisation, functioning, supervision and advertising of medical devices and respective accessories, and transposes Directive 2007/47/EC into national law. The rules applicable to the advertising of medical devices are identical to the rules applicable to medicinal products.

Advertising to the general public of medical devices that require the intervention and prescription of a healthcare professional, namely implantable devices, is not allowed. Apormed, the Portuguese

association of companies manufacturing and marketing medical devices, has issued a Good Commercial Practice Code with guidelines regarding the relations between companies and healthcare professionals. Supervision of the compliance of companies with these rules might not be as rigorous as it is in the pharmaceutical sector, however in Infarmed's Plan of Activities for 2015, the reinforcement of the monitoring of medical devices advertising is set as a priority.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The Code of the Medicinal Products provides the legislative framework for granting marketing authorisations and manufacturing authorisations, and for the import, export, marketing, labelling, provision of information, advertising, pharmacovigilance and use of medicinal products for humans. This extensive Code transposes six European Union directives into Portuguese law and regulates the entire life cycle of medicinal products in Portugal. In 2013, the Code was substantially amended by Decree-Law No. 20/2013 (14 February 2013), which transposed into Portuguese law three EU directives, and Decree-Law No. 128/2013 (5 September 2013), which transposed a further three EU directives. Two areas are regulated under separate legal frameworks: clinical trials (which are ruled by Law 21/2014, 16/04 - in addition, from 28 May 2016 onwards, Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 will be directly applicable in all EU countries, including Portugal); and medicine pricing and reimbursement (which are ruled by Decree-Law 48-A/2010 of 13/05 and most recently Decree-Law 97/2015 of 01/06).

17 Which authorities may grant marketing authorisation in your jurisdiction?

The sole entity with powers to grant marketing authorisations in Portugal is Infarmed, which is a public institute under the direct administration of the state. Although Infarmed has administrative and financial autonomy, it follows the aims of the Health Minister and acts under the Minister's supervision.

18 What are the relevant procedures?

The procedures that must be followed to obtain a marketing authorisation in any member state of the European Union are regulated by:

- Regulation 726/2004 (31 March 2004) regarding the centralised procedure that must be filed at the European Medicines Agency (EMA) for certain types of medicinal products; and
- EC Directive 2001/83/EC (6 November 2001) regarding the national procedure, the mutual recognition procedure and the decentralised procedure, transposed into Portuguese national law by the Code of Medicinal Products.

The centralised procedure at EMA is mandatory for certain medicinal products, such as those developed by means of a biotechnological process, advanced therapy medicinal products, new active substances for which the therapeutic indication is the treatment of very serious diseases (eg, HIV, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions and viral diseases) and orphan medicinal products.

The centralised procedure may also be followed, on a non-mandatory basis, for active substances that constitute a significant therapeutic, scientific or technical innovation, or that are in the interests of patients' health.

The three relevant procedures that may be filed at Infarmed to obtain a marketing authorisation are as follows:

- the national procedure to obtain a national marketing authorisation;
- the mutual recognition procedure with a view to obtaining recognition in Portugal of a marketing authorisation granted in another member state or vice versa; and
- the decentralised procedure, in which case the applicant files the procedure simultaneously with several agencies of several member states, one of which will act as the reference member state with the responsibility to prepare the assessment report on the medicinal product.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

A marketing authorisation will elapse and cease to be valid if the medicinal product has not been effectively marketed on the Portuguese market for a continuous period of three consecutive years. The holder of the marketing authorisation must notify Infarmed of the date of the commencement of the effective marketing of the medicinal product. If the medicinal product is not marketed during the legal period, the marketing authorisation will become invalid, and such fact shall be published on Infarmed's website. The marketing authorisation holder may challenge the invalidity within 10 days of its publication on Infarmed's website. The invalidity may not be declared by Infarmed, even if the medicinal product has not been sold, in any of the following circumstances:

- the medicinal product was not on the market as result of a legal imposition or a judicial decision imputable to Infarmed;
- there is no therapeutic alternative or alternative manufacturers for the medicinal product in question;
- the medicinal product is a vaccine or a medicinal product for in-patients only that has not been selected in a public tender to supply the NHS;
- the medicinal product at stake may be used in cases of disaster or in pandemic situations;
- if Portugal acts as the reference member state for that specific medicinal product and the validity of the marketing authorisation is therefore necessary to ensure the continuity of the supply in the other member state involved;
- the medicinal product at stake will be exported to a third country; or
- the request to obtain state reimbursement is pending a decision.

20 Which medicines may be marketed without authorisation?

In principle, medicinal products marketed in Portugal must all have a marketing authorisation. However, there are exceptional cases where Infarmed may grant a special-use authorisation or exceptional authorisation (see question 21).

Homeopathic medicinal products may be marketed without an authorisation. These products are subject to a simplified registration process if they do not have specific therapeutic indications placed on the label or on any product information. Furthermore, to qualify for the simplified registration procedure, such products must have a certain pharmaceutical form (oral or external) that does not represent any risk to people.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Named patient programmes are specifically regulated by the Code of Medicinal Products. In exceptional cases, Infarmed may grant a special-use authorisation or exceptional authorisation to medicinal products that are not authorised by the common procedures.

Special-use authorisations may be granted in certain cases listed in the Code, such as in cases where there are medical justifications because the medicinal product is absolutely essential for certain pathologies; the medicinal product is required to combat the spread of harmful agents; or the products are purchased by hospital pharmacies for named patients.

Exceptional authorisations are granted strictly for public health reasons.

On 6 August 2015, Deliberation 1546/2015 of the Health Ministry and Infarmed was published, approving the new regulation regarding the procedures for granting exceptional use authorisations and the marketing authorisation for those medicinal products for which there is a pending application for a medicinal product authorised in another member state for which there is no authorisation or registration in Portugal.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

The market prices of medicinal products are regulated by law. The legal framework applicable to the pricing of reimbursed medicinal products, whether subject to medical prescription or not, is ruled by Decree-Law 97/2015 of 1 June 2015, which created the National System for the Evaluation of Health Technologies (SiNATS) integrating all private and

public entities within the health sector. The health technologies covered by the new Decree-Law include medicinal products, medical devices, or medical or surgical procedures, as well as prevention, diagnosis and diseases treatment measures used in healthcare. SiNATS has as its aim a shift of the paradigm in the manner of use and acquisition of health technologies, including medicinal products and medical devices, contributing to the achievement of health gains and its harmonisation with other European systems aimed at achieving the same goal. This system will allow health technologies to be the subject of evaluation and re-evaluation within an integrated context and with preferential recourse for the establishment of objectives through contracts with authorised marketing authorisation holders. The prices of medicinal products not subject to medical prescription and not reimbursed by the NHS may be freely fixed by intermediary agents in the sales circuit.

The prices of medicinal products subject to medical prescription and products reimbursed by the NHS must comply with very strict rules regarding the calculation of the maximum price for sale to the public (outpatients). These rules are based on an international reference system. The government is responsible for establishing the three reference countries for this purpose on an annual basis; in 2016, the reference countries were Spain, France and Slovakia. Pricing reviews are carried out on an annual or extraordinary basis.

The maximum prices for reimbursed medicinal products must be approved by Infarmed. The annual review of prices for the sale of reimbursed medicinal products to outpatients is established in Ministerial Order 195-C/2015 (30 June 2015). The annual prices review of branded products must be requested by companies each year before 15 December, and the new prices will be applicable from 1 January of the next year. The review of the prices of generic products must be requested by companies each year by 15 January, and the new prices will apply from 1 February of the following year. The annual price review of branded products is based on the average prices in the reference countries on the first day of the month prior to the prices review. The prices of generics must be reviewed based on the price of the reference medicinal product, and may not exceed 50 per cent of the maximum price of the reference medicinal product.

Prices of medicinal products that are subject to restricted medical prescription for hospital use must pass an evaluation test based on Infarmed's technical, scientific and economic criteria to obtain evidence on the respective added therapeutic value and economic benefit.

Following a favourable evaluation, Infarmed will approve the maximum price for sale to NHS hospitals. Decree-Law 34/2013 (27 February 2013) further established an international pricing scheme for medicinal products to be purchased by NHS hospitals that is applicable to medicinal products that are not subject to the prior evaluation procedure. The reference member states for such purpose are the same countries that set the prices of medicinal products to be sold to outpatients (eg, Spain, France and Slovenia).

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

There are two stages involved in negotiations with public healthcare providers. In the first stage, suppliers of the NHS are selected through centralised public tenders, where the manufacturers or holders of the marketing authorisation bid with the maximum price applicable to all NHS hospital and services, pursuant to the rules of the Code of Public Contracts (approved by Decree-Law 18/2008 of 29 January 2008, last amended by Decree-Law 214-G/2015 of 2 October), which is presently being subject to a legislative review by the government. The NHS enters into public supply agreements with the selected suppliers.

In a second stage, regulated by the same Code, each hospital addresses an invitation to suppliers to propose better conditions and win the hospital's contracts, which may involve a negotiation phase.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

The NHS reimburses the cost of certain medicinal products, provided that the following cumulative requirements are met (pursuant to Decree-Law 97/2015 of 1 June 2015): there is technical and scientific evidence of the added value in therapeutic terms or of the therapeutic equivalence for the therapeutic indications of the products; and there is evidence of the economic benefit. Furthermore, reimbursement by the NHS may also depend on the product filling a therapeutic gap in the

Update and trends

In May 2016, Infarmed announced a new programme called Infarmed Simplex with a view to implementing several measures to simplify administrative procedures, namely licensing procedures for the opening of pharmacies. Measures for the replacement of the paper medical prescription by digital prescription have also been approved. Furthermore, namely to encourage the business of pharmacies that have been penalised with considerable decreases in the prices of medicinal products in the past few years, the government approved measures allowing pharmacies to render further services to the community and granted a special remuneration for the sale of generic medicinal products that correspond to the increase of the share of sales of generics by each pharmacy. The good distribution practices for medical devices were approved by the government in Ministerial Order 256/2016 of 28 September 2016, establishing rules and principles that must be respected by all distributors carrying out distribution activities within Portuguese territory, whether they are established in Portugal or not.

market, having new active ingredients, or having a similar composition to other marketed and reimbursed medicinal products but having a price that is 5 per cent lower when compared with the branded equivalent. Reimbursement will also arise in several other cases, essentially following the added therapeutic value or economical added value criteria, or both.

Reimbursement follows a regressive scale of 100 per cent in certain cases for medicinal products subject to restricted medical use (in-patients) or in the case of certain serious pathologies (in-patients and outpatients), and can range from 90 per cent to 15 per cent in other cases (outpatients). Medicines for compassionate use must be provided for free by the manufacturer to the subject of clinical trials even after the trial is completed, if the physician considers that it is essential and that there are no therapeutic alternatives.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

According to the legal framework for pricing established in Decree-Law 97/2015, the competent body for decisions regarding the pricing and reimbursability of medicinal products, whether subject to medical prescription or not, is Infarmed.

Infarmed is competent to authorise the maximum prices for sale to NHS hospitals of medicinal products for restricted hospital use (Decree-Law 97/2015 and Ministerial Order 195-C/2015).

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

Discounts (reducing the maximum fixed prices) are allowed throughout the entire medicinal product circuit (ie, by manufacturers, distributors and retailers), but they are not mandatory. The law sets the maximum marketing margins, calculated as a percentage of the price to the public, which are granted to wholesalers and retailers, but these margins are commercial and do not have the nature of a discount.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Directive 2011/62/EU (8 June 2011), which introduced changes as regards the prevention of the entry into the legal supply chain of falsified medicinal products, was transposed into national law by Decree-Law 128/2013. The definition of 'falsified medicinal product' and of 'brokering of medicinal product' was introduced into national law by reproducing the definition established in Directive 2011/62/EU. According to these new rules, manufacturers and distributors must notify Infarmed and the marketing authorisation holder immediately if they become aware of falsified medicinal products, or if they have any suspicion in that respect. In addition, distributors must verify that the medicinal products received are not falsified by checking the safety features on the outer packaging. The outer packaging of medicinal products (where there is no outer packaging, the immediate packaging), must include safety features enabling distributors and persons authorised or entitled

to supply medicinal products to the public to verify the authenticity of the medicinal product and identify individual packs, as well as a device allowing verification of whether the outer packaging has been tampered with. Infarmed is the responsible entity to receive notifications regarding falsified medicinal products. Most recently, Infarmed published Deliberation 47/CD/2015 of 19 March, approving the regulation regarding good distribution practices for medicinal products for human use, in accordance with article 59(10) of the Code of Medicinal Products. The good distribution practices now approved replace those established by Ministerial Order 348/98 of 15 June. The new regulation provides a special chapter concerning falsified medicinal products. This regulation entered into force on 1 July 2015.

Under the Criminal Code, medicine and food counterfeiting activities are classified as crimes punishable by up to five years' imprisonment. However, the application of this legal provision requires that evidence of a threat to life or a serious physical threat to individual health be produced. These requirements have been an obstacle to pharmaceutical companies seeking to combat counterfeiting.

The Industrial Property Code also states that counterfeiting activities involving any product protected by proprietary rights are sanctioned with a fine or up to three years' imprisonment.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

Publicly reimbursed electronic prescriptions for medicinal products and diagnostic means have been mandatory for physicians in the public and private sectors since August 2011. The prescription of medicinal products by international non-proprietary name (INN) has been subject to new rules over the years. In 2012, further rules were passed restricting the prescription and dispensing of medicinal products, namely Law 11/2012 of 8 March 2012. Recently, Ministerial Order 224/2015 of 27 July was published, and has as an objective to introduce electronic prescription with the dematerialisation of the medical prescription. The mentioned rules impose the mandatory sale of the cheapest medicinal products available, except in cases where the patient opts for another medicinal product with the same INN. The medical prescription must be written in the following form: INN, pharmaceutical form, dosage, presentation and posology. A prescription including a brand name is only allowed in the following circumstances: the medicinal product does not have any reimbursable generic alternatives, and the original branded medicinal product and licence are unique; and in admissible exceptional cases, such as when the physician provides a valid technical justification for the use of the prescribed medicinal product in certain situations. Such prescription (which must be hand written) is only allowed in exceptional situations, and the word 'exception' must be inserted under the logo of the Ministry of Health.

Infarmed and the ACSS published a Joint Informative Note (01/INFARMED/ACSS) establishing specific guidelines on this matter, which were addressed to patients, as well as to prescribers and pharmacies. Pharmacists shall inform patients of the cheapest medicinal products on the market that comply with the medical prescription, and must maintain a stock of at least three medicinal products of each homogeneous group (chosen from the five medicinal products with lower prices on the market), and must sell the cheapest one to the patient. The cost of the 'fifth lower price' is registered in a database provided by Infarmed to companies in the sector on a daily basis.

When dispensing, pharmacists must inform patients about cheaper medicinal products, reimbursed by the NHS, that are available in the pharmacy if they comply with the medical prescription. Patients must be informed of their right to choose a medicinal product that is in compliance with a medical prescription, and of their right to have the cheapest medicinal product on the market made available to them. When such medicinal product is not currently available at the pharmacy, it must be made available within 12 hours and at no additional cost.

Moreover, the above-mentioned joint informative note establishes rules that are applicable in three different situations:

- prescription by INN (or absence of exceptions) when a homogeneous group is involved;
- prescription by INN (or absence of exceptions) when no homogeneous group is involved; and
- prescription by brand when the treatment exceeds 28 days.

Patients may request information regarding the price of prescription-only medicinal products, and regarding the situations under which they have the right to opt for another product, from their doctor or a pharmacist. This information is also available on Infarmed's website. Whenever a patient is entitled to opt for another product, the statement 'right to opt' must be written on the back of the prescription.

29 Outline major developments to the regime relating to safety monitoring of medicines.

Recent amendments to the Medicinal Products Code, established by Decree-Law No 20/2013 (14 February 2013) and Decree-Law 128/2013 (5 September 2013), mainly concern medicine safety matters. Directive 2010/84 (15 December), which amends Directive 2001/83/EU as regards pharmacovigilance, was transposed into national law in 2013. This reformulated the Portuguese National Pharmacovigilance System, and included new requirements to prevent, detect and assess adverse reactions to medicinal products placed on the EU market, as the full safety profile of medicinal products can only be known after they have been placed on the market. Directive 2012/26/EU (25 October 2012) also amended Directive 2001/83/EU as regards pharmacovigilance, and further strengthens the European rules respecting the safety and monitoring of medicinal products, and was transposed into national law in 2013.

All developments regarding the safety monitoring and, specifically, the pharmacovigilance of medicinal products that are placed on the Portuguese market, including those that are sent by EMA, are published on a daily basis on the Infarmed website.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

Portugal has had a National Vaccination Programme (NVP) in force since 1965 that covers the entire population at no cost. The NVP provides a vaccination schedule recommended by the health authorities in Portugal. However, it is not confined to the vaccinations recommended at national level; in addition, there are vaccination programmes for special groups, such as immuno-compromised individuals, health professionals at risk, travellers to endemic areas and others, which also form part of the provisions and guidelines of the National Health General Directorate. Each person has a personal health booklet, implemented by Decree-Law 46621/65 (27 October), in which the vaccines are registered. The NVP currently in force was approved by Order 5786/2015 of 1 June.



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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The Ministry of Health (MOH) oversees the regulation of healthcare in Singapore. There are various statutory boards established under the oversight of the MOH, including the Health Sciences Authority (HSA) (established by the Health Sciences Authority Act and the Health Promotion Board (established by the Health Promotion Board Act)).

The HSA was formed on 1 April 2001, and integrated five highly specialised agencies, namely the Centre for Drug Evaluation, Institute of Science and Forensic Medicine, National Pharmaceutical Administration, Product Regulation Department and Singapore Blood Transfusion Service. The HSA has been designated as the authority responsible for the administration of Singapore's health laws and regulations such as the Health Products Act, Medicines Act, Tobacco (Control of Advertisements and Sale) Act and Poisons Act.

Singapore promulgated the Health Products Act in 2007 with the intention that the Health Products Act (and all subsidiary legislation promulgated thereunder) will consolidate legislation regulating all health products (including medicinal products). Prior to 1 November 2016, the Health Products Act only regulated medical devices and cosmetics. The Medicines Act and other related legislation regulated the manufacturing, sale and distribution of medicinal products. There is also specific legislation regulating the use of radiation-emitting devices, contact lens substances and condoms. However, as part of the HSA's ongoing initiative to update and streamline the existing regulatory controls for health products and bring them under a piece of single legislation, namely the Health Products Act, so as to ensure that the controls remain relevant and adequate to different operational and business models, with effect from 1 November 2016, the HSA pharmaceutical products, conventionally termed as chemical and biologic drugs, have been introduced as a new category of health products in the First Schedule of the Health Products Act using the term 'therapeutic products'. Therefore, the existing controls for pharmaceutical products under the Medicines Act and the Poisons Act no longer apply to pharmaceutical products.

Medical practitioners in Singapore must be registered under the Medical Registration Act (MRA). The Singapore Medical Council (SMC), constituted under the MRA, governs all registered medical practitioners. The SMC has promulgated the Singapore Medical Council Ethical Code and Ethical Guidelines (SMC Ethical Code). In September 2016, the SMC issued the 2016 edition of the Ethical Code and Guidelines (2016 SMC Ethical Code) together with the 2016 Handbook on Medical Ethics, which contains additional materials on the 2016 SMC Ethical Code and explains their applications and provides advice on best practices. The 2016 SMC Ethical Code will come into effect on 1 January 2017. All registered medical practitioners are required to adhere to the SMC Ethical Code. In addition, the Singapore Medical Association (SMA), which is the national medical organisation representing the majority of medical practitioners in both the public and private sectors in Singapore, has published the SMA Code of Ethics (SMA Ethics Code).

Singapore also established the Allied Health Professions Act 2011 (AHPA), which came into effect on 8 April 2013. The AHPA regulates the allied health professionals listed under Schedule 2 of the AHPA (such as occupational therapists, physiotherapists, speech therapists). The Allied Health Professions Council, which is constituted under the

AHPA, is the body that regulates all allied health professionals covered under the AHPA.

Further, hospitals and private medical clinics are regulated under the Private Hospitals and Medical Clinics Act.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

Singapore adopts a mixed financing system that provides multiple tiers of financing for its citizens' healthcare expenditure.

There are four tiers of healthcare financing. The first tier consists of subsidies from the government, which provides a subsidy of up to 80 per cent of the total bill in acute public hospital wards to qualifying Singaporeans.

The second tier is the Medisave scheme, which is a compulsory individual medical savings account scheme where all working Singaporeans and their employers contribute a part of the employee's monthly wages into the account to save for the employee's future medical needs.

The third tier, MediShield, is a basic, low-cost catastrophic medical insurance scheme that allows Singaporeans to effectively pool the financial risks of major illnesses. MediShield is administered by the Central Provident Fund (CPF) Board. Singaporeans may also supplement their basic MediShield coverage by applying for a Medisave-approved Integrated Shield Plan directly from one of the private insurers under the Private Medical Insurance Scheme. These integrated private insurance policies are made up of the MediShield plan and an enhancement plan for treatment in the private sector. From the end of 2015, the MediShield scheme will be replaced by the MediShield Life scheme, which will offer better protection and higher payouts to Singapore citizens and permanent residents for life, regardless of changes in their health or life circumstances.

Medifund is a medical endowment fund set up by the government to further assist needy Singaporean patients who cannot afford to pay their medical bills despite utilising the first three tiers.

Separately, the government also administers other subsidy schemes, such as the Community Health Assist Scheme (CHAS) (formerly known as the Primary Care Partnership Scheme), Interim Disability Assistance Programme for the Elderly (IDAPE) and the Medication Assistance Fund.

Under the CHAS, general practitioners and dental clinics that have agreed to partner with the MOH will provide common outpatient medical treatment and basic dental services to needy elderly or disabled patients at subsidised charges. The CHAS covers 15 chronic diseases and medical conditions, namely, diabetes mellitus, hypertension (high blood pressure), lipid disorders (eg, high cholesterol), stroke, asthma, chronic obstructive pulmonary disease (COPD), schizophrenia, major depression, dementia, bipolar disorder, osteoarthritis, benign prostatic hyperplasia (enlargement of prostate gland), anxiety, Parkinson's disease and nephritis/nephrosis (chronic kidney disease). From 1 June 2015, the CHAS will cover four more chronic conditions, which are epilepsy, osteoporosis, psoriasis and rheumatoid arthritis. The eligibility criteria for the scheme has been enhanced with effect from 1 January 2014, with the removal of the qualifying age for the CHAS (which was previously stipulated at 40 years old), raising of the qualifying property annual value criteria for economically active households (from S\$13,000 to S\$21,000) and raising of the income criteria from S\$1,500 to S\$1,800 per capita monthly household income.

In addition, the IDAPE scheme provides financial help to elderly Singapore citizens who become disabled but who are not eligible for EldersShield when it was launched in 2002 because they had exceeded the maximum entry age or have pre-existing disabilities.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

With effect from 1 November 2016, the advertisement of medicinal products and therapeutic products are governed by the Medicines Act and the Health Products Act and their subsidiary legislation, including the Health Products (Advertisement of Therapeutic Products) Regulations 2016. Pursuant to section 76 of the amended Medicines Act, the Medicines (Advertisement and Sale) Act and the Sale of Drugs Act are repealed and any subsidiary legislation made under those Acts has been revoked. There will be no changes to the regulatory requirements of advertisement control for other product groups that continue to remain under the Medicines Act, for example, complementary health products, which include Chinese proprietary medicines, traditional medicines, homeopathic medicines and quasi-medicines (vitamin and mineral preparation, medicated plasters, etc). The HSA Guide on Advertisements and Sales Promotion of Medicinal Products (HSA A&S Guide), the Singapore Code of Advertising Practice (third edition, 2008) (SCAP) and the HSA Explanatory Guidance to the Health Products (Advertisement of Therapeutic Products) Regulations 2016 also set out guidelines pertaining to the advertisement of medicinal products and therapeutic products to the general public. The Singapore Association of Pharmaceutical Industries' (SAPI) Code of Marketing Practices and OTC Medicine Code of Advertising and Promotion Practices (SAPI OTC Code) further prescribe standards of advertising or promotion that should be adhered to (see question 9). The Singapore Manufacturing Federation's (SMF) Medical Technology Industry Group's (MTIG) Code of Ethical Conduct for Interactions with Healthcare Professionals (MTIG Code) in turn sets out principles for ethical collaboration between organisations that develop, manufacture, sell, market or distribute medical technologies (ie, products, technologies and related services and therapies used to diagnose, treat, monitor, manage and alleviate health conditions and disabilities) in Singapore.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

In Singapore, advertising directed at healthcare professionals must abide by the same rules and principles as those directed at the general public (see question 5).

Therapeutic products

From 1 November 2016, any person intending to issue any medical advertisement or conduct any sales promotion in relation to medicinal products that are now classified as therapeutic products no longer needs to obtain an advertising permit but the advertisements of therapeutic products must comply with the broad principles of advertising therapeutic products as described in the Health Products (Advertisement of Therapeutic Products) Regulations 2016. Sales promotion includes any sales campaign (including door-to-door sales), exhibition, competition or any other activity for the purpose of introducing, publicising or raising the profile or public awareness or visibility of the therapeutic product for the purpose of promoting the sale or use of any therapeutic product.

Advertisements directed to healthcare professionals are exempted from the certain restrictions on advertisements directed to the general public, namely:

- advertisements of therapeutic products must not contain comparative claims involving another named therapeutic product or brand;
- prohibition of advertisements of therapeutic products relating to the specified diseases and conditions listed in the Second Schedule to the Health Products (Advertisement of Therapeutic Products) Regulations 2016;
- prohibition of advertisements of prescription-only medicines;
- mandatory advisories for advertisements of pharmacy-only medicines; and
- conducting sales promotion activities such as the offer of any prize, for example, the offer of any health or medicinal product with the therapeutic product or of any sample of the therapeutic product.

Advertisements that are made to healthcare professionals are also permitted to:

- advertise prohibited diseases and prescription-only medicines;
- advertise on corporate websites subject to controls under the Health Products Act and the Health Products (Advertisement of Therapeutic Products) Regulations 2016;
- disseminate advertising materials relating to unregistered therapeutic products or unapproved uses at pharmaceutical trade fairs and exhibitions where attendance is not opened to the general public; and
- offer medicinal and other health products (eg, as banded offers) as part of sales promotions intended for healthcare professionals or healthcare institutions. Samples of registered therapeutic products to qualified healthcare professionals may also be distributed at trade fairs and exhibitions where there is no attendance by the public.

Medicinal products

There is an exception for medical advertisements, sales promotions and representations directed exclusively to a person in his or her business premises who may lawfully sell or supply any medicinal product in the course of his or her trade, business or profession (eg, healthcare professionals).

Reference advertisements and trade advertisements as well as any medical advertisements issued or published by any public authority or any person authorised to issue or publish such advertisement by the Minister for Health are also exempted from the requirement to obtain an advertising permit.

Reference advertisements are advertisements containing a brief description of a medicinal product, its use, any contraindications and warnings relating thereto or of any device, instrument, apparatus or contrivance used or represented to be used for a medicinal purpose appearing without charge in a publication consisting mainly of such advertisements, and where the publication is sent or delivered to practitioners and pharmacists by a person not commercially interested in the product.

Trade advertisements are advertisements relating to a medicinal product or any device, instrument, apparatus or contrivance used or represented to be used for a medicinal purpose that is issued by means of a catalogue, price list or other document for the purpose of a sale by way of wholesale dealing, but that does not contain any recommendation relating to the use of the same other than as part of the name of the medicinal product or device, or as part of any heading or sub-heading indicating a therapeutic classification.

Advertisements made to healthcare professionals must not be false or misleading. Section 50 of the Medicines Act states that an advertisement may be false or misleading if it is made to a practitioner for the purpose of inducing him or her to prescribe or supply medicinal products of that description. A person who makes a false or misleading advertisement is guilty of an offence and may be liable to a fine of up to S\$5,000 or to imprisonment of up to two years, or both.

5 What are the main rules and principles applying to advertising aimed at the general public?

Pursuant to section 20 of the Health Products Act, advertisements relating to health products, which includes therapeutic products, may be false or misleading if they falsely describe the health product or give false information or if it is likely to create an erroneous impression regarding the formulation, composition, design specification, quality, safety, efficacy or uses of the health product.

In addition, pursuant to section 19 of the Health Products Act, an advertisement an advertisement cannot falsely advertise a product as a health product and advertisements in relation to registered health products must not represent the registered health product as being usable for any purpose other than that for which it has been registered. Section 21 of the Health Products Act also prescribes that advertisements should comply with such requirements as may be prescribed by the HSA.

Therapeutic products in Singapore are classified into three categories to reflect the different levels of access control to these products, namely:

- prescription-only medicines, which are therapeutic products that can only be obtained from a doctor or a dentist, or from a pharmacist with a prescription from a doctor or a dentist;

- pharmacy-only medicines, which are therapeutic products that can be obtained from a licensed pharmacist at a retail pharmacy; and
- general sales list (or over-the-counter (OTC)), which are therapeutic products that can be freely obtained from any retailer.

OTC medicines can be marketed and advertised to the public. Any direct-to-consumer advertisements of pharmacy-only medicines must clearly and prominently reflect the mandatory advisories.

From 1 November 2016, advertising permits are no longer required for the advertisement of therapeutic products, but all advertisements of therapeutic products must comply with the broad principles of advertisement of therapeutic products as described in the Health Products (Advertisement of Therapeutic Products) Regulations 2016. In addition to the requirements under the Health Products Act, the advertisement of therapeutic products should also comply with the HSA Explanatory Guidance to the Health Products (Advertisement of Therapeutic Products) Regulations 2016, which states that advertisements of therapeutic products should among other things:

- substantiate assertions of uniqueness and prominence by facts or robust objective evidence from credible sources, including the publication of any testimonials, whether directly or through linkages to third party websites or advertising platforms;
- present information in a balanced, objective and accurate manner and must be referenced by reflecting the appropriate citations (where relevant);
- not directly or indirectly, cause the reader to self-diagnose or self-treat any serious diseases;
- not diagnose, or suggest that medical interventions (eg, surgical operations) are not required by using the therapeutic product featured in the advertisements;
- not encourage inappropriate or excessive use of the therapeutic product;
- state truthfully the nature, quality and properties of the therapeutic product and must not directly or indirectly mislead the reader or give rise to unrealistic expectations with regard to the safety, quality or efficacy of the therapeutic product in the advertisements;
- not directly or indirectly cause fear, alarm, distress to consumers or abuse the trust or exploit the lack of knowledge of any consumer; and
- not include any recommendation by any healthcare professional or any person who, because of the person's celebrity, social or professional status, is likely to encourage the use of the therapeutic product, in the advertisement.

There will be no changes to the regulatory requirements of advertisement control for other product groups which continue to remain under the Medicines Act, for example, complementary health products that include Chinese proprietary medicines, traditional medicines, homeopathic medicines and quasi-medicines (vitamin and mineral preparation, medicated plasters, etc).

Such advertisements must comply with the Medicines Act (for product groups which remain under the Medicines Act) and the Health Products Act (for health products, which includes therapeutic products). Both Acts prescribe that advertisements must not be false or misleading.

Medicinal products

Under section 50 of the Medicines Act, an advertisement may be false or misleading if it:

- is made to a patient or client of a practitioner for the purpose of inducing him or her to request the practitioner to prescribe medicinal products of that description;
- is made to a person for the purpose of inducing him or her to purchase medicinal products of that description from a person selling them by retail;
- makes a representation relating to the product, which consists of or includes unauthorised recommendations;
- falsely describes the description of the medicinal products to which it relates; or
- is likely to mislead as to the nature or quality of medicinal products of that description or as to their uses or effects.

A person who makes a false or misleading advertisement is guilty of an offence and may be liable to a fine of up to S\$5,000 or to imprisonment of up to two years, or both.

In addition, advertisements to the public relating to medicinal products must comply with the HSA A&S Guide, as well as the SCAP.

The HSA A&S Guide states that the advertisements should, among other things:

- truthfully state the nature, quality and properties of the medicinal product, and not mislead in any way by ambiguity, exaggeration, omission or otherwise;
- make only substantiated claims (ie, the supporting literature should be of established sources);
- not inaccurately state recommendations relating to the use of medicinal products in moderate terms;
- not contain comparisons with other medicinal or related products unless scientifically proven; and
- not directly or indirectly encourage indiscriminate use of medicinal products.

The SCAP prescribes that, generally, advertisements of medicinal products should not, among other things:

- claim or imply the cure of any ailment, illness or disease;
- offer to diagnose, advise, prescribe or treat any ailment, illness or disease;
- claim to provide rejuvenation to prevent, retard or reverse the physiological changes and degenerative conditions brought about by, or associated with, increasing age;
- cause the advertisement audience unwanted anxiety lest they are suffering from any disease or condition of ill health, or falsely suggest that any product is necessary for the maintenance of health or the retention of physical or mental capacities;
- offer any product for any condition that requires the attention of a registered medical or other qualified practitioner;
- encourage the indiscriminate, unnecessary or excessive use of health or medicinal products;
- make exaggerated claims;
- contain any offer to refund money to dissatisfied users; or
- rest on claims that a product does not contain a given ingredient that is in common use in competitive products in any way that may give the impression that the ingredient is generally unsafe or harmful.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The HSA and government authorities do not make such information publicly available.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

There is no legislation in Singapore specifically prohibiting the use of medicinal products in off-label indications. However, section 4.1.4 of the SMC Ethical Code provides that:

A doctor shall treat patients according to generally accepted methods and use only licensed drugs for appropriate indications. A doctor shall not offer to patients, management plans or remedies that are not generally accepted by the profession, except in the context of a formal and approved clinical trial.

Sections B5(9) and B5(10) of the 2016 SMC Ethics Code provide that:

(9) If you use 'off-label' drugs, you must ensure that it is in the patients' best interests, there is rational basis, patients have justifiable medical indications, you have assessed the risks and benefits of such use and patients' consent to such use has been obtained if they are able to give it.

(10) You must not use unlicensed drugs, devices or instruments on your patients unless you have obtained the necessary approvals. You must ensure that such usage is in-patients' best interests and you must obtain-patients' (or their legal representatives') consent, where possible, before using such unlicensed treatment modalities.

Section 4.4 of the HSA Explanatory Guidance to the Health Products (Advertisement of Therapeutic Products) Regulations and Regulation

9 of the Health Products (Advertisement of Therapeutic Products) Regulations 2016 provide that advertising materials relating to unregistered therapeutic products or unapproved uses of registered therapeutic products may be disseminated only at pharmaceutical trade fairs or exhibitions or scientific conferences and forums, where attendance is not opened to the general public (eg, it is restricted to the medical and scientific professionals) provided that the unregistered therapeutic product or the unapproved use has been registered or licensed elsewhere globally. The information presented must not be false or misleading and must be substantiated by objective scientific evidence and must prominently indicate that the therapeutic product or its use is not approved locally. The sale or supply of unregistered therapeutic products or therapeutic products with unapproved uses at these events is strictly prohibited.

Section 50(2) of the Medicines Act prohibits the making of any advertisements that consists of or includes unauthorised recommendations in relation to medicinal products that have been licensed. Any person guilty of an offence shall be liable on conviction to a fine not exceeding S\$5,000 or to imprisonment of a term not exceeding two years, or both.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

There is no specific legislation governing the collaboration of the pharmaceutical industry with healthcare professionals. However, the SMA and the SAPI have prepared a joint paper (SMA-SAPI Joint Paper), which states that healthcare professionals are expected to place patients' health and welfare above any financial or commercial gains, whereas the pharmaceutical industry is expected to invest in research and development, to develop new and improved treatment options for the benefit of patients and market them ethically. The relationship between the pharmaceutical industry and healthcare professionals must always be seen to be impartial, honest and in compliance with the ethical codes promulgated by the SMA, the SMC, the SAPI as well as the SMF MTIG.

Further, any advertisements or promotions offered by the pharmaceutical industry to healthcare professionals must comply with the Medicines Act and Health Products Act (and the subsidiary legislation thereunder), the SCAP and any other guidelines issued by the HSA pertaining to the advertising of or supply of health or medicinal products.

The same rules generally apply to physicians in the outpatient and in-patient sectors.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The pharmaceutical industry must comply with the general principles of advertising as provided for in the Medicines Act and Health Products Act (and the subsidiary legislation thereunder), the SCAP and any other guidelines issued by the HSA pertaining to the advertising of or supply of health or medicinal products, as well as the SMA Ethics Code, SMC Ethical Code (and the 2016 SMC Ethical Code), SAPI Code of Marketing Practices, SAPI OTC Code and the MTIG Code.

The SMA-SAPI Joint Paper sets out recommendations in relation to the marketing practices of the pharmaceutical industry including promotions, gifts, symposiums or congresses, sponsorship and the supply of samples, as well as consultancy arrangements between the pharmaceutical industry and healthcare professionals. The SMA and the SAPI maintain a strict oversight of the relationship between individual doctors and the pharmaceutical industry, particularly in relation to the acceptance of gifts, promotional items and educational materials by doctors, the invitations from pharmaceutical companies for doctors to travel overseas to attend medical conferences and travel grants associated therewith. The SMA-SAPI Joint Paper also recommends that continuing medical education programmes provided by pharmaceutical companies must be organised through a registered and recognised academic or professional medical society or institution. Where pharmaceutical companies organise marketing talks about their new products, doctors are encouraged to analyse the information presented at such talks critically.

Further, section 50 of the Medicines Act prohibits advertisements to practitioners that have the purpose of inducing such

practitioners to prescribe or supply medicinal products of that description. Contravention of section 50 of the Medicines Act is an offence for which an offender may be liable to a fine of up to S\$5,000 or to imprisonment of up to two years, or both.

Section 19 of the Health Products Act prohibits the advertisement of any product as a health product (which includes therapeutic products) if it is not a health product within the meaning of section 2 of the Health Products Act. Similarly, advertisements of registered health products that portray that they are usable for any other purpose other than that for which they have been registered are prohibited. In addition, advertisements must not be false or misleading, and must comply with any requirements that may be prescribed by the HSA prior to its approval of the advertisement. A contravention of the above provisions under the Health Products Act is an offence for which an offender may be liable to a fine of up to S\$20,000 or to imprisonment of up to 12 months, or both.

While there are no rules and principles specific to the collaboration of the pharmaceutical industry with healthcare professionals under the SAPI Code of Marketing Practices, it nonetheless prescribes that, generally, the following standards of promotion should be adhered to:

- data is substantiated;
- false or misleading claims are not allowed;
- unapproved products and indications are not promoted;
- material and data are presented in good taste;
- unqualified superlatives are not allowed;
- new products are clearly identified;
- comparative statements must be used carefully;
- imitation that may give rise to confusion is not allowed;
- medical ethics are adhered to;
- distinction of promotional material is clearly defined;
- products, activities or representatives of other pharmaceutical companies must not be disparaged;
- medical and scientific opinions of opinion leaders and healthcare professionals must not be disparaged;
- pre-printed prescription pads that carry product-specific advertisements are prohibited; and
- doctors' names or photographs must not be used in any way that is contrary to medical ethics.

The SMC Ethical Code (as well as the 2016 SMC Ethical Code) states that doctors should only engage in promotion of vitamins, tonics and health and nutrition supplements where the content of such promotions (ie, what they say, write or broadcast) is supportable by good-quality scientific evidence.

In addition, the SMC Ethical Code (as well as the 2016 SMC Ethical Code) does not prohibit doctors from sponsoring, donating, participating or rendering services for any charitable endeavours. However, where a doctor participates in a medical event, conference, talk or publication, or on an educational website sponsored by pharmaceutical companies or any company marketing health or medical products, such doctor must ensure that his or her participation does not occur in such a way as to appear to endorse such products, or to persuade patients or the general public to use those products. Additionally, the doctor must not permit the publication of any details of services provided by the doctor in relation to such participation. A doctor who is sponsored by a company to participate in an educational event, or who reports research sponsored by a company, must declare all such potential conflicts of interest to the audience.

The MTIG Code sets out the following general principles to ensure that the medical device industry's collaborations with healthcare professionals are made in the best interest of consumers and patients:

- **Advancement:** the company's relationship with healthcare professionals must be for the purpose of advancing medical technology, innovation and patient care.
- **Integrity:** the company must interact with healthcare professionals in an honest, truthful and fair manner.
- **Independence:** the company may not provide anything of value to improperly influence a healthcare professional from making medical decisions that are based on the best interests of patients.
- **Appropriateness:** interactions must be modest and/or reflect fair market value, and be for legitimate purposes.
- **Transparency:** the company must be open regarding significant financial relationships with healthcare professionals.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

The HSA and government authorities do not make such information publicly available.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

There is no specific legislation governing the collaboration of the pharmaceutical industry with patient organisations. However, the collaboration of the pharmaceutical industry with patient organisations is indirectly regulated by the Medicines Act and Health Products Act (and the subsidiary legislation thereunder), the SCAP and any other guidelines issued by the HSA pertaining to the advertising of or supply of health or medicinal products, as well as the SAPI Code of Marketing Practices.

The SAPI Code of Marketing Practices prescribes general advertising or promotion principles that the pharmaceutical industry must comply with (see question 9).

12 Are manufacturers' infringements of competition law pursued by national authorities?

Pursuant to the Competition Act, a person who believes that an entity is in breach of competition law may make a complaint to the Competition Commission of Singapore (CCS). The CCS may also choose to initiate its own investigation into alleged anticompetitive behaviour. The CCS can take action against pharmaceutical manufacturers that enter into anticompetitive agreements, engage in an abuse of their dominant position or enter into mergers that substantially lessen competition (or is expected to substantially lessen competition) within any market in Singapore. Where the CCS, upon completion of an investigation, decides that there has been an infringement of competition law, it may, *inter alia*, impose financial penalties, issue directions or take other appropriate measures to remedy, mitigate or prevent the harmful effect of the infringement, and to prevent recurrence.

13 Is follow-on private antitrust litigation against manufacturers possible?

Only after the CCS has found a party to be in breach of competition law in Singapore, and after the expiry of any applicable appeal period, can third parties bring actions under section 86 of the Competition Act for loss or damage suffered directly as a result of a manufacturer's infringement of competition law. There is a two-year time limit for the commencement of such private actions from the time the CCS issues the infringement decision or from the determination of the appeal, whichever is later. To date, there have been no instances where a party has brought a follow-on private action against a manufacturer.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

There is no specific legislation in Singapore on the anti-corruption and transparency rules applicable to pharmaceutical manufacturers. However, the Prevention of Corruption Act (PCA) is the primary statute dealing with corruption offences in Singapore. The PCA criminalises corruption in both the public and private sectors and is enforced by the Corrupt Practices Investigation Bureau (CPIB).

Sections 5 and 6 of the PCA prohibit bribery in general. Under section 5 of the PCA, it is an offence for a person (whether by him or herself or in conjunction with any other person) to:

- corruptly solicit, receive, or agree to receive for him or herself or for any other person; or
- corruptly give, promise or offer to any person, whether for the benefit of that person or of another person, any gratification as an inducement to or reward for or otherwise on account of:
 - any person doing or forbearing to do anything in respect of any matter or transaction whatsoever, actual or proposed; or
 - any member, officer or servant of a public body doing or forbearing to do anything in respect of any matter or transaction whatsoever, actual or proposed, in which such public body is concerned.

Any person convicted of an offence under section 5 of the PCA may be liable to a fine not exceeding S\$100,000 or to imprisonment for a term not exceeding five years or to both.

Section 6 of the PCA sets out the offence of corrupt transactions with agents. It is an offence under section 6 of the PCA for:

- any agent to corruptly accept or obtain any gratification as an inducement or reward for doing or forbearing to do, or for having done or forborne to do, any act in relation to his or her principal's affairs or business;
- a person to corruptly give or agree to give or offer any gratification to any agent as an inducement or reward for doing or forbearing to do, or for having done or forborne to do any act in relation to his principal's affairs or business; or
- a person to knowingly give to an agent a false or erroneous or defective statement, or an agent to knowingly use such statement, to deceive his or her principal.

Any person who is convicted of an offence under section 6 of the PCA may be liable to a fine not exceeding S\$100,000 or to imprisonment for a term not exceeding five years or to both.

In addition, the ethical codes of the SMA, the SMC, the SAPI as well as the SMF MTIG promulgate the principle that the relationship between the pharmaceutical industry and healthcare professionals must always be seen to be impartial and honest.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

The advertising of medical devices is regulated under the Health Products (Medical Devices) Regulations 2010.

A 'medical device' includes any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article that is intended by its manufacturer to be used, whether alone or in combination, for humans for one or more of the specific purposes of:

- diagnosis, prevention, monitoring, treatment or alleviation of any disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
- investigation, replacement, modification or support of the anatomy or of a physiological process;
- supporting or sustaining life;
- control of conception;
- disinfection of medical devices;
- providing information for medical or diagnostic purposes by means of *in vitro* examination of specimens derived from the human body; and
- such item that does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its intended function by such means.

Under Regulation 19 of the Health Products (Medical Devices) Regulations 2010, advertisements of medical devices must not contain any statement that expressly or implicitly suggests that the use of the medical device is promoted or endorsed by the HSA. Advertisements for medical devices that are intended for direct delivery to the general public or for direct use by the general public must not contain any statement concerning the intended use and efficacy of the medical device unless such statement has been verified by objective evidence and such objective evidence has been furnished to the HSA at the time the application to register the medical device was made.

Where the advertisement of a medical device contains any statement, assertion, certification, award or feature of uniqueness or prominence differentiating the medical device from any other competing or similar medical device, the statement, assertion, certification, award or feature must be substantiated by facts or evidence (Regulation 20 of the Health Products (Medical Devices) Regulations 2010). For example, the identity of the certifying or awarding body and the date the certification or award was granted should be stated. Where the advertisement makes

any claim of historical precedence in the use or administration of the medical device for the purpose of medical treatment, information on the outcome of that use or administration of the medical device should also be stated.

Regulation 21 of the Health Products (Medical Devices) Regulations 2010 states that 'no person shall advertise any registered 'professional use only' medical device, unless the advertisement is distributed only to, or is contained in a publication intended for circulation mainly among, qualified practitioners'.

Contravention of any of the above provisions is an offence for which an offender may be liable to a fine of up to S\$20,000 or imprisonment of up to 12 months, or both. In contrast to the penalties prescribed under the Medicines Act, the penalties prescribed under the Health Products (Medical Devices) Regulations 2010 are more stringent.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

All medicinal products imported into or sold in Singapore are required to be licensed by the Health Products Regulation Group of the HSA. A person who imports or sells medicinal products in Singapore without a valid product licence commits an offence and may be liable to a fine of up to S\$5,000 or to imprisonment of up to two years, or both. A medicinal product is defined in the Medicines Act as 'any substance which is to be used for administration to human beings and animals for the diagnosis, prevention or treatment of ailments including preparations intended for the promotion of health, for anaesthesia or for contraception'. The onus of applying for a product licence rests with the licence holder, which is a locally registered company responsible for the safety, quality and efficacy of the product. The HSA may impose licence conditions requiring the medicines to be marketed in accordance with specific requirements.

With effect from 1 November 2016, the requirement for a product licence under section 5(1) of the Medicines Act for therapeutic products (pharmaceutical products, commonly known as chemical or biologic drugs) will be replaced by product registration under section 15(1) the Health Products Act. Any person who supplies any unregistered health product shall be liable on conviction to a fine of up to S\$50,000 or to imprisonment of up to two years, or both. Under the Health Products Act, the activity-based licensing framework will require product registrants to hold an importer's licence or a wholesaler's licence if they intend to import or wholesale their own registered therapeutic products. Companies will be subject to good distribution practice compliance before they will be granted these licences. Companies importing unregistered therapeutic products on behalf of healthcare institutions for patients' use are required to hold an importer's licence and wholesalers' licence and are required to obtain approval for the specific consignment. Healthcare institutions importing unregistered therapeutic products for patients' use are not required to hold an importer's licence for importation but are required to obtain approval for the specific consignment prior to importation.

Advertisements for therapeutic products will not require an advertising permit and prior approval by the HSA. Notwithstanding, anyone who advertises or causes any product to be advertised as a therapeutic product will still be required to comply with the provisions on the advertisement of health products under the Health Products Act and the Health Products (Advertisement of Therapeutic Products) Regulations.

Under the Medicines (Traditional Medicines, Homeopathic Medicines and Other Substances) (Exemption) Order, traditional medicines, homeopathic medicines, quasi-medicinal products, raw materials used as ingredients in the preparation or manufacture of any medicinal product and medicated oil and balms are exempted from the requirement to be licensed by the HSA. Similarly, Chinese proprietary medicines are exempted from the requirement to be licensed by the HSA under the Medicines (Chinese Proprietary Medicines) (Exemption) Order.

17 Which authorities may grant marketing authorisation in your jurisdiction?

The HSA is the government authority endowed with the powers and functions to grant marketing authorisations in Singapore. Subject to

certain exceptions, it is a requirement under the Medicines Act and Health Products Act that all medicinal products and health products be registered with the HSA before they can be marketed in Singapore. The marketing of medicinal products and health products must be in accordance with any relevant guidelines issued by the HSA. However, from 1 November 2016, the marketing of therapeutic products do not require prior approval by the HSA.

18 What are the relevant procedures?

Therapeutic products

A company seeking to market a therapeutic product in Singapore must obtain marketing approval from the HSA through making an application for product registration.

A therapeutic product registered under the Health Products Act is specific to the product with respect to its:

- proprietary or brand name;
- pharmaceutical formulation;
- pharmaceutical dosage form (ie, physical presentation) and strength; and
- indication(s) and dosing regimen.

Different formulations, dosage forms and strengths of the same chemical or biologic entity are considered as different products and will require separate registrations for the individual product.

Forensic classification

Upon satisfying the regulatory requirements for quality, safety and efficacy, a therapeutic product may be registered under one of the following forensic classifications, which determines the level of control for access:

- prescription-only medicine (POM);
- pharmacy-only medicine (P); or
- general sale list medicine (GSL).

An applicant making an application for the registration of a therapeutic product must ensure that all information contained in the application is truthful and is not misleading. An applicant must inform the HSA of any emerging information that may affect the benefit-versus-risk assessment of the therapeutic product to which the application relates, as soon as the applicant becomes aware of such information. The HSA may require a statutory declaration by the applicant verifying any information contained in or relating to the application.

Based on the HSA's Draft Guidance on Therapeutic Product Registration in Singapore, the registration process involves the following steps:

- pre-submission preparation;
- application submission;
- application screening;
- application evaluation;
- regulatory decision; and
- post-approval changes.

Pre-submission preparations

In respect of new product registration, an application can either be in respect of a new drug application or a generic drug application.

A generic product applies to a therapeutic product that contains one or more chemical entities, and that is essentially the same with a current registered product with respect to its qualitative and quantitative composition of active ingredients, pharmaceutical dosage form and clinical indication.

There are four types of evaluation routes for registering a new therapeutic product, namely the full route, the abridged route, the verification route and the verification-CECA route. The full route applies to any new product that has not been approved by any drug regulatory agency at the time of submission. The abridged route applies to any new or generic product that has been evaluated by at least one drug regulatory agency. The verification route applies to any new or generic product that has been evaluated and approved by one of the HSA's reference drug regulatory agency, which includes Australia's Therapeutics Goods Administration, the European Medicines Agency, Health Canada, the UK Medicines and Healthcare Products Regulatory Agency and the US Food and Drug Administration. The verification-CECA route applies to any generic product manufactured in India that has been evaluated and approved by one of the HSA's reference drug regulatory agency, which

includes Australia's Therapeutics Goods Administration, the European Medicines Agency, Health Canada, the UK Medicines and Healthcare Products Regulatory Agency and the US Food and Drug Administration.

Applicants are encouraged to contact the HSA by email or request a meeting or notification prior to the submission of an application if questions arise or clarification is required.

Application submission

All applications are to be made in two parts: through an online submission through the HSA's PRISM web portal and a hard-copy submission of the registration dossier, which is to be submitted within two working days from the PRISM submission. The registration dossier is to be in the common technical document format, based on the 'Common Technical Document for Registration of Pharmaceuticals for Human Use' as promulgated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Humans.

Application screening

After submission, the HSA will screen the application to ensure that the correct application type has been chosen and that there are no deficiencies that would delay the process. The HSA puts in place a stop-clock whenever it raises any queries in relation to the application. The stop-clock ends when a complete and satisfactory response is received by the HSA.

Application evaluation

Once the application is accepted, evaluation by the HSA commences. A stop-clock is again put in place in respect of any queries raised.

Regulatory decision

Once the application has been evaluated, the HSA will issue a regulatory decision of 'approval', 'approvable', 'non-approvable' or 'rejection'.

Approval and rejection are final decisions issued by the HSA. If an approvable regulatory decision has been reached, the conditions for approval will be stated in writing and the applicant will be required to fulfil these conditions within the stipulated time frame. If a non-approvable regulatory decision has been reached, the applicant will be informed of the non-approvable issues in writing, and a reply should be made within the specified time frame if the applicant wishes to continue with the application. The reply should be based on the original data set as submitted to the HSA; additional data that require evaluation will not be accepted.

An application will be considered withdrawn if the applicant fails to reply within the stipulated time frame subsequent to an approvable or a non-approvable decision. Once an application is withdrawn, it is considered closed and the applicant will be required to submit a new application according to prevailing submission requirements if the applicant wishes to pursue the regulatory approval for the product concerned. Upon an approval regulatory decision, the product will be added to the Register of Therapeutic Products.

HSA may register the product subject to post-approval commitments and the applicant will be required to furnish a letter of commitment stating the undertakings concerned.

Post-approval changes

Upon the registration of a product, product registrants are responsible for ensuring the product's quality, efficacy and safety to the end of its life cycle. HSA must be notified of any changes to the product's quality, efficacy and safety.

Confidentiality

Pursuant to Regulations 26 and 29 of the Health Products (Therapeutic Products) Regulations 2016, confidential information received in support of the registration of an innovative therapeutic product is protected for a period of five years from the date of receipt, during which HSA will not use the information to determine whether to grant any other registration applications. Confidential supporting information refers to trade secrets and information that has commercial value that would be, or would likely be, diminished by disclosure. A five-year period of exclusivity is granted for a therapeutic product for which safety and efficacy data has been generated in support of its registration. During the exclusivity period, a subsequent similar therapeutic product will not be able to rely on such data generated for the earlier therapeutic product to obtain registration.

Patent protection

Pursuant to Regulation 23 of the Health Products (Therapeutic Products) Regulations 2016, an application for the registration of a therapeutic product is required to make a declaration on whether the therapeutic product for which registration is sought is subject to a subsisting patent. A person who makes any statement or furnishes any document which the person knows or has reason to believe is false in a material particular or intentionally suppresses any material fact, furnishes information which is misleading and shall be guilty of an offence under Regulation 25 of the Health Products (Therapeutic Products) Regulations 2016 and shall be liable to a fine up to S\$20,000 or to imprisonment for a term up to 12 months or to both.

Medicinal products

All applications to obtain a product licence in respect of a medicinal product must be in compliance with the Medicines Act, the Poisons Act, the Misuse of Drugs Regulations (subsidiary legislation promulgated under the Misuse of Drugs Act) as well as the HSA's Guidance on Medicinal Product Registration in Singapore (Drug Registration Guidance).

The considerations that the HSA would take into particular consideration in determining whether to grant a product licence as set out in section 12 of the Medicines Act include:

- safety;
- efficacy;
- quality, according to the specification and the method or proposed method of manufacture, and provisions proposed for securing that the products sold or supplied would be of that quality; and
- whether the grant of the product licence would be in the public interest.

Based on the Drug Registration Guidance, the registration process involves the following steps:

- pre-submission preparation;
- application submission;
- application screening;
- application evaluation;
- regulatory decision; and
- post-approval changes.

Pre-submission preparations

In respect of new product licences, an application can either be in respect of a new drug application or a generic drug application.

A generic product is essentially similar to a currently registered product in Singapore (known as the 'Singapore reference product') but excludes biologics. 'Essentially similar' is defined as having the same qualitative and quantitative composition in terms of active substances, having the same pharmaceutical form and being bioequivalent. By extension, the concept of essentially similar also applies to different conventional immediate release oral dosage forms (ie, tablets and capsules) that contain the same active ingredient or ingredients.

There are three forms of evaluation routes, namely the full dossier, the abridged dossier and the verification dossier. The full dossier route applies to any product that has not been approved by any drug regulatory agency at the time of submission. The abridged dossier route applies to any product that has been evaluated by at least one drug regulatory agency. The verification dossier route applies to any product that has been evaluated and approved by one of the HSA's reference drug regulatory agency, which includes the European Medicines Agency, the US Food and Drug Administration, Health Canada, Australia's Therapeutics Goods Administration and the UK Medicines and Healthcare Products Regulatory Agency.

Applicants are encouraged to make an appointment with the HSA for a pre-submission consultation.

Application submission

All applications are to be made in two parts: through an online submission through the HSA's PRISM web portal and a hard-copy submission of the registration dossier (which is to be submitted within two working days from the PRISM submission). The registration dossier is to be in the CTD format, based on the 'Common Technical Document for Registration of Pharmaceuticals for Human Use' as promulgated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Humans.

Application screening

After submission, the HSA will screen the application to ensure that the correct application type has been chosen and that there are no deficiencies that would delay the process. The HSA puts in place a stop-clock whenever it raises any queries in relation to the application. The stop-clock ends when a complete and satisfactory response is received by the HSA.

Application evaluation

Once the application is accepted, evaluation by the HSA commences. A stop-clock is again put in place in respect of any queries raised. Application evaluations take between 60 working days (for verification evaluations) to 270 working days (for full-dossier evaluations).

Regulatory decision

Once the application has been evaluated, the HSA will issue a regulatory decision of 'approval', 'approvable', 'non-approvable' or 'rejection'.

Approval and rejection are final decisions issued by the HSA. If an approvable regulatory decision has been reached, the conditions for approval will be stated in writing and the applicant will be required to fulfil these conditions within the stipulated time frame. If a non-approvable regulatory decision has been reached, the applicant will be informed of the non-approvable issues in writing, and a reply should be made within the specified time frame if the applicant wishes to continue with the application. The reply should be based on the original data set as submitted to the HSA; additional data that require evaluation will not be accepted. No extension of timeline will be considered, unless mutually agreed between the HSA and the applicant.

An application will be considered withdrawn if the applicant fails to reply within the stipulated time frame subsequent to an approvable or a non-approvable decision. Once an application is withdrawn, the applicant may submit a new application according to prevailing submission requirements. Upon an approval regulatory decision, a product licence will be issued.

Post-approval changes

Upon issuance of a product licence, applicants will be responsible for maintaining the product's quality, efficacy and safety to the end of its life cycle. Any aspect of the product may change throughout its life cycle – for example, there can be a change in the manufacturer or manufacturing process, in the indication or dosage regimen, or in the safety profile. The HSA must be notified of any changes to the product's quality, efficacy and safety.

Confidentiality

Pursuant to section 19A of the Medicines Act, (introduced in 1998 to enable Singapore to comply with its obligations under article 39 of the World Trade Organization TRIPS Agreement), the HSA is obliged to maintain the confidentiality of information received in respect of innovative medicinal products, subject to the exclusions set out in section 19B of the Medicines Act (which include disclosing the confidential information if, in the opinion of the HSA, it is necessary to protect the health or safety of members of the public; disclosing the confidential information to another governmental department or statutory body, if the HSA is of the opinion that such department or body would take reasonable steps to protect the confidentiality of such information; and disclosing the confidential information to any specific international bodies, such as the World Health Organization (WHO)).

Patent protection

Pursuant to section 12A of the Medicines Act, all applications for new product licences must be accompanied by patent declarations in the form set out in Part I of the Sixth Schedule of the Medicines (Licensing, Standard Provisions and Fees) Regulations. Such patent declaration forms must be submitted at the time of application submission, and at any other time as the HSA may require. Generally, a confirmatory declaration will be requested when an approvable regulatory decision is issued. The applicant is required to furnish the confirmatory declaration within the time frame stipulated by the HSA.

Such an application may not be made earlier than 18 months before the expiry of the patent if:

- there is a patent in force in respect of the medicinal product to which the application relates;

- the applicant is not the proprietor of the patent;
- the proprietor has not consented to or acquiesced in the grant of the product licence; and
- the applicant is requesting the grant of a product licence after the expiry of the patent (ie, a Category A3 patent declaration).

Medical devices

A company that wishes to register a medical device on the Singapore Medical Device Register may make an application to the HSA via the HSA's MEDICS web portal.

The HSA classifies medical devices based on a series of factors, including:

- how long the device is intended to be in use;
- whether the device is invasive;
- whether the device is implantable;
- whether the device is active; and
- whether the device contains a drug or biologic component.

The HSA applies the following risk level classifications for medical devices:

Class	Risk level	Device examples
A	Low risk	Wheelchairs/tongue depressors
B	Low to moderate risk	Hypodermic needles/suction equipment
C	Moderate to high risk	Lung ventilator/bone fixation plate
D	High risk	Heart valves/implantable defibrillator

The HSA has adopted the guidance developed by the Global Harmonization Task Force in developing Singapore's risk classification model.

With effect from 1 May 2012, the HSA has exempted all Class A medical devices except for sterile devices from the registration requirements. Sterile devices with the 'CE' mark will also be cleared faster.

From 1 September 2012, the registration process for Class B medical devices has also been expedited. For instance, a Class B medical device may be immediately registered where it has already been approved by any two of the following independence reference agencies specified by the HSA – the US Food and Drug Administration, the European Union Therapeutic Goods Administration, Australia's Therapeutic Goods Administration, Canada's Medical Devices Bureau and Japan's Ministry of Health Labour and Welfare – and has been marketed for at least three years without safety concerns.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

There is no specific expiry date if the medicinal product or therapeutic product is not marketed by the applicant company once approved by the HSA. However, under the SAPI Code of Marketing Practices, the date of first use of all promotional materials circulated to the market shall not be more than two years from the date of approval. Any materials used beyond this point must be reapproved by the SAPI, which will maintain a local register of all approved materials, the approval folder and a sample of each approved item. All published promotional materials should be dated and updated regularly, and the date of print must be printed on the promotional or advertisement document.

20 Which medicines may be marketed without authorisation?

In Singapore, medicines and therapeutic products may not be marketed without authorisation. However, it is possible for a doctor or a pharmacist (pursuant to a prescription given by a doctor or dentist) to apply for special approval to import an unregistered medicinal product on a named-patient basis. It should be noted, however, that this would not apply to medicines containing ingredients controlled under the Poisons Act or the Misuse of Drugs Act (and their subsidiary legislation). For such medicines, the relevant licences must be obtained as required under the respective laws.

The application to import an unregistered medicinal product on a named-patient basis must be made to the Therapeutic Products Branch of the HSA. The application must include details of the product to be imported for use and the particulars of the importer, the physician responsible as well as the patient to be treated, and submitted to

the Therapeutic Products Branch. The consignment of the medicinal product must be imported into Singapore within six months from the approval date, unless otherwise stated. Currently, no fee is charged for approval. Both the importer and the physician responsible must maintain proper records on the supply and use of the medicinal product.

Unregistered therapeutic products may be also imported by any of the following:

- a licensed hospital or clinic for use by a registered doctor or dentist practising at that hospital or clinic and for use in any patient under the care of that doctor or dentist;
- a licensed retail pharmacy acting on behalf of a registered doctor or dentist pursuant to a valid prescription; or
- a company acting on behalf of a licensed hospital or clinic.

In order to import and supply such unregistered therapeutic products, the relevant licences and approvals under the Health Products (Therapeutic Products) Regulations must be obtained from HSA. Importers, wholesalers and other suppliers (including hospitals, clinics and retail pharmacies) of unregistered therapeutic products are required to maintain records of, among other things, every receipt and supply of the unregistered therapeutic products. These records must be retained for at least two years from the date of supply, and must be made available when requested by HSA.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

An application will need to be made to the HSA to obtain special approval from the HSA to import the unregistered medicinal products or therapeutic products into Singapore. Such approvals are granted on a case-by-case basis (see question 20).

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

The market price of a medicinal product is not generally governed by law or regulation in Singapore. However, the MOH administers several drug subsidy schemes (the Standard Drug List (SDL), Medication Assistance Fund, in-patient drug subsidy, etc).

The SDL, which is modelled on the WHO essential drug lists, consists of drugs assessed to be cost-effective and essential to the provision of medical care to all Singaporeans. Currently, the SDL comprises approximately 1,000 drugs (see www.moh.gov.sg/content/moh_web/home/costs_and_financing/schemes_subsidies/drug_subsidies.html).

The Drug Advisory Committee (DAC) is responsible for assessing whether a drug should be included in the SDL. The DAC, with inputs from other clinicians and the Pharmacoeconomics and Drug Utilisation Unit (which operates under the purview of the HSA), reviews the SDL on a yearly basis to take into account changes in clinical practice and advances in medical science. It considers three main factors when determining whether a drug should enter into the SDL:

- whether the drug is essential for the treatment of medical conditions that are important causes of morbidity and mortality in Singapore;
- whether the drug offers a major improvement in terms of efficacy and effectiveness, as compared with existing standard drugs; and
- whether there is sufficient evidence of long-term safety and cost benefits of the drug.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

Public healthcare providers generally purchase drugs through a tender process, and it may be possible that the terms of the supply (including the prices) would be negotiated between the public healthcare providers and the pharmaceutical manufacturers.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

As mentioned in question 2, the national health insurance system in Singapore comprises multiple tiers. In general, there is heavy subsidy of services and medicinal products provided by the national healthcare institutions to qualifying Singaporeans. In addition, all Singaporeans must maintain an individual medical savings account

scheme, Medisave. A secondary level of medical insurance scheme, MediShield, allows Singaporeans to pool against the financial risks of major illnesses, whereas ElderShield allows Singaporeans to pool against the financial risks of suffering a severe disability. Integrated Shield Plans are also available as an additional level of insurance for Singaporeans. Further, Medifund is available as a safety net for those who cannot afford the subsidised bill charges, despite Medisave and MediShield coverage. The Medication Assistance Fund (which was implemented in August 2010) also assists patients who require costly medication. Through the CHAS, the government has also engaged private general practitioners to provide common outpatient medical services to needy Singapore citizens at subsidised charges. Finally, the government has also introduced the Pioneer Generation Package, whereby Singapore citizens who were aged 16 and above in 1965 and who obtained Singapore citizenship on or before 31 December 1986 are eligible for additional subsidies for their healthcare costs for life.

It should be noted that Medisave, MediShield, ElderShield and any Integrated Shield Plans do not reimburse the cost of medicines only, but also provide the patient with reimbursement for hospitalisation and certain outpatient expenses.

Claims under MediShield can be made through the hospital where the patient is being treated. The hospital will inform the CPF Board that the patient is insured under the MediShield scheme and submit the claim to the CPF Board. After determining the amount payable to MediShield, the CPF Board will make payment directly to the hospital, and the outstanding amount may be settled with the patient's Medisave or by cash payment, or by a combination of the two. The withdrawal limits for Medisave depend on the type of treatment required by the patient. From the end of 2015, the MediShield scheme will be replaced by the MediShield Life scheme, which will offer better protection and higher payouts to Singapore citizens and permanent residents for life, regardless of changes in their health or life circumstances.

Medifund assistance is available to Singapore citizens who are subsidised patients receiving treatment from a Medifund-approved institution. A patient who wishes to apply for Medifund assistance must demonstrate that the patient and family have difficulty affording the medical bill despite the available government subsidies and contributions from MediShield and Medisave. Such patients (or their family members) may approach a medical social worker at a Medifund-approved institution for assistance. Every Medifund-approved institution has a Medifund committee to consider and approve applications, and decide on the appropriate quantum of assistance to provide. The Medifund committee comprises independent volunteers, most of whom are actively involved in community social work and are familiar with the needs and problems faced by lower-income Singaporeans. The actual amount of assistance provided will depend on the patient's financial and social circumstances, as well as the size of the medical bill incurred.

The Medication Assistance Fund is available to patients who face difficulties affording their medical bills, after MediShield or Medisave claims or deductions. Patients who are prescribed with Medication Assistance Fund-listed drugs can apply for the Medication Assistance Fund by approaching a medical social worker in the restructured hospitals and institutions or polyclinics. At present, only a very limited number of drugs are eligible under the Medication Assistance Fund.

Under the CHAS, low to middle-low income or disabled Singaporeans with any of the following 15 chronic diseases or medical conditions – diabetes mellitus, hypertension (high blood pressure), lipid disorders (eg, high cholesterol), stroke, asthma, COPD, schizophrenia, major depression, dementia, bipolar disorder, osteoarthritis, benign prostate hyperplasia (enlargement of prostate gland), anxiety, Parkinson's disease and nephritis/nephrosis (chronic kidney disease) – enjoy subsidised charges when seeking common outpatient medical treatment or basic dental charges at participating clinics. From 1 June 2015, the CHAS will cover four more chronic conditions, which are epilepsy, osteoporosis, psoriasis and rheumatoid arthritis.

In addition, the government introduced the Pioneer Generation Package in February 2014 to help over 450,000 eligible senior citizens with their healthcare costs for life, including the provision of financial subsidies for outpatient treatment (in terms of both services and medications) at polyclinics and specialist outpatient clinics, Medisave top-ups (amount dependent on date of birth) and further subsidies for MediShield Life premiums.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

As mentioned in question 22, the Drug Advisory Committee is the competent body for decisions regarding the pricing of certain medicinal products under the SDL.

The reimbursement of medical costs (including hospitalisation costs and costs of medicines) under the Medisave, MediShield and ElderShield schemes is decided by the CPF Board. The Medifund Committee determines the reimbursement of medical costs under the Medifund scheme, whereas the MOH is responsible for reimbursements under the Medication Assistance Fund.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

No; there are no statutory obligations on manufacturers or distributors of medicinal products to give a discount.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

There is no specific legislation in Singapore on counterfeiting that applies across all products or industries, or that applies specifically to medicines. However, there are relevant provisions in various existing legislative provisions that are relevant in protecting against counterfeit drugs, including the following that govern the manufacture, importation and supply of medicinal products:

- the Medicines Act; and
- the Poisons Act.

Medicinal products legislation

Section 31 of the Medicines Act makes it an offence to adulterate medicinal products by adding a substance to or abstracting a substance from a medicinal product so as to affect injuriously the composition of the product. It is also an offence to sell or supply such adulterated medicinal products. A contravention of any of the above provisions may attract a fine up to S\$5,000 or imprisonment of up to two years, or both.

Additionally, section 5 of the Poisons Act makes it an offence for a person to possess for sale, or to sell or offer for sale any poison without holding a licence to do so. A poison means any poison that is listed under the Poisons List in the Schedule of the Poisons Act. There is an exemption under section 7 of the Poisons Act in respect of medicines supplied by medical practitioners, registered dentists and veterinary surgeons for purposes of medical, dental or animal treatment, as well as medicines dispensed by licensed pharmacists. Such medicines must be distinctly labelled with the name and address of the firm or person by whom it is supplied or dispensed and with a serial or other identification number or mark. Section 8 of the Poisons Act also provides for certain exemptions in respect of poisons sold (eg, sale of poisons to a person or institution concerned with scientific education or research where the poison is required for educational or research purposes) or poisons being exported (eg, exemption applies for sale of poisons to be exported from Singapore to a place other than Malaysia). A person who commits an offence under the Poisons Act may be liable to a fine of up to S\$10,000 or to imprisonment of up to two years, or both.

Trade Marks Act

If a Singapore trademark holder's trademarks are infringed in the manufacture and sale of such counterfeit drugs, the Trade Marks Act provides further protection and sanctions, such as commencing an action for the infringement of trademark as a civil liability, or a criminal offence. It may also be possible to commence an action under the common law of passing-off.

Patents Act

Further, it is possible that a Singapore patent may have been granted in relation to the medicinal product. If a counterfeit product infringes a patent (eg, the counterfeit product with a particular active ingredient uses a formulation that falls within a patented formulation), the Singapore patent holder may be able to commence patent infringement proceedings under the Patents Act. The Singapore patent holder

may seek, among other remedies, an injunction to prohibit the sale of the counterfeit product against the seller or damages, or both.

Health Products Act

In addition, section 15 of the Health Products Act prohibits the supply of any health product unless that health product is registered. A person who contravenes section 15 will be guilty of an offence and may be liable to a fine of up to S\$50,000 or to imprisonment of up to two years, or both.

The supply of health products, which includes therapeutic products from 1 November 2016, that are adulterated, counterfeited or that have been tampered with is an offence under section 16 of the Health Products Act. An offender may be liable to a fine of up to S\$100,000 or imprisonment of up to three years, or both.

The supply of health products that are unwholesome health products is also an offence under section 16 of the Health Products Act, and may attract a fine of up to S\$50,000 or imprisonment of up to two years, or both.

To facilitate the general public in making more informed choices as well as in protecting themselves from the dangers of illegal health products, the HSA has compiled a list of detected and tested illegal health products. Consumers and healthcare professionals who wish to obtain more information may conduct a search on illegal health products via the HSA's website (www.hsa.gov.sg/publish/hsaportal/en/for_public/illegal_health_products/ihp_search_page.html).

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

With the transfer of the legislative controls for pharmaceutical products from the Medicines Act to therapeutic products under the Health Products Act in November 2016, the requirement for a product licence under section 5(1) of the Medicines Act is replaced by product registration under section 15(1) of the Health Products Act. All registered therapeutic products are entered into the Register of Therapeutic Products. The Register is a searchable database published on HSA's website (ie, HSA InfoSearch) and an annual fee is payable for retaining the therapeutic product on the register, referred to as the retention fee.

Regulation 17 of the Health Products (Therapeutic Products) Regulations 2016 provides that a relevant person may dispense a therapeutic product only if the package or container of the therapeutic is labelled with all of the following information in English:

- the name of the person to whom the therapeutic product is to be administered;
- the name, address and any identification number or logo of the licensed healthcare institution or licensed retail pharmacy where the therapeutic product is supplied or dispensed;
- the date that the therapeutic product is dispensed;
- the directions for use of the therapeutic product;
- the name of the therapeutic product, being either the proprietary name or the appropriate non-proprietary name; and
- where the appropriate non-proprietary name is included on the label, the appropriate quantitative particulars of any active ingredient of the therapeutic product.

The Health Products (Therapeutic Products) Regulations 2016 also states that prescription-only medicine may be dispensed only in accordance with the following requirements:

- where the qualified practitioner giving the prescription does not specify that the prescription is to be repeated, the relevant person dispensing the prescription-only medicine must:
 - when dispensing, mark the prescription in a manner so as to permanently attach the person's name and address and the dispensing date to the prescription; and
 - retain the prescription for a period of at least two years after dispensing; or
- where the qualified practitioner giving the prescription specifies that the prescription is to be repeated, the relevant person dispensing the prescription-only medicine:
 - must not dispense more than the total number of times specified on the prescription;
 - when dispensing, must mark the prescription in such a manner as to permanently attach the person's name and address and the dispensing date to the prescription; and

Update and trends

Regulation of therapeutic products under the Health Products Act

The Health Products Act was introduced in 2007 with the aim to consolidate and streamline the regulatory controls of health products under a single Act. The consolidation has been carried out in phases to cover a range of health products. Pursuant to the latest round of amendments, pharmaceutical products, commonly known as chemical or biologic drugs, are now regulated as 'therapeutic products' under the Health Products Act. The existing controls under the Medicines Act and the Poisons Act are no longer applicable to pharmaceutical products.

The following six pieces of legislation were introduced in the Health Products Act for the regulation of therapeutic products:

- Health Products Act (Amendment of First Schedule) Order 2016;
- Health Products (Therapeutic Products) Regulations 2016;
- Health Products (Clinical Trials) Regulations 2016;
- Health Products (Therapeutic Products as Clinical Research Materials) Regulations 2016;
- Health Products (Advertisement of Therapeutic Products) Regulations 2016; and
- Health Products (Licensing of Retail Pharmacies) Regulations 2016.

Correspondingly, the following three pieces of legislation for the controls of medicinal products under the Medicines Act and medical devices under the Health Products Act used in clinical trials or clinical research have been updated to ensure that they are aligned with the controls of therapeutic products under the Health Products Act:

- Medicines (Clinical Trials) Regulations 2016;
- Medicines (Medicinal Products as Clinical Research Materials) Regulations 2016; and
- Health Products (Medical Devices) (Amendment) Regulations 2016.

These new pieces of legislation were finalised and gazetted on 15 July 2016 and come into effect on 1 November 2016.

SMC Ethical Code and Ethical Guidelines

In September 2016, the SMC issued the 2016 edition of the Ethical Code and Guidelines (2016 SMC Ethical Code) together with the 2016 Handbook on Medical Ethics, which contains additional materials on the 2016 SMC Ethical Code and explains their applications and provides advice on best practices. The 2016 SMC Ethical Code will come into effect on 1 January 2017.

- must retain the prescription for a period of at least two years after dispensing for the last time.

Section 4 of the Medicines (Labelling) Regulations also requires that the container of a dispensed medicinal product (ie, supplied by a doctor or dentist to a patient, or dispensed by a pharmacist) be labelled to show certain particulars, including:

- the patient's name;
- name and address of the medical or dental practice, pharmacy, hospital or other institution;
- date upon which the medicinal product was dispensed;
- name of the medicinal product; and
- where the appropriate non-proprietary name is labelled, the appropriate quantitative particulars of the active ingredients of the medicinal product.

There are also specific requirements, such as the requirement that the above particulars, when printed on a label or on the package of a medicinal product, must not be less than 1.5 millimetres in height, and shall be clearly legible and appear conspicuously in a prominent position on the label so as to be easily read by an intending purchaser or user of the medicinal product under normal conditions of purchase or use.

29 Outline major developments to the regime relating to safety monitoring of medicines.

The Vigilance and Compliance Branch and Product Vigilance Advisory Committee (PVAC) of the HSA employs a number of post-marketing risk assessment approaches to ensure the continued safe use of health products. Persons who hold a product licence under the Medicines Act or who is a manufacturer, importer, supplier or registrant of a health product under the Health Products Act must report any adverse drug reactions, while health professionals are strongly encouraged to do so. The Vigilance and Compliance Branch, together with the PVAC publishes an Adverse Drug Reaction News Bulletin three times a year and distributes the Bulletin to all medical practitioners, dentists and pharmacists. The aim is to increase awareness of adverse drug reactions among healthcare professionals and to promote adverse drug reaction reporting. The HSA also maintains a list of 'Dear Healthcare Professional Letters' on its website, which detail product recalls, product alerts and other news related to medicinal and health products (see www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Dear_Healthcare_Professional_Letters.html).

The PVAC encourages the reporting of any events that are considered as medically significant in the judgement of the healthcare professional. Some examples are events that are fatal or life-threatening, result in or prolong hospitalisation, cause persistent or significant incapacity or disability, or cause birth defects. Reports can be made by healthcare professionals and pharmaceutical companies in respect

of drugs and complementary health products as well as vaccines using the relevant form available on the HSA's website (www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Report_Adverse_Events_related_to_health_products.html).

All adverse event reports submitted to the Vigilance and Compliance Branch are keyed into a national computer database for use in aggregate analysis. The HSA will then communicate safety information through press releases, Dear Healthcare Professional Letters posted on the Ministry of Health - Health Professional Portal website and the Adverse Drug Reaction News Bulletin. These Adverse Event Reports are also submitted to the WHO-Uppsala Monitoring Centre in Sweden for collation into the world bank of adverse drug reactions.

Where the adverse event reported identifies an unexpected adverse event or indicates that certain adverse events occur more commonly than as previously expected, or that some patients are more susceptible to some problems than others, the HSA may decide to change the marketing authorisation for that particular product. For instance, the HSA may impose restrictions on the use of the product, or make refinements to the instructions for use or require the printing of specific warnings of adverse events in the product package insert. Rarely, when the HSA considers that a hazard is unacceptable, a registered health or medical product may have to be withdrawn from the market.

Further, there are mandatory record-keeping requirements on all pharmacists for the supply of pharmacy-only medicines to ensure accountability and traceability, as well as to enhance the safe and responsible use of medicines. The information required to be recorded includes the date of supply of the medicine; the name, identity card number, address, phone number and email of the person to whom the medicine is dispensed; the name, strength and quantity of medicine dispensed; and the dose, frequency and purpose of the treatment.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

It is a legal requirement for all children in Singapore to be vaccinated against the diseases specified under the Fourth Schedule of the Infectious Diseases Act (namely, diphtheria and measles). However, under the National Childhood Immunisation Programme (NCIP), it is generally recommended that all children are also vaccinated against mumps and rubella, tuberculosis, hepatitis B, pertussis, tetanus and poliomyelitis, as well as against human papillomavirus (for females aged nine to 26 years). In addition to these, children may commonly also receive vaccinations against other diseases such as haemophilus influenza type B, influenza, chickenpox, meningococcal and pneumococcal.

The NCIP is based on the recommendations of the Expert Committee on Immunisation, which comprises senior officials from the MOH, consultant paediatricians and experts in communicable disease control. The Committee monitors and reviews the NCIP in

Singapore, and consults with the WHO and other international bodies when necessary.

The Health Promotion Board's Health Surveillance and Informatics Department, Research and Strategic Planning Division maintains a National Immunisation Registry (NIR), which collects and maintains the vaccination records of children from birth to 18 years of age. All vaccinations given at polyclinics will automatically be updated into the NIR's records. For vaccinations given at family or paediatric clinics, the doctor will keep the NIR updated as and when a vaccination is completed. If a child misses any vaccination, the NIR will send a reminder letter to the parents.

Under the NCIP immunisation schedule, the first vaccinations (against tuberculosis and hepatitis B) are administered when the child is born. Subsequently, parents would need to bring their child for regular vaccinations at a family clinic, polyclinic or paediatric clinic. The following three types of vaccinations are provided free-of-charge to Singapore citizens through polyclinics:

- DTPa - a three in one vaccination against diphtheria, tetanus and acellular pertussis;
- MMR (vaccination against measles, mumps and rubella); and
- BCG (vaccination against tuberculosis). Singapore permanent residents are required to pay a discounted rate for these vaccinations. School-going children may also receive free vaccinations provided by the School Health Service according to the NCIP (ie, at six to seven years of age, and at 10 to 11 years of age) and where their parents or guardians give consent.

According to statistics published by the WHO in 2014, the immunisation coverage among one-year-olds in Singapore for diphtheria, tetanus and toxoid, hepatitis B and measles over the past decade has been 93 to 97 per cent. The NIR aims to achieve 95 per cent coverage for immunisations under the NCIP.

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

Healthcare in Slovenia is organised as a public service, provided through the public health-service network and by physicians and private legal entities providing services on the basis of concessions from the Ministry of Health. Healthcare services provided by private physicians are paid directly and in full by the patient.

The public health-service network is organised on three levels (primary, secondary and tertiary), which differ in many aspects, including, but not limited to, differences in organisation, allocation of providers in the territory and also from the perspective of specialisation and complexity of services provided.

Primary level care is organised through a wide spread network of providers established by local authorities and private providers with concessions granted from municipalities. The primary level health-service network, which should provide equal accessibility to all people without discrimination, provides initial contact with doctors for diagnostics and treatment of acute and chronic diseases, promotion of health and healthy lifestyles, disease prevention, counselling and patient education. On the primary level, provision of urgent and emergency medical services and the ambulance service is also organised. The majority of all health services are provided by general practitioners, paediatricians, gynaecologists and dentists, and their scope is limited to outpatient services.

Secondary level care is organised by the state and consists of public hospitals and different private entities that have obtained concession from the Ministry of Health. Compared to the primary level, the network of providers is less widespread, although designed in a manner that should provide easy accessibility to health services for all patients. At the secondary level outpatient and in-patient health services are provided by specialised physicians. The scope of services provided does differ slightly from one hospital to another, principally because of the differences in hospital size and the territories they cover. Private legal entities with concession predominantly provide outpatient services, although the number of private hospitals with concession also providing in-patient services has risen in recent years and the same trend is expected to continue in the future.

Tertiary level care currently consists of two university medical centres located in Ljubljana and Maribor, which work very closely with medical faculties in Ljubljana and Maribor. In both institutions, the most complex operations and treatments, research and educational activities are conducted simultaneously with healthcare services that are usually provided within the secondary level.

An integral part of the Slovenian healthcare system is the Health Insurance Institute of Slovenia (ZZZS), which provides compulsory health insurance while also being actively involved in all activities that determine the scope of health service programmes.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The Slovenian healthcare system is based on solidarity with a relatively high level of spending on health and social security alongside participation in a compulsory health insurance system. This is financed through three sources of funding: public funds and revenue; private funds collected through voluntary health insurance; and private funds

for self-paying services. Both in-patient and outpatient sectors are financed in the same manner.

The majority of public funds are collected from healthcare insurance, which is compulsory for all citizens with permanent residence in Slovenia. Therefore, everyone pays contributions to the ZZZS, which afterwards distributes the collected funds to the healthcare providers as well as to other beneficiaries. The amount of contributions is determined proportionally under the solidarity principle, taking into account a person's income or other circumstances. Compulsory insurance healthcare services are either covered as a whole or as a proportion. Complete coverage of costs is provided mostly only for children, students and for certain illnesses and conditions. As for situations where the compulsory insurance does not cover the whole service, the difference in costs can be covered either by direct payment by the patient, payment by the insurance company, where the patient has concluded their voluntary health insurance, or, in some cases, from the government budget (prisoners, war veterans, etc).

In 2014, the healthcare expenditure in Slovenia amounted to €3,188 million. The structure of financing consisted of 71 per cent of public funds and 29 per cent of private funds. In 2014, the costs for in-patient services represented 47.3 per cent of total current expenditure for care; costs for outpatient services represented 22.3 per cent; and costs for medicines and other medicinal products represented 22.2 per cent.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

Advertising medicinal products to the general public and healthcare professionals is governed by the Medicinal Products Act (ZZdr-2) and the rules on advertising of medicines are adopted on its basis. In connection with advertising homeopathic and traditional medicines, rules on homeopathic medicines for human use and rules on the traditional medicinal products of plant origin are also relevant. The above-mentioned legislation implements rules on advertising contained in EU Directive 2001/83/EC and other relevant EU legislation adopted within the Slovenian legal system.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

The definition of advertising medicinal products is very broad and includes all marketing activities designed to promote the prescription, supply, sale or consumption of medicinal products and is allowed only in connection with medicines that marketing authorisations have been obtained for. The advertising of advanced therapy medicinal products prepared on a non-routine basis is expressly prohibited under the relevant Slovenian legislation.

Advertising activities aimed at healthcare professionals can be conducted through publications in professional and scientific literature and directly through visits of adequately trained medical sales representatives. All advertising activities must be conducted in the Slovene language and in line with the information contained in the summary of product characteristics (SmPC) that was approved by the Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices (JAZMP).

The properties of medicinal products must be described objectively and without exaggeration and all information provided must be accurate, unambiguous, up to date and verifiable, and must promote efficient and safe use of the medicinal product. All quotations, tables and any other illustrative means originating from professional and scientific literature must be reproduced correctly and in a manner that objectively presents essential content and precisely indicates the cited sources. Information on new medicinal products could be also provided within sales promotion events, primarily for professional and scientific purposes, during which any accompanying hospitality must be limited.

Advertising activities conducted through personal visits of medical sales representatives, aimed at healthcare professionals employed by public institutions, are allowed only during the period dedicated to professional preparation. Furthermore, it is expressly forbidden to provide, supply, promise or offer healthcare professionals any gifts, pecuniary advantages or benefits of any kind, unless they are inexpensive and relevant to the practice of medicine or pharmacology. Specimens of medicines may be provided only in cases when provision of special instructions on the application of medicinal products from the healthcare professional is necessary to the patient.

It should be also noted that the Forum of International Research and Development Pharmaceutical Companies, EIG (FIRDPC) adopted a Code on the informing and communication of prescription-only medicines to, and cooperation with, healthcare professionals, which is merely a recommendation and is not legally binding. Nevertheless, the Code is widely accepted and applied throughout the respective medicinal fields, and it is advisable to follow its rules and recommendations.

5 What are the main rules and principles applying to advertising aimed at the general public?

Advertising activities aimed at the general public are only allowed in connection with non-prescription medicinal products. All advertising activities and publications of any information intended for the general public is prohibited in relation to medicinal products containing psychotropic drugs or narcotics. Medicines used in vaccination programmes may only be advertised to the general public under special conditions and under exceptional circumstances.

All advertising activities must be conducted in a manner that makes clear that it is an advertisement and must clearly identify that the product advertised is a medicinal product. Every part of the advertisement, and all its constituent elements, must adhere to the information contained in the SmPC. The description of the medicinal product advertised must be balanced, objective and without any exaggeration regarding its characteristics. Safe and efficient use of medicinal products must be promoted.

All communications of an advertising nature must contain the name of the medicinal product, the international non-proprietary name (INN) of the active ingredient, even if only one is contained in the medicinal product, all information necessary for reasonable, correct and rational use of the medicine and an express legible warning on the importance of the usage instructions, emphasising that the instructions must be read carefully prior to use. It should also contain instructions advising on the potential risks and adverse side effects of the medicinal products, which should be obtained from a doctor or pharmacist. In the case of audiovisual media, this information must be provided both audibly and visually.

Advertising aimed at the general public must also refrain from all communications that could mislead the consumer on the importance of having consultations with healthcare professionals, the possibility of side effects associated with use of the medicinal product, the safety and efficacy of the medicinal product, the fact that the product advertised is a medicinal product and the positive effects the medicinal product could have.

The advertising of traditional medicinal products of plant origin and homeopathic medicinal products is also subjected to strict regulation.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

Based on our experience, the most common infringements have been committed in relation to rules governing advertising to healthcare professionals. In recent years, relevant rules have been changed in a

manner that should decrease the possibilities of undue influence on prescription medicinal products. This is especially evident from the limitations on the visit times of healthcare professionals, the creation of a sales representative's register and the obligation to keep records of all conducted visits. Implementation of the above changes has, in practice, not been easy, which has led to some infringements still occurring.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

Slovenian law prohibits the conduct of any activities of an advertising nature that includes any information, including therapeutic indications, not contained in the marketing authorisation obtained or content of the approved SmPC. Provision of information on off-label use is therefore not allowed. Although it should be noted that in line with the common practice of pharmaceutical companies to seek different and innovative ways in which as much beneficial information as possible is provided, the provision of information regarding off-label use should not be exempt from such endeavours.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sector?

ZZdr-2 governs the collaboration with healthcare professionals for the purpose of conducting non-interventional clinical tests of medicinal products and also from the perspective of donations, gifts and other transfers of value. The same rules apply for the collaboration with physicians in the outpatient and in-patient sector.

Guidance on how the collaboration should be conducted has been further elaborated in several other legal documents (which do not have a basis in legislation), so qualify as soft law. Regardless of their nature, those documents are very important and widely accepted. Such guidelines were, for example, issued by FIRDPC and by the Slovenian Commission for the Prevention of Corruption.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

Rules on collaboration with healthcare professionals are strict and extensive, and apply to, among other things, promotional activities, donations and conduct of clinical trials. The main principles common to the aforementioned are prohibition of undue influence, provision of transparency and protection of public funds.

In respect of promotional activities one of the most important rules is the rule prohibiting supply, offers or promises of gifts, pecuniary advantages or benefits in kind, to persons qualified to prescribe or supply medicinal products, unless they are of small value and relevant to the practice of a healthcare professional. Special limitations also exist in connection with promotional events, which must be predominantly intended for the provision of new knowledge to healthcare professionals and their agenda must be accordingly limited to professional and scientific objectives. Hospitality in the form of accommodation, registration fees and travel expenses is allowed, but must be strictly limited to healthcare professionals (not spouses and family) and be of a reasonable extent and of secondary importance.

Furthermore, it should be also noted that all donations from the pharmaceutical industry should be provided to healthcare institutions and not directly to individual healthcare professionals. As described in question 14, manufacturers are subject to an obligation to disclose transfers of value.

Collaboration with healthcare professionals employed by public institutions, for the purpose of conducting of non-interventional clinical tests, is possible only if consent has been obtained by the employer. All payments made directly to healthcare professionals are allowed only in connection with services provided outside their employment within their spare time.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

Based on past experience, the infringements commonly occurred in connection with donations, which were often in the form of covering

costs for scientific events provided directly to individual healthcare professionals instead of healthcare organisations. There were also numerous cases where excessive hospitality was provided, such as paying for trips and luxury accommodation.

Furthermore, engaging healthcare professionals to provide their services to manufacturers (eg, lecturing, advisory services) has, in certain cases, been abused in order to influence the healthcare professional and gain undue advantage for the manufacturer. Such attempts were observed primarily in relation to healthcare professionals who were members of expert groups with the potential to influence the prescription of medicinal products on a larger scale.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

The law does not govern the collaboration of the pharmaceutical industry with patient organisations. The FIRDPC adopted the Code of practice on relationships between the pharmaceutical industry and patient associations, which corresponds with the rules adopted by the EFPIA. Regardless of their nature, those rules are very important and widely accepted in practice.

In line with the main principles of the Code adopted by the FIRDPC, collaboration must be carried out in a manner that is independent of patient organisations, all partnerships between patient organisations and the pharmaceutical industry must be based on mutual respect and its objectives and scope shall be transparent. Provision of any support must be based upon written agreement and must be clearly acknowledge and publicly disclosed. Patient organisations must not promote particular prescription-only medicine, nor should such action be requested from them. Pharmaceutical companies may not request from a patient organisation that it becomes its sole funder or sole sponsor, or to be granted such status in relation to any of the activities conducted. Rules very similar to those applying to healthcare professionals, apply with respect to the organising of events held by pharmaceutical companies intended for patient organisations.

12 Are manufacturers' infringements of competition law pursued by national authorities?

There is no record of manufacturers' infringements of solely national competition law. In recent years, one of the larger Slovenian manufacturers has been involved in a European Commission procedure against pharmaceutical companies concluding 'pay-for-delay agreements' and was at the end found guilty of the infringement and ordered to pay a fine. Based on publicly available information, the fine has been paid, but legal redress has been sought.

In recent years, there was also a procedure by the Slovenian Agency for Protection of Competition (AVK) against several Slovenian wholesale distributors of pharmaceutical products, which were found guilty of violations of competition law, specifically of illicit concerted practice. The decision delivered by the AVK has been confirmed by the Slovenian Administrative Court and also by the Slovenian Supreme Court. The decision on fines has not yet been issued.

13 Is follow-on private antitrust litigation against manufacturers possible?

Such follow-on private antitrust litigation is possible, but there is no available record of case law in which a claimant succeeded with his or her claim.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

Most of the relevant rules have already been described in question 9. As most funds are public, pharmaceutical manufacturers must also adhere to provisions of the Integrity and Prevention of Corruption Act. Therefore, all transfers of value, including, but not limited to, gifts, must be accordingly reported unless they are of insignificant value. Pharmaceutical companies must also refrain from all actions that could result in undue influence on healthcare professionals or other decision makers in the healthcare sector. All contracts concluded with a public entity with a value in excess of €10,000 must contain an anti-corruption clause, which stipulates that the agreement is null in case

of undue influence in the form of the provision of gifts, pecuniary and non-pecuniary advantages, etc.

In line with ZZdr-2, pharmaceutical manufacturers are obliged to establish a register of sales representatives and have a duty to register all contact between medical sales representatives and healthcare professionals. Information from both registers must be submitted to the JAZMP.

From the perspective of the EFPIA Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organisations adopted by the FIRDPC, under which all transfers of value to healthcare professionals and healthcare organisations from 2015 onwards must be disclosed publicly, is the most important document.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

The provisions of the Act on medical devices on advertising are similar to the provisions in ZZdr-2, but are less detailed and less restrictive from the perspective of advertising to healthcare professionals and the general public. Regulations regarding collaboration with healthcare professionals are also far less detailed. The main reason for less detailed regulation is the absence of EU legislation strictly within the field of medicinal products.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

ZZdr-2 governs the granting of marketing authorisations and the placing of medicinal products on the market. Additional rules are contained in the Rules on the marketing authorisation for medicinal products for human use. Slovenian legislation closely follows EU Directive 2001/83/EC on the Community code relating to medicinal products for human use.

17 Which authorities may grant marketing authorisation in your jurisdiction?

The JAZMP is authorised to conduct a national procedure for the marketing authorisation of medicinal products and it also acts as a representative of Slovenia and delivers decisions in respect of Slovenia in the mutual recognition procedure and decentralised procedure governed by EU law. Both procedures laid down by EU legislation were accordingly implemented in the Slovenian legal system.

The marketing authorisation for medicinal products could be also obtained within the centralised procedure conducted in accordance with Regulation (EC) No. 726/2004, which must be read in conjunction with Regulation (EC) No. 1901/2006 of the European Parliament and the Council on medicinal products for paediatric use and Regulation (EC) No. 1394/2007 on advanced therapy medicinal products.

18 What are the relevant procedures?

Marketing authorisation may only be granted to an applicant established within EU territory. As stated in question 17, marketing authorisation could be obtained within the national procedure run by the JAZMP, or within the mutual recognition or decentralised procedure in which the JAZMP acts as Slovenia's representative and delivers decisions for Slovenia at the end of the procedure. Irrespective of the procedure chosen, an application must be accompanied by particulars listed in article 8, paragraph 3 of Directive 2001/83/EC. Easements regarding documentation are applied to the marketing authorisation of generic medicinal products.

If marketing authorisation for the medicine has already been obtained in the centralised procedure, prior to the marketing of the medicinal product, a national identification must be obtained from the JAZMP.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

The JAZMP has the authority to withdraw the marketing authorisation it has granted if the medicinal product under the same proprietary name has not been marketed for three consecutive years from the time that the marketing authorisation became effective.

In particularly substantiated cases, the JAZMP may decide that marketing authorisation for the medicinal product will not be withdrawn if it is necessary for the provision of an uninterrupted supply of medicinal products or for the protection of public health.

20 Which medicines may be marketed without authorisation?

Marketing without marketing authorisation is possible for galenic preparations prepared in pharmacies for direct distribution that are described in the *European Pharmacopeia* and its Slovenian appendices are in line with formulations described therein and extemporaneous preparations prepared in line with prescriptions issued by a doctor, dentist or veterinarian. Marketing without authorisation is also possible for certain veterinary medicinal products intended solely for use with certain animal species.

In respect of advanced therapy medicinal products prepared on non-routine basis, a special permit for preparation is required in place of a marketing authorisation.

Also, a marketing authorisation is not required for conducting clinical trials. Under extraordinary circumstances (eg, infections, threat of epidemic and pandemic outbreak, intoxication or radiation), the marketing of certain medicinal products without marketing authorisation could be allowed. Physicians responsible for a patient's treatment can also demand medicine that has not been granted a marketing authorisation (see question 21). On the grounds of prior permission from the JAZMP, distribution of medicinal products under the compassionate-use programme could be allowed in accordance with article 83 of Regulation (EC) No. 726/2004.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Article 5(1) of EU Directive 2001/83/EC has been implemented within the Slovenian legal system, which provides physicians providing a patient's treatment with an option to, under his or her full personal responsibility, demand medicinal products without a marketing authorisation for Slovenia, if he or she finds it necessary. A concluding opinion to such a demand must be obtained by the head of the Slovenian clinic that specialises in the treatment of the relevant diseases. On these grounds, the application for a temporary marketing authorisation could be filed with the JAZMP by wholesale distributors of pharmaceutical products.

Manufacturers of medicinal products that sponsor ongoing clinical trials that are approved by the JAZMP, or an applicant for a marketing authorisation in a centralised procedure according to article 6 of Regulation (EC) No. 726/2004, may file an application for a permit for distribution of medicinal products under the compassionate use programme, under which it is allowed to distribute to groups of patients with chronic or severe diseases who cannot be sufficiently cured with medicines that have marketing authorisations.

Rules for both of the above-mentioned exceptions are further elaborated by Regulations on the conditions and procedures for granting import permits for medicinal products for human use.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

Rules on price regulation do not differ between the outpatient and in-patient sectors. Prices of medicinal products not financed from public funds are not regulated and are freely determined by the manufacturer or distributor.

In respect of medicinal products financed from public funds, the maximum allowed price (MAP) is determined in the mandatory procedure run by the JAZMP, which must be initiated by an authorisation holder prior to launching the medicinal product on the market for the first time (question 25).

Due to ongoing efforts to reduce healthcare expenses, the JAZMP's competence to declare mutual interchangeability of medicinal products

Update and trends

ZZdr-2 was adopted in 2014, therefore we do not expect any material changes in the near future. However, due to the fact that most of the regulations adopted under the previous Medicinal Products Act (ZZdr-1) have been prolonged, a number of executive acts providing more detailed rules and guidelines are expected to be adopted in the next few years.

on the grounds of the application filed by the holder of a marketing authorisation, or on the grounds of the initiative of an expert institution, is also relevant as compulsory health insurance run by the ZZS, in respect of medicinal products from certain therapeutic groups, only covers the costs of medicinal products with the most effective balance between costs and the product's therapeutic effectiveness. Irrespective of the limitation described, costs of medicinal products listed on the positive or intermediary list are covered if it is required for treatment due to health reasons.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

Slovenian legislation does not govern any mandatory negotiations, as the majority of decisions are delivered within the administrative procedure.

The decisive factor for the coverage of costs of medicinal products is inclusion of the product on the positive or intermediary list, as proportions of coverage differ. A decision on inclusion on the positive or intermediary list is delivered by the ZZS in the administrative procedure. As indicated in question 22, decisions delivered by the JAZMP on the MAP and mutual interchangeability of medicinal products are also very important in respect of the coverage of costs.

Irrespective of the MAP decided upon, holders of marketing authorisations and wholesalers of medicinal products might, on a voluntary basis, enter into negotiations and conclude separate agreements for lower prices of medicinal products with the ZZS, providers of health services funded from public revenue and several other subjects.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

Rules on the coverage of costs do not differ between the outpatient and in-patient sectors. As indicated in question 23, the ZZS, as provider of compulsory health insurance, covers the costs for the most effective medicinal products from certain therapeutic groups, unless, due to health reasons, treatment with other medicinal products from a positive or intermediary list is required. Coverage of costs does differ from one list to another (see question 2).

The value of costs covered (not the percentage of coverage), is determined by the ZZS for medicinal products from each therapeutic group, taking into account the JAZMP's decision on the MAP and interchangeability of medicinal products. The value must not be lower than the price of the cheapest medicinal product from certain therapeutic groups. Costs of medicinal products prescribed under the compassionate use programme are covered by the manufacturer.

As sole responsibility for the prescription of medicinal products lies with physicians, a patient cannot be sanctioned for a prescription for off-label purposes. Therefore, medicinal products are issued to the patient under the standard terms and conditions of health insurance described above. Although the ZZS is competent for ex-post prescriptions' supervisions, if irregularities are discovered, contractual penalties could be imposed on providers of health services.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The decision regarding the pricing of medicinal products that are financed from the public revenue is delivered by the JAZMP in a procedure stipulated by ZZdr-2 and by the Rules on the Pricing of Medicinal Products for Human Use. The same rules also stipulate the criteria and procedures for determination, amendments and publications of regulated prices of medicinal products.

MAPs are determined on the principle of external price referencing, taking into account prices of medicinal products in Austria and France and Germany. If the medicinal product is not marketed in any of the reference countries, MAPs are formulated that take into account the value of the manufacturer's element of price and the profit margin pharmaceutical wholesale distributors are entitled to. MAPs are determined twice a year and a decision is usually delivered within 90 days.

In cases when, due to the size and other characteristics of the Slovenian market, the MAP does not enable authorisation holders to supply the market, under article 159 of ZZdr-2, an extraordinary higher allowed price (EHAP) may be determined for medicinal products for human use. Such a procedure falls within the JAZMP's competence and is further defined by the Rules on the Pricing of Medicinal Products for Human Use.

ZZZS is the competent authority for the delivery of public revenue finance within the administrative procedure, which is regulated by the Healthcare and Health Insurance Act. As indicated in question 23, the percentage of purchase cost coverage differs between different lists of medicinal products, varying from zero per cent for unlisted medicinal products up to 100 per cent for medicinal products listed on positive lists. The ZZZS's decision regarding listing on one of the lists is based upon several different factors including, but not limited to, the importance of the medicine for public health, priority tasks of the healthcare programme, therapeutic importance of the medicine and the assessment of the medicine's pharmaceutical economic data. Another medicinal product from a therapeutic group can be added to any of the lists only if it can be demonstrated that it has equal or greater therapeutic and economic value compared to an existing medicinal product.

The percentage of purchase costs of the medicinal products not covered by the ZZZS is usually covered by the voluntary health insurance. (For additional information, see question 2.)

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

Under ZZdr-2, mandatory discounts for medicinal products can be determined where it can be established that such a discount is in the public interest for the purpose of securing financial sustainability for the financing of medicinal products from the public revenue, or in cases where competition does not exist or is not sufficient. Discounts are prescribed by a decree issued by the Minister for Health for a 12-month period.

Discounts do not apply to medicinal products' distribution, which is permitted under the compassionate use programme and for medicinal products included on the list of essential or necessary medicinal products. It does not apply to medicinal products included on the list of interchangeable medicinal products that an MAP has been determined for and to medicinal products that an EMAP has been determined for. A marketing authorisation holder can also avoid such discounts if a special discount is proposed for certain subjects.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Under article 23 of ZZdr-2, all subjects included in the marketing of medicinal products are obliged to immediately notify the JAZMP of any suspicion that medicinal products have been falsified or are of inadequate quality. In order to aid detection of falsified medicinal products, packaging of certain groups of medicinal products must contain protective element. The JAZMP has the authority to deliver its decision on whether a medicinal product should be recalled and decide whether the public should be notified. Pharmaceutical inspectors organised within the JAZMP are authorised to search premises, prohibit the marketing of medicinal products and to order the destruction of medicinal products.

The above-mentioned provision of ZZdr-2 implements the provisions of Directive 2011/62/EC, amending EU Directive 2001/83/EC in the Slovenian legal system. One of the main reasons for adopting ZZdr-2, which was enforced in 2014, was the implementation of EU legislation within the Slovenian legal system.

As counterfeiting and illegal distribution of medicinal products may also infringe trademarks or patent rights or both, a holder also has an option to file an application for customs action governed by EU Regulation 608/2013.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

As described in question 5, advertising of prescription-only medicinal products to the general public is not allowed. Although in recent years, the central database of medicinal products, which also includes an approved summary of product characteristics and instructions for use, has been made publicly available.

29 Outline major developments to the regime relating to safety monitoring of medicines

In order to implement the provisions of Directive 2010/84/EU and EU Directive 2012/26/EU on pharmacovigilance in the Slovenian legal system, the ZZdr-2 was adopted in 2014. The rules and guidelines are further stipulated by the rules on pharmacovigilance of medicinal products for human use. Healthcare professionals are obliged to report any suspicions of adverse reactions to medicinal products to the national pharmacovigilance centre (University Medical Centre, Ljubljana) within 15 days of its identification. Such a report could be also submitted by patients or their relatives. The obligation to establish a sufficient pharmacovigilance system is also imposed on holders of marketing authorisations. Therefore, authorisation holders are obliged to appoint responsible persons who are sufficiently qualified, who must provide that the pharmacovigilance system is established and maintained and that all relevant information is sent to the JAZMP, European Medicines Agency, European Commission and the EudraVigilance database.

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Vaccination

30 Outline your jurisdiction's vaccination regime for humans

The vaccination regime in Slovenia is regulated with the Contagious Diseases Act (ZNB) and Rules on vaccination, immunisation and protection against the spread of infectious diseases. Under article 22 of the ZNB, vaccination is mandatory for haemophilus influenzae type B, diphtheria, tetanus, whooping cough, infantile paralysis, measles, mumps, rubella and hepatitis B. In certain situations, obligatory vaccination can be also instructed for rabies, yellow fever, typhus, tick-borne encephalitis, influenza, tuberculosis and, for specific epidemiologic reasons, for other contagious diseases. Mandatory vaccination may be omitted only in exceptional cases (eg, when vaccination is not possible due to health reasons).

A vaccination record must be kept in the patient's medical record and in the patient's vaccination booklet. Upon vaccination, the National Institute for Public Health must be also notified. During several different stages in life (eg, before children enter nursery, before students start with their higher educational level in their school programme, at first employment), when an individual is examined by a physician, the physician must verify whether or not all mandatory vaccinations have been performed. The physician is obliged to carry out any missing vaccinations.

Obligatory vaccinations are financed through compulsory health-care insurance, while voluntary vaccinations are financed through direct payment by the patient, or in some cases, the patient's employer. Costs for voluntary vaccination are not recoverable.

In Slovenia, the vaccination rate for mandatory vaccinations in 2014 (the last available data) was fairly high, reaching the 94.9 per cent rate for vaccinations against haemophilus influenzae type B, diphtheria, tetanus, whooping cough and infantile paralysis, and the 93.7 per cent rate for vaccinations against measles, mumps and rubella. It has, however, still not reached the World Health Organization (WHO) target rate of 95 per cent. On the other hand, the rates for voluntary vaccination are still very low. The vaccination rate for tick-borne encephalitis is estimated at 7 per cent and for influenza, only 3.3 per cent. A particular problem concerns the estimated at 7 per cent and for influenza only 3.3 per cent against influenza in the 65 and above age group, which stands at only 10.9 per cent. Slovenia therefore falls within the group of European countries with the lowest rate of vaccinated people for influenza aged 65 and above, missing the WHO target rate of 75 per cent.

South Africa

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Adams & Adams

Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The Constitution of South Africa provides that everyone has the right of access to healthcare services and that no one may be refused emergency medical treatment.

South Africa's health system, as in most other jurisdictions, is made up of a public sector component catering for the majority of the population, and a smaller private sector component providing health services to patients who can afford payment or have medical insurance. The healthcare provided varies from basic healthcare offered free by the state to highly specialised private-sector services available to those who can afford it.

Although South Africa's health system is centralised in the National Department of Health as regards policy and legislation, it is decentralised as far as training and delivery is concerned, and aims to offer accessible and free basic packages of primary healthcare to all of its citizens. These goals are presented in the National Health Act 61 of 2003 (National Health Act), which establishes the structure for the implementation of a national healthcare system based on primary healthcare and regional healthcare systems operated by district health systems. The healthcare system thus comprises national health, provincial health and district healthcare systems. The Department of Health is headed by the Minister of Health, as regards policy, and the Director General, who must ensure the implementation of national health policy and issue guidelines on its implementation. Provincial health must ensure implementation of national health policy and must provide various health-related services such as the provision of specialised hospital services, the evaluation of the rendering of health services and the consultation with communities regarding health matters, to name but a few. The district health system consists of various health districts, and the boundaries of health districts generally coincide with district and metropolitan municipal boundaries. District health must assign and delegate such health services to a municipality in its province as necessary under the Constitution.

On the other hand, the market-based private sector caters mainly for medium to high earners that are generally members of medical schemes, and often also for foreigners looking for relatively affordable yet advanced surgical procedures. A great many of the country's health professionals are also attracted to work in the private sector.

A national health insurance policy paper has been drafted that will ensure that everyone has access to appropriate, efficient and quality health services, but this is not yet in force. However, a pilot project has been commenced (a report is available on the Department of Health website). Implementation of a national health insurance is, therefore, from the government's side at least, seen as a certainty in the near future.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

There is a two-to-three tier system in South Africa that consists of a nationally funded public healthcare system and a privately funded healthcare system. The third 'tier' is for cash-paying patients, who receive primary care and medicines from general practitioners. The public healthcare system is wholly subsidised by the state and aims to provide medicines at a primary healthcare level free of charge, mainly

to persons with an income below a certain level. A national list of medicines – the Essential Drug List – is drawn up periodically by the Department of Health and consists of medicines for use in the national healthcare system. The private healthcare system is not subsidised by the state, and is paid for by individuals or private medical schemes that they are party to.

The public health budget is allocated and spent by the nine provinces, and the standard of healthcare delivered and method of allocation varies between provinces; poorer provinces like the Eastern Cape face many more problems in respect of healthcare delivery than wealthier provinces such as Gauteng.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

There are different legislative and other instruments that regulate the advertising of medical products to the public and to healthcare professionals. Advertising in South Africa is also generally regulated by the Advertising Standards Authority of South Africa in terms of an Advertising Code. The Medicines and Related Substances Act 101 of 1965 (Medicines Act) and the General Regulations issued under this Act are of particular importance, as well as provisions of the Foodstuffs, Cosmetics and Disinfectants Act 54 of 1972 and the Consumer Protection Act 68 of 2008.

Section 18C of the Medicines Act empowers the Minister of Health, after consultation with the pharmaceutical industry and other stakeholders, to make regulations relating to the marketing of medicines, including an enforceable code of practice, while section 20 prohibits the publication or distribution of false or misleading advertisements concerning medicines.

Publication, in terms of the Medicines Act, of a South African Code of Practice for the Marketing of Health Products (Marketing Code) occurred and the Marketing Code has been effective since 13 September 2013. The Marketing Code is administered by the Marketing Code Authority (MCA), established by the Marketing Code. The MCA comprises representatives from all health product trade associations and 'independents'.

Regulation 45 of the General Regulations issued under the Medicines Act prescribes the manner in which medicinal products may be advertised and marketed.

Other legislation includes the Pharmacy Act 53 of 1974 (Pharmacy Act), the Good Pharmacy Practice in South Africa Standards, the Foodstuffs, Cosmetics and Disinfectants Act 54 of 1972, the Labelling and Advertising of Foodstuffs Regulations promulgated in terms of the Foodstuffs, Cosmetics and Disinfectants Act 54 of 1972, the Medical Schemes Act 131 of 1998 (Medical Schemes Act) and the Copyright Act 98 of 1978.

Until recently, the Medicines Act, as well as the Marketing Code, did not extend to complementary medicines. In November 2013, amendments to the General Regulations to the Medicines Act extended their application to complementary medicines in certain circumstances. Due to pressure from industry players, however, further amendments are being proposed that will ease restrictions on complementary medicines.

It is further important to note that, pending proclamation by the President, sections 18A, B and C of the Medicines Act shall be amended such that the definition for 'advertisement' shall in future extend to a product, medical device and an in vitro diagnostic medical device. A 'product' shall also extend to cosmetics and foodstuffs, but only insofar as it contains a scheduled substance. A further amendment Bill (Bill 6 of 2014) to the Medicines Act is currently before Parliament and will establish a new regulatory authority (SA Health Products Regulatory Agency (Sahpra)) for medicines, devices and in vitro diagnostic devices, and will expand the regulatory oversight to all cosmetics and foodstuffs.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

Regulation 45 of the General Regulations issued under the Medicines and Related Substances Act 101 of 1965 prescribes which medicines and the manner in which these medicines are permitted to be advertised to the public and to healthcare professionals, including medical practitioners, dentists, veterinarians and pharmacists. Regulations 8 to 10 also prescribe the information and other features to be adhered to in the labelling of medicinal products, package inserts, patient information leaflets, etc.

In terms of the ethical rules of conduct under the Health Professions Act 56 of 1974 (Health Professions Act), a practitioner shall not participate in the manufacture for commercial purposes or in the sale, advertising or promotion of any medicine or medical device or in any other activity that amounts to selling medicine or medical devices to the public or keeping an open shop or pharmacy. A practitioner shall not engage in or advocate the preferential use or prescription of any medicine or medical device that, save for the valuable consideration he or she may derive from such preferential use or prescription, would not be clinically appropriate or the most cost-effective option. The above provisions shall not prohibit a practitioner from owning shares in a listed company, or manufacturing or marketing medicines while employed by a pharmaceutical concern or dispensing in terms of a licence issued under the terms of the Medicines and Related Substances Act of 1965.

Furthermore, the Medicines and Related Substances Act, the Health Professions Council of South Africa (HPCSA) Guidelines and the Marketing Code contain guidelines as to what is appropriate with regard to the relationship between pharmaceutical companies and healthcare professionals.

5 What are the main rules and principles applying to advertising aimed at the general public?

In terms of Regulation 45 of the General Regulations issued under the Medicines Act, medicines may not be advertised to the public if they are prescription-only medicines.

An advertisement may not contain any statement that is in conflict with, exceeds or deviates from the approved medicine registration application with regard to the safety, quality or efficacy of the medicine.

Written advertisements must set out the proprietary name (and alternative proprietary name, if applicable) of the medicine, the approved name and quantity of each active ingredient, and the registration number if the medicine has been registered. A medicine that did not previously require registration, but later does, may be advertised provided that an application for registration has been submitted.

If the medicine is homeopathic, the regulations require that the advertisement must state that the medicine must be administered in accordance with homeopathic principles. When a medicine is advertised verbally for the first time to medical practitioners, it must be accompanied by a written document containing the above information.

In terms of the Act, the General Regulations and advertising standards, no person shall publish or distribute any false or misleading advertisement concerning any medicine; and any advertisement in respect of a medicine may not contain any statements that deviate from, are in conflict with, or go beyond the evidence contained in the medicine registration application.

The Marketing Code also lists a number of principles that regulate advertising medicines to the general public. These principles require, for example, that advertisements should not be misleading, ambiguous, disparaging or contain claims that are unfair, untruthful, inaccurate or confusing, as well as other general regulatory principles. For example, advertising or promotions shall not be aimed principally or exclusively at children under 12 years of age, and no advertising or

promotion shall show children using or within reach of medicine without adult supervision.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

It is difficult to determine which infringements are the most common regarding advertising rules. However, as discussed above, advertising in South Africa is strictly regulated. Cases before the MCA since 2013 and to date have concerned unsubstantiated statements, advertisements on publicly accessible websites and links to international websites for scheduled medicines, and whether particular advertisements based on the outcomes of post-registration studies constitute off-label advertisements (ie, whether they are in line with the package insert).

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

In South Africa, various stipulations of the Medicines and Related Substances Act and the Regulations issued under this Act, particularly Regulation 45(3), prohibit the dissemination of information regarding the off-label use of medication. Regulation 45(3) stipulates that no advertisement for medicine may contain a statement regarding its safety, quality or efficacy that deviates from the purpose for which and the manner in which it was registered.

Section 20(1)(b) of the Act forbids any advertisement from making any claim regarding the therapeutic efficacy and effect other than that for which it is registered (and as indicated in the labelling thereof). The definitions of 'advertisement' and 'public' as contained in section 1 of the Act are very wide, and the latter is defined so as to include medical health professionals. In effect, no written or oral information regarding the safety, quality or efficacy of the off-label use of medicine may be disseminated to the public or to medical practitioners by the manufacturer or distributor. Furthermore, the Marketing Code provides that the advertisement of a medicine must be consistent with the package insert and the terms of the registration.

Off-label use may only be permissible if the conditions of the registration have been amended. If a product is used by a healthcare professional for a condition where such use is not approved, he or she may be liable to civil proceedings. However, practitioners may request information from companies' medical departments in relation to off-label use and the effects thereof (eg, adverse events reported when products are used during pregnancy or on children).

Specific permission may be granted for products that are registered elsewhere or are registered for other indications elsewhere to be advertised to conference goers when an international conference is held in South Africa.

As registration of products and new indications takes an exceedingly long time in South Africa, and due to the global nature of health information and information-sharing at conferences, off-label use may be more prevalent for products already registered for other indications.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

The most important legislation governing the pharmaceutical industry in general is the Medicines Act, the Pharmacy Act and the Health Professions Act. Other relevant legislation includes the National Health Act, the Medical Schemes Act, the Public Service Act 103 of 1994 (Public Service Act) (which is relevant in the context of healthcare professionals who are public employees), the Preventing and Combating of Corrupt Activities Act 12 of 2004 (Corruption Act) and the Competition Act 89 of 1998 (Competition Act).

The Marketing Code and the Advertising Code are of particular importance with regard to the advertising and promotion of medicines.

Various guidelines issued by the Medicines Control Council (MCC or Council) deal with, inter alia, clinical trials, good manufacturing practice, good distribution practice, and licensing and registration of medicines.

Furthermore, the Pharmacy Council has issued a good pharmacy practice manual. The HPCSA has also issued various guidelines that are applicable to health professionals, such as the Guidelines on Over-servicing, Perverse Incentives and Related Matters (HPCSA Guidelines).

Apart from that, various professional bodies such as IPASA, NAPM and Pharmisa have signed up to the Marketing Code, and their own internal constitutions make compliance with the Code a precondition of membership. The Marketing Code, and in particular the Guidelines to the Marketing Code, make specific provision for various types of interactions (eg, at continuing professional development (CPD) events, gifts (reminder items, items of medical utility (eg, academic journals) for speakers and sponsorships). Monetary limits are set for sponsorships and gifts, and guidelines are set regarding the nature of these. Honoraria must be reasonable, and contracts between companies and speakers, key opinion leaders and beneficiaries of sponsorships should exist.

There appears to be no distinction drawn between doctors and other healthcare professionals in the outpatient and in-patient sectors with regard to the pharmaceutical industry. However, a distinction exists between medical practitioners and pharmacists regarding the pricing policy of medicines (ie, the dispensing fees that they may level).

New proposals issued by the Department of Health in the form of regulations under section 18A of the Code aim to further regulate the relationship between the industry and suppliers of medicines, with the intent to outlaw various 'incentive schemes' ranging from free services to the payment of marketing and other fees.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The Medicines Act, the HPCSA Guidelines and the Marketing Code contain guidelines as to what would be appropriate conduct between a pharmaceutical company and a doctor or other healthcare professional, both in the private and public sectors.

The Medicines Act prohibits 'bonusing' (section 18A) or the free supply of medicines to doctors (section 18C – sampling). The HPCSA Guidelines contain rules with regard to, inter alia:

- preferential usage or prescription of medicines;
- receiving a commission or financial gain or other valuable consideration for the supply of any goods, substances or materials used by a healthcare professional in his or her practice;
- the charging or receiving of fees; and
- CPD events and international conferences, and expenses relating thereto.

The Marketing Code contains rules with regard to hospitality, sponsored meetings and events including CPD, consultancy services, inducements and gifts.

The Corruption Act deals with offences relating to corrupt activities of public officers and non-public officers.

The Public Service Act prohibits government employees, such as state-employed doctors, from engaging in remunerative work outside the public service, other than as is permitted in their contracts of employment, without the consent of the relevant authorities.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

Infringements regarding contravention of the Marketing Code are the most common infringements in South Africa.

Under the provisions of the Marketing Code, companies, organisations and individuals are permitted to organise or sponsor meetings and events, including CPD.

The following should be adhered to, as provided in the Marketing Code:

- the merit and focus of the meeting should be clearly scientific, educational, or both;
- the venue and hospitality should be secondary to the meeting both in terms of time allocation and focus;
- the venue should be appropriate and conducive to the scientific or educational objectives and the purpose of the event or meeting;
- hospitality, meals and entertainment should be modest;
- inappropriate financial benefit or material benefits, including excessive hospitality, cannot be offered or extended to healthcare professionals;
- for product launches, no sponsorship or payment of travel and accommodation can be extended to healthcare professionals; and

- for speakers, payment of reasonable honoraria and reimbursement of out-of-pocket expenses, including travel, are permissible provided this is in terms of a written contract.

With regard to CPD meetings:

- no product promotion is allowed in the CPD meeting room, although company branded items are permissible;
- speakers should use the international non-proprietary name of products during CPD events;
- companies must make it known to speakers that the use of trade names is not permitted;
- product promotional material displayed outside the CPD meeting room should not be accessible to the general public if it is not permissible to market such product directly to the public;
- for local CPD events and product launches that are held in major cities, reasonable travel arrangements or travel reimbursement can be made to ensure that healthcare professionals that do not reside or practise in major cities are able to access the applicable information;
- the criteria for selection of attendees or invitees must be transparent and available to the MCA on request for scrutiny for medical or scientific congresses, conferences or seminars held in South Africa or internationally, or international meetings organised overseas and held in South Africa;
- meetings organised by pharmaceutical companies, other organisations or individuals at venues outside South Africa that are educational and scientific in nature and involve South African healthcare professionals are acceptable; and
- the rationale for any meeting or sponsorship to attend a meeting must be transparent, valid and cogent.

For medical or scientific congresses, conferences or seminars held in South Africa or internationally, or international meetings organised overseas and held in South Africa:

- meetings organised by pharmaceutical companies, other organisations or individuals at venues outside South Africa that are educational and scientific in nature and involve South African healthcare professionals are acceptable;
- the reason for any meeting or sponsorship to attend a meeting must be transparent, valid and convincing;
- consideration must be given to the educational programme's overall cost, facilities, etc;
- payment of registration fees, travel and accommodation must be made to the professional organisers; and
- sponsored speakers may receive reasonable honoraria.

Other interactions with healthcare professionals

Consultancy services

The engagement of a healthcare professional to provide genuine consultancy or other genuine services to a company is permitted. Healthcare professionals that provide consulting services to a company and are still practising their profession must declare their employment arrangement with the company whenever they write or speak in public about a matter that is the subject of the employment or any other issue relating to that company. Such an arrangement must be formalised in a written agreement.

Inducements

There should be no personal enrichment of healthcare professionals or other healthcare providers. No gift, benefit or any other pecuniary advantage shall be offered or given to members of the health professions, administrative staff, government officials or the general public as an inducement to prescribe, supply, stock, dispense, administer or buy any medicine. No donation should unjustifiably enrich healthcare professionals performing a health-related service.

Gifts and promotional items

Occasional gifts and promotional items to healthcare professionals and appropriate administrative staff are acceptable provided that they are inexpensive and of minimal intrinsic, educational or scientific value, are of benefit to the patient or are relevant to the practice. Monetary limits are set in the Guidelines to the Marketing Code.

Promotional items

It is permissible to brand promotional items. The minimum information for a medicine as required does not have to be included on a promotional aid provided that no promotional claims are made.

Corporate social investment

Donations to meet identified corporate social responsibility projects may also be made if judged on their merits, approved by the responsible persons in each company or organisation and documented.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

See questions 8, 9 and 10.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes. South Africa has a state-run Competition Commission that investigates alleged anticompetitive behaviour. Competition law is regulated by the Competition Act. One of the most recent cases concerned an exclusive agreement between a local generic manufacturer and an international supplier of an active ingredient. The complaint was lodged by Médecins Sans Frontières – Doctors without Borders.

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes, follow-on private civil litigation is possible.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

The Prevention and Combating of Corrupt Activities Act 2004 applies to all settings and all industries, including the pharmaceutical industry. It creates a general offence of corruption, namely:

Any person who, directly or indirectly:

- accepts or agrees or offers to accept any gratification from any other person, whether for the benefit of himself or herself or for the benefit of another person; or
- gives or agrees or offers to give to any other person any gratification, whether for the benefit of that other person or for the benefit of another person, in order to act, personally or by influencing another person so to act, in a manner:
 - that amounts to the:
 - illegal, dishonest, unauthorised, incomplete, or biased; or
 - misuse or selling of information or material acquired in the course of the, exercise, carrying out or performance of any powers, duties or functions arising out of a constitutional, statutory, contractual or any other legal obligation;
 - that amounts to:
 - the abuse of a position of authority;
 - a breach of trust; or
 - the violation of a legal duty or a set of rules;
 - that is designed to achieve an unjustified result; or
 - that amounts to any other unauthorised or improper inducement to do or not to do anything, is guilty of the offence of corruption.

The Act also makes the reporting of instances of alleged corruption by someone who knew, or 'ought to have known' of 100,000 rand or more, mandatory. This is then reported to the National Head of the Directorate for Priority Crime Investigation.

The Marketing Code compels the disclosure of all sponsorships at all 'meetings and proceedings'. Agreements relating to registries 'may be called from time to time'. Honoraria payments may be scrutinised by the MCA. Where equipment is placed, it must be done in accordance with an agreement that should be made available. In cases of complaints, materials associated with the complaints have to be provided. The MCA Adjudication Committee is empowered by the Code to request and review all instances where the Code requires documents to be kept, agreements to be entered into, etc.

In terms of the Promotion of Access to Information Act, 2000 (PAIA), any entity may request information that pertains to the exercise

of their rights. It is therefore possible for any entity to request for a document, such as a doctor payment, to be made. Access to information may only be declined on the grounds listed in PAIA. There is also provision for mandatory disclosure of information where:

- '(a) the disclosure of the record would reveal evidence of:
- (i) a substantial contravention of, or failure to comply with, the law; or
 - (ii) an imminent and serious public safety or environmental risk; and
- (b) the public interest in the disclosure of the record clearly outweighs the harm contemplated in the provision in question.'

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Yes. Manufacturing, advertisement and use of medical devices is regulated by the Code of Marketing Practice, and the South African Medical Device Industry Association is a member of the MCA. A separate section in the Code deals with medical devices, and most of the other provisions of the Code, where possible, also apply to devices. This includes, for example, the provisions on interactions with healthcare professionals.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The Medicines Act governs the manufacture, distribution, sale and marketing of medicines, and governs the granting of marketing authorisations or registration. Pricing regulations for medicines require that a product obtain a 'single exit price' (SEP) prior to product launch.

17 Which authorities may grant marketing authorisation in your jurisdiction?

The registration of medicines is approved by the MCC. The MCC was established by the Medicines Act. No medicine that is subject to registration may be sold until such registration has been approved as defined in section 14 of the Act, except in very limited circumstances, wherein the Council may approve the sale of unregistered medicines. Bill 6 of 2014, once passed in Parliament as an amendment to the Medicines Act, will create a new authority – Sahpra – that will be responsible for the registration of nearly all health products in the future.

18 What are the relevant procedures?

Any person residing or doing business in South Africa may make an application to the Registrar of Medicines for the registration of a medicine. On the prescribed application form, the applicant will set out the following:

- (i) the particulars of the person with appropriate knowledge of all aspects of the medicine who shall be responsible for communication with the Council;
- (ii) the particulars of the applicant and the prospective holder of the certificate of registration, including:
 - name;
 - business address;
 - postal address;
 - telephone number;
 - fax number;
 - email address; and
 - contact details of the person referred to in (i);
- (iii) particulars of the medicine, including:
 - proprietary name;
 - dosage form (a separate application is made for each dosage form and each strength of dosage);
 - strength per dosage unit;
 - route of administration;
 - country of origin and registration status outside South Africa;
 - category and pharmacological classification;

- name of the manufacturers; and
 - approved name; and
- (iv) where the medicine has been registered outside South Africa, the following information must be provided:
- copy of the certificate of registration;
 - package insert;
 - conditions of registration; and
 - any other information as determined by the Council.

The prescribed application form shall also be accompanied by:

- a properly completed screening form obtainable from the registrar;
- a proposed label for use on the medicine;
- where applicable, a copy of the manufacturing licence together with the current good manufacturing practice certificate from the regulatory authority of the medicine's country of origin;
- in the case of specified schedule 5, 6, 7 and 8 substances, a certified copy of a permit to manufacture such substances;
- data on the safety, efficacy and quality of the medicine, whether positive or negative, as may be determined by the Council;
- proof of the existence of a manufacturing site (ie, a site master file);
- any other information as the Council may determine; and
- an application fee.

Three technical committees (Pharmaceutical and Analytical, Clinical and Naming and Scheduling) must recommend registration, and may require various changes prior to making a final recommendation for registration to the Council.

Once the registration is approved, a registration number is issued and the details of the registration are inserted in the Medicines Register. A registration is valid for between three and five years, and can be renewed as specified in section 15 of the Medicines Act read with Regulation 22 of the General Regulations issued under the Medicines Act.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

A licence to dispense or compound and dispense medicines, to manufacture or to act as a wholesaler or to distribute medicines is valid for five years. Licence fees must be paid yearly. The licence does not become invalid per se, but does require renewal if the medicine is not marketed within a specific time period. There is no exception made in terms of the length of each of the above specified time periods.

It is possible that a condition is placed in a licence agreement and in terms of section 22E(1) of the Medicines Act. The contravention of this condition may cause the Director General of the Department of Health or the Council to call upon that person to show him or her why that licence should not be suspended or revoked.

Many companies retain products no longer actively being marketed on the medicines register. There is no prohibition against this. The only requirement would be that renewal fees must be paid on both product registrations and company licences.

20 Which medicines may be marketed without authorisation?

The Council may authorise the sale of unregistered medicines as specified in section 21 of the Medicines Act. Unregistered medicines may also be allowed to be marketed where such medicine is compounded in the medical setting by a medical practitioner for use in a particular patient in a quantity no greater than that required for the treatment of the patient, or for use by a pharmacist in a quantity not greater than that prescribed by regulation for sale in the retail trade, subject to the conditions likewise prescribed, or in a quantity for a particular person or animal as prescribed by a medical practitioner, dentist or veterinarian, or a practitioner or nurse or other person registered under the Health Professions Act 1974.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

We understand that there are a number of named patient programmes in South Africa, for example in the oncology and cardiology sectors. Section 21 of the Medicines Act makes provision for the MCC to authorise any person to sell a specified quantity of any particular medicine that is not yet registered for a specific period.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

The pricing of medicine is regulated by the government. The Pricing Regulations promulgated under the Medicines Act in terms of section 22G deal with the pricing of medicines. The Pricing Regulations commenced on 2 May 2004. A Pricing Committee was established in terms of the Medicines Act.

The Medicines Act and the Pricing Regulations make provision for an SEP (that is, the price set by the manufacturer or importer of a medicine or scheduled substance combined with the logistics fee and VAT) and was, when the SEP was initially set for products in 2004, the price of the lowest unit of the medicine or scheduled substance within a pack multiplied by the number of units within a pack. The SEP is the only price at which manufacturers may sell medicine, and medicines may not be sold at a price higher than the SEP. The SEP for medicines has to be set at the date of commencement and in accordance with the Pricing Regulations, and cannot be increased for a period of one year thereafter.

The extent to which the SEP may be increased is determined annually by the Minister of Health on the recommendation of the Pricing Committee, with regard to the average consumer price index for the preceding year, the average producer price index for the preceding year, international pricing information relating to medicines and scheduled substances, comments received from interested persons, and the need to ensure the availability, affordability and quality of medicines and scheduled substances. A manufacturer may decrease the SEP at any time during a year, but may only once a quarter increase it up to the level of the SEP for that year. No price differentiation is possible at all.

It is important to note that the Pricing Regulations only apply to the private sector, and not to medicines that are sold to the government or state hospitals.

Low prices also come about because the government sometimes threatens drug companies with compulsory licensing to ensure a lower price. This is done under the provisions of section 56(1)(d) of the Patents Act 57 of 1978 and article 31 of the Trade-Related Aspects of Intellectual Property Rights. Compulsory licensing is also a remedy available under the Competition Act.

Reimbursement is governed by medical scheme formularies and treatment protocols (ie, even if a product has an SEP, there is no guarantee that it will be funded by medical schemes in the private sector).

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

The supply of medicines to the public sector (from primary care clinics to various levels of state hospitals) is carried out under a tender system and is linked to the Essential Drugs List. Tender prices are monitored and compared with international prices. The procurement of tenders is aimed at securing the lowest available prices, but preference will be given to companies (multinational or national) that manufacture products locally for designated tenders. Ten points out of 100 points in every tender also counts to the broad-based black economic empowerment) score of a company. Bidders are approached prior to the awarding of a tender so as to drive prices down. Apart from this interaction, which is solely at the discretion of the Department of Health, there is limited opportunity to negotiate prices in the public sector. The government reserves the right to consider international procurement, and also allows for parallel importation of medicines.

Tenders are often awarded to more than one supplier. Where a successful bidder cannot supply, the Department of Health will buy from other suppliers under the 'buy-outs' process. Failure to supply sometimes occurs when suppliers can no longer supply at the prices under which they won the tender (eg, due to exchange rate changes).

Apart from the state tender system, conducted in terms of the General Treasury Regulations issued under the Public Finance Management Act, there are opportunities to access the public sector market for products used in the tertiary system, where such medicines are used as part of the education and training system. This is called 'discretionary spend', and may be funded via tertiary grants provided by the Department of Health.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

South Africa does not have a national health insurance system (although the implementation of a national health insurance system is expected: see question 1); however, it does have a private healthcare reimbursement process. The Medical Schemes Act determines certain prescribed minimum benefits (PMBs). Any benefit option that is offered by a medical scheme must pay for the PMBs in full, without co-payment or the use of deductibles. The rules of the medical scheme must, in respect of any benefit option, provide that the diagnosis, treatment and care costs of a PMB be covered, but the scheme has two options to manage the cost of the full funding of the PMBs:

- by appointing a designated service provider (DSP), and to then only pay in full if those services are obtained from the DSP in respect of that condition; or
- managed care. However, if a scheme uses managed care, it must ensure that it does so as prescribed in the applicable regulations. The managed care tools (ie, formularies and protocols) must be based on the principles of evidence-based medicine, taking into account cost-effectiveness and affordability.

Although South Africa does not yet have a national health insurance policy in place, certain medicines are subsidised in full or in part by the state. All drugs provided at the primary care level are supplied free of charge to patients who earn up to a certain income bracket, while at the secondary and tertiary care levels, co-payment arrangements can be made for certain drugs supplied by the state.

The National Healthcare Policy is funded by the Department of Health, and the supply of medicines to state hospitals is by tender. The procurement of essential drugs and medical supplies for the public sector is undertaken at national level, but medicine procurement and distribution for the public sector is based in larger part on drugs that are on the Essential Drugs List for South Africa.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The pricing of medicines is governed by the Pricing Committee that is constituted under section 22G of the Medicines Act (see question 22).

Reimbursement varies from medical scheme to medical scheme and is governed by the rules governing that particular medical scheme (see question 24). There is no reimbursement on a national scale as there is no national health insurance system.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

There is currently no obligation for a manufacturer or distributor to give a discount. New proposed regulations under section 18A of the Medicines Act will ban all discounts, rebates and incentives schemes.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

As stated in question 20, the Medicines Act prohibits the sale of unregistered medicines. Furthermore, the Act also sets out penalties for making false or misleading statements during the course of the sale of a medicine, and for the sale of any medicine or scheduled substance upon whose container a false or misleading statement in connection with the contents is written. Penalties are also imposed for false advertising and labelling and the failure to obtain the requisite licences. The maximum penalty imposed for such offences is 10 years' imprisonment.

In terms of the Regulations to the Medicines Act, a medicine may be seized if it:

- is unregistered and sold in contravention of the Act;
- is suspected to be counterfeit;
- is misbranded;
- has expired;
- is suspected to be stolen;
- is scheduled and possessed by an unauthorised person, or by an authorised person but in unauthorised quantities;
- has been declared undesirable (not fit for public consumption) in terms of the Act;
- belongs to the state and is found to be possessed by an unauthorised person; or
- is used in an unauthorised clinical trial.

Generally, illegal or counterfeit medicines are dealt with according to the above. However, in the event that such terms cannot be invoked, it is possible that recourse can be made to the Counterfeit Goods Act 37 of 1997, which deals with counterfeiting of all products and not only counterfeit medicines. This Act allows for the seizure of counterfeit goods and provides for criminal sanctions for counterfeiting. Although this Act does not apply to products that are counterfeit imitations of another product as such, it applies where the counterfeit product entails an imitation of trademarks or copyright associated with the original goods.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

The MCC website provides various updates for the public, stakeholders and industry relating to various aspects of medicine registration and control.

Sections of the Medicines Act and Regulations thereto deal with the information that must be included in package inserts and on containers regarding scheduling, dosage, etc.

Access to information regarding prescription-only medicine is generally dealt with by the stakeholders themselves rather than by government bodies.

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29 Outline major developments to the regime relating to safety monitoring of medicines.

The MCC has a Pharmacovigilance Committee, which monitors the safety of medicines. Furthermore, medicine safety alerts are posted on the MCC website for the attention of medical practitioners, or companies are obliged by the MCC to issue safety updates, urgent safety updates or Dear Healthcare Professional letters.

According to the regulations, permit holders are also obliged to report adverse drug reactions that have either been reported to them or of which they become aware to the Council.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

South Africa's immunisation schedule is in line with the World Health Organization recommendations on how children should be vaccinated. According to the South African Vaccination and Immunisation Centre, the prescribed vaccination regime is as follows:

Age	Vaccine
Birth	BCG (anti-tuberculosis vaccine) TOPV (trivalent oral polio vaccine)
Six weeks	TOPV RV (rotavirus vaccine) DTP-IPV/Hib (diphtheria, tetanus, pertussis vaccine, inactivated polio vaccine, haemophilus influenzae type B vaccine) Hepatitis B PCV7 (7-valent pneumococcal vaccine)
10 weeks	DTP-IPV/Hib Hepatitis B
14 weeks	RV DTP-IPV/Hib Hepatitis B PCV7
Nine months	Measles PCV7
18 months	DTP-IPV/Hib Measles
Six years	Td (tetanus and diphtheria vaccine)
12 years	Td

Vaccines are generally administered free of charge at public clinics. Private institutions also administer vaccines, but at a charge.

In addition to the above, South Africa has rolled out an HPV vaccination programme in all schools. Cervarix is provided in two doses (although registered for three) for girls in grade 4 (between nine and 12 years of age) at state cost.

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Sweden

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

Healthcare in Sweden is the shared responsibility of the state, county councils and municipalities. The state is responsible for the overall health and medical care policy.

The Ministry of Health and Social Affairs acts to meet the objectives set by the Swedish Parliament and the government. Several independent agencies answer to the Ministry of Health and Social Affairs. The following agencies support the Ministry's activities in the area of health and medical care: the National Board of Health and Welfare, the Medical Responsibility Board, the Swedish Council on Health Technology Assessment, the Medical Products Agency (MPA), the Swedish Agency for Health and Care Services Analysis, the Dental and Pharmaceutical Benefits Agency and the Health and Social Care Inspectorate. In addition, the Swedish E-health Agency and the Public Health Agency were implemented on 1 January 2014.

The Swedish healthcare system is regulated by the Health and Medical Service Act (1982:763), which, inter alia, sets out the respective responsibilities of county councils and municipalities for health and medical care. The Health and Medical Service Act states that the aim in Sweden is good health and medical care on equal terms for the entire population. Medical care shall be provided with due respect for the equal worth of all people and the dignity of the individual. Priority shall be given to those who are in the greatest need of health and medical care.

The Swedish laws are in many respects adapted to the applicable EU legislation. The EU directives are transposed into acts and ordinances by the government and into provisions by the relevant authorities, inter alia, the MPA.

The re-regulation of the former state-owned monopoly over pharmacies was conducted in 2009 and since then several private organisations have entered the pharmacy market.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

In Sweden, the healthcare system is mainly financed through tax revenues. Fees play a relatively limited role as a source of finance. A large part of publicly funded healthcare is provided by private care providers that have contracts with a county council or municipality. Private care, where patients themselves pay the entire cost, represents only a small part of the healthcare system. There is also a relatively small amount of private health insurance, but the number of people covered has increased in recent years.

There are 20 county councils in Sweden, with responsibilities that often require considerable resources. The county councils' most important task is health and medical care, and the major portion of their budgets is spent on health and medical care and dental care. County councils are responsible for organising their services so that all citizens have access to adequate care.

Approximately 70 per cent of the county councils' services are financed by county council taxes. County councils also receive revenue from patient charges and the sale of services. State support is in the form of general central government grants. The state also gives targeted grants to increase access to care and to pharmaceutical benefits.

Medicinal products have three financial sources in Sweden: the county councils, the state and patients. The county councils pay all costs for medicinal products for in-patient care. They are responsible for providing healthcare to the population, and they have the right to levy taxes to finance their duties. The county councils receive a specific government grant for prescription medicinal products for outpatient care.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

The Marketing Practices Act (2008:486) governs advertisements in general in Sweden and is also applicable to advertisement of medicinal products. The Act protects consumers from misleading advertising and other unethical marketing practice, and it states, inter alia, that marketing practices shall be consistent with generally accepted marketing practices, generally accepted business practices or other accepted norms, and be fair towards consumers and traders. The Radio and Television Act (2010:696) is also applicable.

In addition, the Medicinal Products Act (2015:315) and the provision (2009:6) from the MPA published in the Agency's Code of Statutes, LVFS, govern the advertising of medicinal products.

The legislation includes a number of important requirements on advertising, such as being up to date, being matter-of-fact and being balanced. The advertising must not be misleading and must be in accordance with best practice for the advertisement of pharmaceuticals. This includes advertising both to the public and to healthcare professionals. Fundamental rules also stipulate that only approved medicinal products may be advertised in Sweden, and that advertising aimed towards children and advertising of prescription-only medicinal products is not allowed (except for campaigns for vaccination against human infection diseases). The Medicinal Products Act stipulates that pharmaceutical companies are responsible for the surveillance of their advertising through an in-house function with scientific competence.

The research-based pharmaceutical industry in Sweden has, through its trade organisation LIF, developed a system of self-regulation in the pharmaceutical sector. LIF has thus adopted ethical rules and a self-regulation system concerning, inter alia, advertisement to the public sector and healthcare professionals in 'The Ethical Rules for the Pharmaceutical Industry' (LIF Ethical Rules), which came into force on 1 October 2007 and were last revised on 19 April 2016 (valid from 15 June 2016).

The LIF Ethical Rules play a very important role in the pharmaceutical industry, even though they are not legally binding. These Rules are also often applied by the courts as an expression of fair and ethical marketing.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

In addition to the more general regulations in the Marketing Practices Act and the Medicinal Products Act, the LIF Ethical Rules (see question 3) specify in greater detail the requirements on information that is addressed to doctors and other healthcare personnel. The basic principle is laid down in Chapter 1, article 1 of the LIF Ethical Rules, and states that the information on medicinal products must include accurate, objective, meaningful and balanced particulars dealing adequately with

the favourable and unfavourable properties of the medicinal products. The LIF Ethical Rules are extensive and specify, for example, that:

- the information should be within the formulation of the summary of the product characteristics (SPC);
- the product information may not be offensive and shall be compatible with good taste and practice;
- the information must be truthful and not misleading and must also be easy to recognise as such;
- the information as to the quality and efficacy shall be capable of substantiation by means of documentation;
- the information, including comparisons between effects, must be presented in a fair way; and
- product samples must be distributed in a very restricted manner: at most, one per product per year to one and the same person.

It is the responsibility of the pharmaceutical company, or its representatives in Sweden, to observe the LIF Ethical Rules, and the pharmaceutical company should be able to substantiate any facts, statements, claims and other representations in words or pictures contained in its product information.

5 What are the main rules and principles applying to advertising aimed at the general public?

Advertising or marketing is a broad definition under Swedish law, and a lot of the information on the particular medicinal product is considered as marketing material.

According to the Medical Products Act, advertising of prescription-only medicines to the general public is prohibited (with the exception of vaccination campaigns against human infectious diseases) it is, however, permitted to advertise non-prescription medicines, though not to children.

Information to the general public for prescription medicinal products shall therefore be supplied only to the extent permitted in the MPA's provisions or other applicable laws and regulations. According to LIF Ethical Rules Chapter 1, section 2, article 102, information to the general public regarding prescription medicinal products may be done through Fass.se or such aids from the pharmaceutical industry that are intended to be handed to patients by physicians or other healthcare personnel in order to facilitate the correct use of their medicinal products. To ensure public access to required and comprehensible information on prescription medicinal products, information that fulfils certain requirements may also be provided on websites established and administered by pharmaceutical companies. The information may be provided solely on condition that pre-examination has taken place and resulted in an approval in accordance with certain requirements.

Section 2 of the LIF Ethical Rules, which regulates information in connection with marketing of medicinal products that is targeted at the general public, stipulates that the information must be compatible with good business practices, and must be presented in such a way that it gains credibility and a good reputation. In technical terms, the rules concerning product information aimed at the general public have been formulated mainly with reference to the rules for medicinal products information aimed at healthcare personnel. The basic principle applying to advertising aimed at healthcare professionals in Chapter 1, section 1, article 1 of the LIF Ethical Rules is correspondingly applicable to information aimed at the general public. In applying this fundamental principle, special attention shall be paid to the general public's need for factual information for guidance in the area of self-medication and to the importance of supplying the information in an easily accessible manner to the general public.

Information for the general public normally includes, as a minimum, the following particulars:

- the name of the medicinal product;
- its dosage form;
- its active ingredients, specified by generic name or in some other suitable way;
- the use of the medicinal product to which the information relates, as well as the statement of any necessary warning or limitations that are applicable to its use;
- the name of the manufacturer concerned or of his or her representative who is responsible for the medicinal product information in Sweden and clearly visible information on the manufacturer's or the representative's address or telephone number or web address;

- a clear statement of the year of publication or, in the case of internet information, the date when the site was most recently updated, as well as a designation that makes it possible to identify the information without difficulty;
- if the information regards human medicinal products, an explicit and easily legible invitation to carefully study the information contained in the leaflet or, as applicable, on the outer packaging; and
- as regards non-prescription medicinal products that are effective against a disease or symptoms of a disease that require contact with a physician for diagnosis or treatment, the medicinal product information to the general public must include a clear recommendation to consult a physician before using the medicinal product.

Advertising aimed at the general public may not contain recommendations from healthcare professionals.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The most common infringements by manufacturers with regards to the advertisement rules are (to our knowledge) the following:

- they claim qualities that are not supported in the SPC;
- the advertisement contains misleading information regarding, for example, safety issues;
- documentation is not cited in a balanced and fair way (eg, the results of various studies or statements of comparisons between different medicinal products are not presented in a balanced, correct and fair way);
- information that contains comparisons between effects, active ingredients, costs of treatment, etc, is not presented in a fair and correct way; and
- the product information is not complete.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

Advertisement of medicinal products that are not authorised for sale in Sweden is not allowed. In provision (2009:6) from the MPA, it is stated that advertisement of a medicinal product shall in all parts comply with the particulars listed in the SPC, and that all advertising of medicinal products to healthcare professionals must include basic information compatible with the SPC and the medicinal product classification. According to the LIF Ethical Rules for the pharmaceuticals industry in Sweden, it is expressly stated in Chapter 1, article 2 regarding the content of information that the 'summary of product characteristics (SPC) that has been adopted for a medicinal product constitutes the factual basis for information about the medicinal product' and if 'an SPC has not yet been set, the applicable catalogue text according to Fass.se shall constitute the factual basis for information about the medicinal product instead'. It is further stated that 'the information may only refer to medicinal products that have received marketing approval in Sweden', and that the information 'may not contain indications or dosages other than those approved of for the medicinal product, unless otherwise permitted by the Medical Products Agency'. It should, however, be mentioned that the constitutional law authorises information that does not constitute advertising that is within the reach of freedom of speech and freedom of information.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

There is no specific legislation governing the collaboration of the pharmaceutical industry with healthcare professionals. Chapter 2 of the LIF Ethical Rules contains rules governing agreements on forms of collaboration with the healthcare sector. The same rules apply regarding physicians in the outpatient and in-patient sectors.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The Swedish Association of Local Authorities and Regions, LIF, Swedish Medtech and Swedish Labtech have agreed on common rules for how employees and senior management in the healthcare

system and the industries (pharmaceutical industry, medical technology industry and laboratory technology industry) shall cooperate and interact with each other. It is the view of the parties that collaboration between healthcare professionals and industries is an important part of the development of both the healthcare system as well as the industries. With these rules, the parties wish to safeguard the continued development of collaboration in a trusted manner. The rules have been jointly developed in response to external demands for increased transparency, moderation in all collaboration, and the need for a clearer allocation of responsibilities between healthcare professionals and the industries, such as the responsibility of healthcare authorities to training their employees. The parties shall work to ensure that the members of each party, respectively, have a properly functioning self-regulatory system for the purpose of maintaining a good level of compliance with the rules. The agreement has been effective as of 1 January 2014, and has been implemented in Chapter 2 of the LIF Ethical Rules.

The basis for all collaboration is documentation, transparency and reasonability, and the collaboration shall be of benefit to all parties. In the event that the collaboration involves a transfer of value, the rules in Chapter 2, section 3 of the LIF Ethical Rules shall be applied to that transfer. The following basic principles shall always apply to any collaboration: the benefit principle, the transparency principle, the proportionality principle, the moderation principle and the documentation principle.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

Some years ago there was a public debate regarding sponsored conferences for doctors and others, which resulted in a revision of the cooperation agreement with the municipalities and the county councils restricting, for example, the place where such conferences should take place, the length of the total trip and the content of the social activities. All kinds of sponsoring, travels and events are still under scrutiny and several investigations have been initiated with regard to the financial support to healthcare. Assessments of possible infringements are made by the Pharmaceutical Industry's Information Examiner and the Information Practices Committee, and can be found on the LIF's website at www.lif.se/etik/igm-och-nbl/. Common infringements include, inter alia, unnecessarily luxurious locations for conferences, leisure activities in connection with conferences and insufficient information regarding marketing in invitations to events that include marketing. As of 1 January 2015, the LIF Ethical Rules stipulate that travel and accommodation for individual participants at meetings may not be paid for by the industry or requested by individual participants.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

Chapter 3 of the LIF Ethical Rules includes rules regarding the interaction of the pharmaceutical industry with organisations and politicians, and section 1 includes ethical rules as to the collaboration between pharmaceutical companies and user organisations or interest groups.

The purpose of the ethical rules is to ensure that any collaboration between organisations and pharmaceutical companies takes place in a responsible and meaningful manner, and that any cooperation, information and training are also conducted in such a manner that the parties' independence from one another is not jeopardised or questionable from either a legal or ethical standpoint; this means that the chosen collaborative projects may not comprise an overwhelming share of the organisation's activity or economic resources, or both.

The following principles serve as guidance for all collaboration between pharmaceutical companies and various organisations:

- respect for each other and each other's roles;
- reciprocity in relationships;
- common responsibility for planning and implementation;
- openness and transparency to the outside world; and
- restriction of the choice of collaborative fields.

These ethical rules are applicable to pharmaceutical companies. Certain organisations and companies have set their own rules as to collaboration, and such rules are to be seen as being complementary to the ethical rules.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes; infringements are pursued by the Swedish Competition Authority or by the European Commission.

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes, follow-on private antitrust litigation against manufacturers is possible in Sweden. Private enforcement actions follow the general procedural rules for damage claims. The lawsuit is filed where the defendant has its legal seat or in the district court in Stockholm, which always has jurisdiction over damages claims under the Swedish Competition Act.

A decision by a district court may be appealed to the Court of Appeal (leave to appeal is required), whose decision may in turn be appealed to the Supreme Court (leave to appeal is also required).

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

There are no mandatory anti-corruption rules aimed particularly at pharmaceutical manufacturers. Instead, Sweden's anti-corruption rules apply to its society on a general level. Sweden is a signatory to multiple international anti-corruption conventions, including, but not limited to, the UN Convention against Corruption and the Council of Europe's Civil Law Convention on Corruption. At state level, anti-corruption rules exist in the form of anti-bribery rules in Chapter 10 of the Swedish Penal Code, as well as the LIF Ethical Rules (although these ethical rules are strictly speaking not mandatory). The Swedish Anti-Corruption Institute has supplemented the anti-corruption legislation with a 'Code on gifts, rewards and other benefits in trade and industry' (the Business Code). This Business Code does not have status as law, but constitutes a clarification of the general anti-corruption legislation, which can be difficult to interpret. The intention is that a business that is following the Business Code should be able to count on their actions being legal. For a fee, the Ethics Committee of the Anti-Corruption Institute may render an assessment of whether or not a contemplated action is compatible with the Business Code. These assessments are found on the institute's website: www.institutetmotmutor.se.

The 2013 EFPIA Code on disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations (the EFPIA Disclosure Code) is applicable to Sweden and the LIF Ethical Rules Chapter 2, section 3 includes the rules regarding disclosure of transfers of value. Pharmaceutical companies that are active in the Swedish market shall publish the persons or organisations in Sweden that have received transfers of value during a given year, and the aggregate value of the transfers. On 31 May 2016, LIF opened its database for reports concerning transfers made during 2015.

Compliance - medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

In order to place medical devices on the market, the company must comply with the regulatory requirements in force. The applicable law in force is based on EU directives and focuses on the safety of patients and healthcare personnel. The medical device directives have been transposed into the Swedish Medical Devices Act (1993:384), the Medical Devices Ordinance (1993:876) and Codes of Statutes from the MPA. The implementation is almost a word-for-word transposition of the text of the directives. According to the Swedish Medical Devices Act and the Medical Devices Ordinance, a medical device must achieve its intended purpose as designated by the manufacturer and involve no unacceptable risk to patients, staff or third parties. The MPA assumes responsibility for market surveillance related to the law on medical devices and issuing codes of statutes with the support of this legislation.

The Swedish law on general product safety, the Product Safety Act (2004:451) is subsidiary to the Medical Devices Act, and is thus, in most cases, not applicable to the advertising of medical devices. However, in cases that are not covered by the Medical Devices Act, the Product

Safety Act may be in force also regarding medical devices (eg, for some self-diagnostics tests and disability aid products).

Proposals to revise the existing legislation framework on medical devices and in vitro diagnostic medical devices by adopting two regulations of the European Parliament, were proposed by the Commission on 26 September 2012. The proposals have been approved and the rules are expected to gradually come into effect once they have been fully revised and translated into the 24 official EU languages.

The Marketing Practices Act is also applicable to the advertisement of medical devices (see question 3).

Advertising is not explicitly regulated in the Swedish Medical Devices Act. However, advertising is deemed to fall within the Act, the Medical Devices Ordinance and some of the MPA's codes of statutes. A medical device must be able to fulfil the purpose and performance described by the manufacturer in the advertisement. The advertising requirements for medical devices can be considered similar to those for medicinal products.

The Swedish Association of Local Authorities and Regions, LIF, Swedish Medtech and Swedish Labtech have entered into an agreement regarding rules of cooperation concerning healthcare financed by public funding, the pharmaceutical industry, the medical technology industry and the laboratory technology industry. The regulations regarding collaboration are similar to those that apply to collaboration in the pharmaceuticals sector (see question 9).

The EU Trade Association Eucomed's Code of Business Practice includes guidelines on interactions with healthcare. This Code includes a rule regarding advertising and promotion.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The Medicinal Products Act, based on EU directives, sets out the regulatory framework for granting marketing authorisations and placing medicines on the market. The Medicinal Products Act is complemented by an ordinance and by several codes of statutes from the MPA. There are also applicable EU regulations, most notably Regulation (EC) No. 726/2004 regarding, inter alia, implementation of EU procedures for authorisation and supervision of medicinal products for human and veterinary use, and Regulation (EC) No. 141/2000 on orphan drugs.

17 Which authorities may grant marketing authorisation in your jurisdiction?

The MPA grants marketing authorisation in Sweden under certain authorisation procedures (see question 18). The European Medicines Agency (EMA) grants marketing authorisation under the centralised authorisation procedure, whose authorisations directly apply in Sweden.

18 What are the relevant procedures?

The MPA grants marketing authorisations under the mutual recognition procedure (MRP), the decentralised procedure (DCP) and the national procedure. The EMA grants marketing authorisations under the EU centralised procedure. Under the MRP, the applicant refers to a marketing authorisation in another member state. In the DCP, an applicant not falling within the mandatory scope of the EU centralised procedure may request one or more member states to approve a draft assessment report, SCP, labelling and package leaflets as proposed by the chosen reference member state. Medicinal products intended for marketing solely in Sweden can also be authorised through the national procedure, under which the applicant must abide by the regulations issued by the MPA, such as showing that the product is of satisfactory quality, is safe and efficient and is not disproportionately harmful in achieving its intended effect. These regulations also apply if the MPA is the reference member state under the MRP or DCP.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

The marketing authorisation holder is required to inform the MPA if its approved medicinal product is available on the Swedish market. Pursuant to section 8f of the Medicinal Products Act, the authorisation holder shall inform the Agency of the actual date when the product

is placed on the market, and also notify it if the product ceases to be placed on the market, either temporarily or permanently, no less than two months before the interruption. In addition, the authorisation holder shall provide the MPA with the reasons why the product has ceased to be placed on the market. These rules are implemented in the Medicinal Products Act from Directive 2012/26/EU, amending Directive 2001/83/EC as regards pharmacovigilance. If an authorised product is not put on the Swedish market within three years of approval, the MPA will invalidate the authorisation. Further, when an authorised product previously placed on the Swedish market is no longer present for three consecutive years, the authorisation shall cease to be valid. Medicinal products authorised within the centralised procedure will be handled centrally by the EMA. In order for a medicinal product to be considered as available on the Swedish market, at least one package of a particular strength, pharmaceutical form or taste must be marketed. An exemption may be granted if there are particular reasons – for example, a lack of suitable alternative suppliers or alternative treatments to the product – that means that there is a potential for an adverse impact on public or animal health, or if the medicinal product is a medicine held as part of emergency arrangements, for example vaccines.

20 Which medicines may be marketed without authorisation?

Swedish law prohibits marketing of medicinal products that have not been approved for sale. In some cases, however, a non-approved medicine (eg, a medicinal product under development) may be prescribed to an individual with the MPA's permission, when an approved alternative cannot be found in Sweden. See question 21 regarding permission to sell medicinal products without authorisation.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Pursuant to section 5 of the Medicinal Products Act, the Medicinal Ordinance and the MPA's Code of Statute (LVFS 2008:1) regarding permission to sell unauthorised medicinal products (licence prescriptions), prescription of an unauthorised medicinal product is possible if the need for a medicinal product cannot be met through an approved medicinal product in Sweden. The MPA can allow prescription of a medicinal product to an individual patient by issuing a special permission on a named patient basis (individual licence). Under certain circumstances, a licence may also be issued to be used for a patient group treated at a clinic or another equivalent institution (general licence), or as an emergency licence that meets all of Sweden's needs for the licensed medicinal products.

This named patient permission is available for prescribers in order to facilitate necessary treatment when medical conditions cannot be treated with approved medicinal products or if approved medicinal products have proved ineffective. A prescriber initiates the application by writing a prescription and by filling out the form for justification of the prescriptions and handing it to a pharmacy. The pharmacy checks the supply and availability of the product and submits an electronic application to the MPA. The MPA makes an individual assessment of each application and the pharmacy responsible for the application is notified of the MPA's decision.

If the MPA has not stated a shorter period, a named patient permission is valid for one year. The prescriber is responsible for informing the patient about the product, and adverse effects must be reported to the MPA. It is not permitted to promote an unauthorised medicinal product.

Pharmacies that manufacture stock formulations, standardised prescription or non-prescription medicinal products that are not approved for sale in Sweden shall make an application for a national licence to the MPA for stock formulations that are produced in quantities exceeding 1,000 packages per year. A granted nationwide licence means a marketing authorisation that is valid for five years or a shorter time decided by the MPA. A national licence may be granted if the product is of good quality and appropriate, and cannot be replaced by an existing approved medicinal product or by a medicinal product available through individual, general or emergency licence.

Article 5(1) of Directive 2001/83/EC is implemented by the Swedish legislation referred to above.

On 1 July 2012, the MPA introduced the Compassionate Use Programme (CUP), giving patients in Sweden an opportunity to get access to unauthorised medicinal products in situations outside the

Update and trends

There is continued focus from the Swedish government and TLV on the pricing and reimbursement of medicinal products and, for example, a three-party collaboration between TLV, county councils and pharmaceutical companies, and national agreements have been developed to provide price reductions for medicinal products. In November 2016, the Swedish government assigned a special investigator to investigate and analyse the current financing, reimbursement and pricing of pharmaceuticals. The investigation shall report its findings in part no later than 1 November 2017 and the final report no later than 1 December 2018.

A number of non-prescription medicines have been allowed to be sold in Sweden at sales points other than pharmacies since November 2009. As of 1 November 2015, non-prescription tablets of paracetamol are no longer available in Sweden at non-pharmacy outlets (retail outlets such as grocery stores and petrol stations). The decision was taken based on an increase in poisonings, where paracetamol has been ingested for intentional self-harm. The accessibility of paracetamol is considered to be a risk factor, which is why the MPA decided to limit ease of access to paracetamol in tablet form (tablets intended for swallowing whole).

The Swedish government has also assigned a special investigator, with the assistance of relevant authorities, to investigate the pharmacy market. The main goal of the investigation is to improve the safety and quality on the pharmacy market and the intention is to achieve a safer and more effective provision of medicinal products. The assignment includes, inter alia, analysing the development of the pharmacy market since deregulation, the authorisation requirements for outpatient pharmacy businesses, what changes may be needed to secure adequate availability of pharmacy services across the country and what changes to current legislation these issues may entail. The investigation shall report its findings to the government on 31 December 2016.

Discussions regarding off-label use of pharmaceuticals have been ongoing for a while in the EU, as well as in Sweden, on a national level. The European Commission is expected to publish a report in late 2016 or early 2017 regarding the need for coordination of off-label use across the EU. In Sweden, a national task force with representatives from the National Board of Health and Welfare and the MPA is working to ensure consensus among Swedish authorities in view of off-label use. A report is expected in late 2016.

licensing procedure described above or through their participation in a clinical trial. The CUP is regulated by Regulation (EC) No. 726/2004 on compassionate use of medicinal products and means that an unauthorised medicinal product may be made available for compassionate use.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

Pharmacies that manufacture stock formulations, a standardised prescription or non-prescription drug that is not approved for sale in Sweden shall make an application for a national licence to the MPA for stock formulations that are produced in quantities exceeding 1,000 packages per year. A granted nationwide licence means a marketing authorisation that is valid for five years or a shorter time decided by the MPA. A national licence may be granted if the product is of good quality and appropriate, and cannot be replaced by an existing approved drug or by a drug available through individual, general or emergency licence.

Article 5(1) of Directive 2001/83/EC is implemented in the Swedish legislation referred to in question 21.

The pricing of non-prescription (over-the counter) pharmaceuticals can be set freely. The patient pays the entire cost for these medicinal products. Prices are regulated for prescribed drugs that are included in the reimbursement system, and the patient makes a co-payment. The prices for in-patient care medicinal products are negotiated in public procurement processes, and the patient pays the patient fee that applies for the in-patient treatment concerned.

The Dental and Pharmaceutical Benefits Agency (TLV), which is an expert state agency, decides to what extent a medicinal product shall be reimbursed, according to the Pharmaceutical Benefits Act (2002:160). The TLV's decision can be appealed to the Administrative Court. For a medicinal product to be covered by the reimbursement scheme, the company applies to the TLV. In the application the company states the price of the product, and health economic documentation is enclosed. The application is granted if the TLV finds that the health economic analysis shows that the requested price is justified on the basis of the value the pharmaceutical delivers in terms of improved health (ie, it is cost-effective and brings marginal benefit). The price is based on general principles such as cost-effectiveness and the principle of prioritising patients with the greatest needs. The reimbursement decision is thus based on value, which is often described in Swedish terms as applying 'the value-based pricing of pharmaceuticals'. In actual fact, prices can be freely set under a value-based ceiling price. There are few countries that apply the value-based pricing of pharmaceuticals. Instead, most EU countries apply international reference pricing in some form. The TLV also decides and sets the retail margin, which is the fee paid by the state when pharmacies sell a prescription drug.

In addition, Sweden has a system for substitution of generically equivalent medicinal products. The system demands that pharmacies dispense the least expensive generic product available to the patient, regardless of the prescription, if the prescribing doctor has

not opposed a substitution for medical reasons in writing. The patient may also refuse a substitution if he or she is willing to pay the difference between the prescribed medicine and the generic alternative. The system was introduced in 2002 and has generated quite a lot of court cases regarding the MPA's decisions on the equivalence of different medicinal products.

From 1 November 2014, there are new rules for the pricing of some older drugs (see TLV's Code of Statute TLVFS 2014:9). The change is based on changes in the Pharmaceutical Benefits Act (2002:160) and means that the TLV will lower the price of medicines by 7.5 per cent when they are older than 15 years. The first price reductions under the new rules came into effect 1 January 2015. The intention is to contribute to a more cost-effective use of medicines in Sweden. The changes were initiated by an agreement on lowering the prices of some older medicinal products, between the government and LIF in 2013.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

The pricing of products differs in outpatient and in-patient treatment. For outpatient care (pharmacies), the TLV sets the AIP (pharmacy purchasing price) for products that are reimbursed and included in the high-cost threshold as regulated by the Pharmaceutical Benefits Act. There is free pricing for products that are not reimbursed, and pharmaceutical manufacturers can negotiate the prices with the pharmacies. The prices for in-patient care (hospitals) are set in county council public procurement processes, which are regulated by the Swedish Public Procurement Act (2007:1091). See also question 22.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

The TLV has been appointed by the government to decide whether the costs of a medicinal product should be reimbursed (see question 23). Such a decision can be appealed to the county administrative court. There are generally three criteria that are taken into account when assessing a medicinal product to be reimbursed: the human value principle; the need and solidarity principle; and the cost-effectiveness principle. Normally, only prescription medicinal products are subsidised by the system. See question 22.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The TLV is the competent body for decisions regarding the pricing and reimbursability of medicinal products (see questions 22 and 23).

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

No.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

There are strong legal frameworks in Sweden and the EU regarding manufacturing, licensing and distribution of medicinal products. The counterfeiting and illegal distribution of medicines is mainly countered by the Medicinal Products Act, the Medicinal Products Trading Act (2009:366), Directive 2001/83/EC and the MPA's Codes of Statutes LVFS 2009:20, LVFS 2013:2 and LVFS 2012:10. On 1 March 2013, the amendments to the Swedish legislation implementing the Falsified Medicines Directive (2011/62/EU) came into effect.

The MPA is, *inter alia*, responsible for the approval and control of medicines. It ensures that individual patients and the healthcare system have access to safe and effective products. In cases of infringement of the rules, fines or imprisonment can be imposed on the offender.

On 1 July 2009, Sweden took over the presidency of the EU for six months. The MPA was responsible for ensuring that progress was made on a number of important issues regarding pharmaceuticals and medical devices, and has covered several important health issues, for example, patient safety, development of safe and efficient pharmaceuticals, illegal trade of medicinal products, as well as sustainable development for the sector.

Both the MPA and LIF (see question 3) participate in a number of international and national cooperation agreements to counter the counterfeiting and illegal distribution of medicines. On 26 May 2010, the Swedish National Bureau of Investigation and Swedish customs presented a report on the situation of illegal medicinal products (including medicines) in Sweden identifying, *inter alia*, the problem with counterfeiting and illegal distribution of medicines.

Sweden participates in Operation Pangea, which is an international week of action tackling the online sale of counterfeit and illicit medicines and highlighting the dangers of buying medicines online. Coordinated by INTERPOL, the annual operation brings together customs, health regulators, national police and private sector players from countries around the world. Activities target the three principal components used by illegal websites to conduct their trade – the internet service provider, payment systems and the delivery service. The operation has gained significant momentum since its launch in 2008. The first phase of the operation brought together 10 countries, and now there are over 100 countries.

On 9 February 2016, the European Commission published the Commission Delegated Regulation (EU) 2016/161, laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use. Two new safety features to be placed on medicinal product packaging are introduced; a unique serialisation identifier and an anti-tampering device. These new safety features need to be implemented for most prescription medicines and some non-prescription medicines no later than 9 February 2019.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

No recent particular measures have been taken by the authorities regarding the general public's access to information on prescription-only medicines. The public is directed to the MPA's homepage, where it is possible to read a list of contents for prescription-only medicines. The MPA also publishes treatment recommendations regarding some diseases.

It is also possible to access information at www.fass.se, which is a compilation of pharmaceutical information from the industry aimed at people handling pharmaceuticals, such as doctors and dentists. This website is also available to the general public. There is also an information service regarding medicinal products, LMU, which the public can call and ask general questions about medicinal products, and also discuss issues related to risks and side effects or other issues surrounding the use of drugs.

29 Outline major developments to the regime relating to safety monitoring of medicines.

There is ongoing work in Sweden to increase the monitoring of the safety of medicines. The MPA, which is responsible for these kinds of issues in Sweden, makes side-effect reports and analyses contraindications to be able to inform the public about any risks involving pharmaceuticals.

European cooperation is also important, and the MPA takes an active role in developing new legislation in cooperation with the other EU member states.

A new procedure for handling recalls was introduced on 15 March 2010 for all products regulated by the Medicinal Products Act, replacing the old procedure that was based on different recall forms depending on the extent or distribution of the concerned product or batch and the degree of seriousness of the recall. The new simplified procedure for the whole market has been implemented with only one recall form for all recalls from retail trade and pharmacies and healthcare. The recall is sent from the pharmaceutical company (the manufacturing authorisation holder or its local representative) to the wholesalers or distributors and further to the pharmacies or retail traders, and finally to the healthcare provider and in serious and urgent cases to the patients or customers, depending on the distribution of the product to be recalled. All the above-mentioned parties are responsible for the distribution of information to the next party.

EU pharmacovigilance legislation came into effect in July 2012 in the form of Directive 2010/84/EU and Regulation (EU) No. 1235/2010. Necessary amendments were made to the Swedish legislation, effective as of 21 July 2012, in order to implement the EU legislation. The MPA has updated the common guideline for the labelling of and package leaflets for medicinal products. The guideline provides explanations and examples of how the current regulations should be interpreted. The purpose of the regulations is to ensure that patients receive clear and relevant information, and to reduce the risk of confusion and misuse.

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Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

In Sweden there is no obligation to vaccinate. However, all children are entitled and recommended to take part in the general vaccination programme. Under this programme, vaccination is given free of charge against certain serious diseases through the child and school health services. Furthermore, some children who are at high risk of infection are also offered vaccination against further diseases through a directed programme. In addition to children, the programme also includes adults in certain risk groups.

According to the Swedish Register for National Vaccination Programmes Act (2012:453), implemented on 1 January 2013, all vaccinations given to children under the general vaccination programme shall be listed in a register administered by the Swedish Institute for Communicable Disease Control. Registration is mandatory, and the data provides means for evaluation of the programme.

Through the Ministry of Health and Social Affairs, the government is responsible for deciding which diseases will be included in the programme. According to the Communicable Diseases Act (2004:168), county councils and municipalities are responsible for the implementation of the programme. According to the Communicable Diseases Act, there shall be a doctor responsible for planning, organising and supervising the work with infectious disease control. Vaccinations shall be carried out by authorised nursing staff according to the Patient Safety Act (2010:659).

In accordance with the Communicable Diseases Act, county councils and municipalities are obliged to offer vaccinations against the diseases listed in the Swedish vaccination programmes. The purpose is to prevent diversification of infectious diseases within the population. The cost of vaccinations included in the programmes is financed by the county councils and municipalities. Consequently, vaccinations are free of charge for the patients within the programmes.

Switzerland

Frank Scherrer

Wenger & Vieli Ltd

Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The Swiss healthcare system is based to a great extent on mandatory health insurance. Mandatory basic health insurance can be contracted with a health insurance company of one's choice and there is the possibility of contracting additional private insurance. Apart from health insurance, there are other types of social insurance. Social insurance pays or reimburses the costs of healthcare providers (hospitals, physicians, pharmacists, etc). The private healthcare sector, which is not financed by social insurance, is also very important. The healthcare system has a federalist structure, and only certain areas are governed by federal law. Many competences and tasks have remained under the control of the 26 cantons (such as the running of public hospitals).

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The healthcare system is mainly financed by social health insurance, private insurance, the Swiss Confederation, the cantons, the communities and the direct payments of patients. In-patient treatment provided by a public hospital is mainly financed by health insurance and the canton to which the hospital belongs. Outpatient treatment is financed mainly by health insurance. The basic health insurance provides for a patient co-payment of, at present (in principle), 10 per cent to a maximum of 700 Swiss francs per year for adults. For both the outpatient and the in-patient sectors, private additional health insurance and direct payment of healthcare services are possible.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

Advertising for medicinal products is governed by:

- the Law on Therapeutic Products (LTP);
- the Ordinance on Advertising for Medicinal Products;
- the Ordinance on Health Insurance (article 65, paragraph 2, and 68, paragraph 1, letter d);
- the Federal Act against Unfair Competition; and
- the Code of Conduct of the Pharmaceutical Industry in Switzerland (Pharma Code), issued by scienceindustries, an association of the Swiss chemical, biotech and pharma industries.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

Advertising aimed at healthcare professionals (HCPs) is generally allowed for all medicinal products authorised in Switzerland. Advertising must not be misleading, inaccurate, against public policy or unethical, or incite excessive, abusive or inappropriate use of medicinal products.

Advertising aimed at HCPs must be in line with the latest product information approved by Swissmedic, the Swiss regulatory agency. Advertising must be accurate, balanced and provable. The claims must be based on and reflect the current state of scientific knowledge. They may only refer to clinical studies conducted in accordance with good clinical practice that are published or accepted for

publication. Publications must be quoted literally, completely and with the exact reference.

Advertisements must not indicate that a medicinal product does not have adverse effects or is without risk or harmless; appear to be an editorial; or indicate that a human medicinal product does not lead to dependency.

Advertising for prescription-only medicinal products on the internet must be limited to HCPs by means of password protection.

5 What are the main rules and principles applying to advertising aimed at the general public?

Advertising aimed at the general public is not allowed for prescription-only medicinal products. It is furthermore not allowed for medicinal products that are reimbursed by the basic health insurance.

Advertising aimed at the general public must not be misleading, inaccurate, against public policy or unethical, or incite excessive, abusive or inappropriate use of medicinal products. It must be in line with the latest Swissmedic-approved product information. It must be objective and without exaggeration and contain an invitation to consult the patient leaflet. Pharmaceutical products must be clearly presented as such. Quizzes, vouchers, testimonials and invitations to contact the marketing authorisation holder are not permitted.

Advertisements in a printed form or on radio, television or in cinemas for analgesics, sedatives, sleeping tablets, laxatives and anorectics must be submitted to Swissmedic for prior approval if the product information of the product mentions a potential for abuse or addiction.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The most common infringements with regard to advertising rules are as follows:

- advertising without correct scientific basis;
- advertising for off-label use or medicinal products that have not yet been authorised;
- claims that are not correctly referenced;
- advertising that lacks the necessary minimum information;
- advertising that is not in accordance with the approved product information;
- advertising to the general public of prescription-only medicines; and
- in advertising to the general public, exaggerations, promises of therapeutic effect and advertising together with products other than medicinal products (cosmetics or food).

It should be noted that the surveillance of advertising aimed at HCPs is mainly performed by a body instituted by the Pharma Code, and not Swissmedic. Swissmedic must act if advertising endangers drug safety.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

Advertising for products that have not yet been authorised in Switzerland, or for off-label use of authorised products, is not allowed. According to the Pharma Code, pharmaceutical companies are, however, allowed to inform without direct or indirect advertising HCPs and the media about products or new indications, fields of use, dosages, Galenic formulations or packages that have not yet been authorised in

Switzerland. The trade name may be used, but always in connection with the international non-proprietary name of the active substance. The companies have to make it clear that the medicinal product, new indication, field of use, dosage, Galenic formulation or package has not yet been authorised by Swissmedic in Switzerland. Information as outlined above should be provided by independent speakers invited by pharmaceutical companies or professionals of the medical service or research department of the pharmaceutical companies.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

The rules governing the collaboration of the pharmaceutical industry with HCPs are located in various acts and ordinances, mainly the following:

- the LTP, especially article 33 and the provisions on clinical trials and vigilance;
- the Ordinance on Advertising for Medicinal Products, especially article 11 on scientific congresses and promotional events;
- the Federal Law on Research Involving Humans and the ordinances depending on it, especially the Ordinance on Clinical Trials;
- the anti-bribery provisions of the Swiss Criminal Code, article 322-ter to 322-decies, and of the Act against Unfair Competition, article 4a;
- the rules governing the employment and function of HCPs; and
- the Federal Act on Academic Medicinal Professions.

In principle, the same rules apply to physicians in the outpatient and in-patient sector. With regard to organisational rules and competences there are, however, important differences among employed and self-employed physicians.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

There are certain types of collaboration for which specific rules of best practice have been developed, and these are mainly set out in a publication of Swissmedic, the Pharma Code, the Code of Conduct of the Pharmaceutical Industry in Switzerland on cooperation with Healthcare Professional Circles and Patient Organisations (Pharma Cooperation Code), issued by scienceindustries, and a guideline of the Swiss Academy of Medical Sciences.

The main legal rule is article 33 of the LTP, which prohibits the offering of financial advantages to physicians, pharmacists, druggists or healthcare establishments that employ such persons for prescribing or dispensing certain medicinal products; the rule also prohibits the acceptance of such advantages.

Financial advantages considered permissible are as follows:

- gifts of a modest value, which are relevant for the professional activity of the recipient (eg, prescription pads); according to practice, gifts are considered to be of a modest value if their total value is not more than 300 Swiss francs per year to each healthcare professional; and
- discounts that are customary in the relevant field or that are justified on business grounds (eg, volume discounts). If given on reimbursed products, such discounts must be passed on to the patient or the insurer that pays for the product.

According to article 11 of the Ordinance on the Advertising for Medicinal Products, hospitality related to scientific congresses or promotional events must be justifiable and must be subordinate to the main (scientific) purpose of the event. Accompanying persons must pay for their own costs.

With regard to the support for the participation of physicians in medical congresses, Swissmedic has issued a publication containing detailed rules. The basic rule is that – with some exceptions – physicians have to make a co-payment of at least 33 per cent of the direct costs of their participation (registration, accommodation, food and beverages, etc).

The Pharma Cooperation Code provides that the signatory companies have to disclose financial advantages granted to HCPs or healthcare organisations (HCOs) on a company website. Disclosure has to be

made in principle on a named basis, listing the value of the advantages granted per calendar year to the respective HCP or HCO per category. In cases where the HCP or HCO does not agree to the named disclosure, disclosure needs to be made on an aggregate basis.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

Besides improper advertising, infringements committed by manufacturers with regard to collaboration with HCPs in general relate to undue financial advantages. Only a few decisions of Swissmedic and the courts, however, have been published in this field. A revision of article 33 of the LTP is pending.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

The main rules and principles contained in the Pharma Cooperation Code are as follows:

- companies shall respect the independence of patient organisations with regard to their political position, their methodology and their activities;
- all partnerships between patient organisations and companies should be based on mutual respect;
- the companies shall neither ask patient organisations to promote certain medicinal products nor respond to corresponding requests by patient organisations;
- the aims, the scope and the agreement of support and partnerships should be transparent and documented in writing;
- a list showing support offered on an individual basis has to be published by companies;
- the aim is for patient organisations to be supported by more than one pharmaceutical company. Pharmaceutical companies may not require patient organisations to let them provide financial or other support as the only pharmaceutical company either overall or for their individual projects; and
- service agreements with patient organisations essentially have to comply with the same requirements as service agreements with HCPs.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Competence for the enforcement of the Cartel Act lies with the Swiss Competition Commission. The Swiss Competition Commission in 2009 imposed fines on Pfizer, Eli Lilly and Bayer for alleged resale price maintenance through the provision to pharmacists of recommended resale prices for their non-reimbursed medicinal products Viagra, Cialis and Levitra. In a first decision of 3 December 2013, the Federal Administrative Court had annulled the decision of the Competition Commission, essentially finding that price competition between pharmacies was anyway excluded due to the advertising restrictions for prescription-only medicines and the 'shame factor' related to these products. This decision was appealed to the Federal Supreme Court. The Federal Supreme Court annulled the decision holding that the Cartel Act is applicable and it remanded the case to the Federal Administrative Court where it is now pending.

Infringements of the Act against Unfair Competition are usually brought forward in a civil procedure; only in very limited circumstances will the authorities act ex officio.

13 Is follow-on private antitrust litigation against manufacturers possible?

The Swiss Cartel Act contains provisions on private lawsuits in the case of breach of cartel law. Private antitrust litigation, however, only plays a very modest role in antitrust enforcement in Switzerland.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

The main mandatory anti-corruption rules applicable to pharmaceutical manufacturers are article 33 of the LTP mentioned in question 9 and the anti-bribery provisions of the Swiss Criminal Code, article 322-ter

to 322-decies. The anti-bribery provisions are in line with the Criminal Law Convention on Corruption of the Council of Europe and therefore very similar to other modern anti-corruption laws. As per 1 July 2016, the provisions against bribery in the private sector were strengthened and became offences that are prosecuted ex-officio.

The main mandatory transparency rule is article 322-decies of the Swiss Criminal Code that requires that certain advantages need to be approved by the organisation of the recipient for being legal. There are many other transparency rules in various acts and ordinances at the federal, cantonal and municipal levels.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Advertising of medical devices and collaboration with patient organisations are currently not as rigorously regulated as advertising for medicinal products. The Ordinance on Medical Devices contains one provision on advertising that sets the following rules (in article 21):

- advertising for medical devices that are intended for the direct distribution to or use by the public must be limited to statements contained in the product information with respect to use, capabilities and efficacy;
- misleading claims of efficacy or capabilities are prohibited; and
- advertising to the general public is prohibited with regard to medical devices that are subject to prescription or are exclusively distributed for use by HCPs.

Article 33 of the LTP on the prohibition of financial advantages in its current wording does not apply to medical devices. The industry association of medical device manufacturers and distributors, FASMED, has issued a code of conduct that provides for similar and more detailed rules than article 33 of the LTP. The general anti-bribery provisions of the Criminal Code and the Act against Unfair Competition apply also to manufacturers and distributors of medical devices.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The rules on the granting of marketing authorisations and the placing of medicines on the market are set out in the LTP and various ordinances depending on it, in particular the Ordinance on the Requirements for Marketing Authorisation of Medicinal Products, the Ordinance on the Simplified Marketing Authorisation of Medicinal Products and Authorisation by Way of Notification, the Ordinance on the Simplified Marketing Authorisation of Complementary and Herbal Medicinal Products, the Ordinance on Establishment Licences and the Ordinance on Medicinal Products.

17 Which authorities may grant marketing authorisation in your jurisdiction?

Marketing authorisations are granted by Swissmedic.

18 What are the relevant procedures?

The relevant procedures are the ordinary, pre-announcement, fast-track and simplified procedures. A marketing authorisation can only be granted to a company or person having its domicile, registered office or a branch office in Switzerland. The applicant must also have a manufacturing, import or wholesale licence.

Ordinary procedure

The application to Swissmedic for a marketing authorisation must be made using standard forms and the common technical document (CTD (or eCTD, when data is submitted electronically)) format of the International Conference on Harmonisation. The required documents are listed in detail in the Ordinance on the Requirements for Marketing Authorisation of Medicinal Products and guidelines issued under it. Swissmedic recommends submitting data electronically.

The conditions for granting a marketing authorisation are that the product is of a high quality and is safe and effective. If a drug or process has already been authorised in another country that has a similar system of marketing authorisation, the results of the examinations carried out for that purpose should be considered by Swissmedic (article 13 LTP). There is, however, no automatic recognition of foreign marketing authorisations. In the case of medicinal products containing an active substance that has already been authorised, Swissmedic, in an article 13 proceeding, limits itself, in principle, to assessing the evaluation reports of the foreign authorities. Swissmedic will not, however, make an assessment of the evaluation reports of the European Medicines Agency or the Food and Drug Administration, provided that these reports are not contradictory and Swissmedic has no essential concerns towards these evaluations.

The normal authorisation process takes about a year at minimum. Swissmedic has issued a guideline setting out its internal targeted time periods and milestones. If Swissmedic has queries, or requests further information or documents, the internal targeted time periods are stopped and the authorisation process can take longer.

Procedure with pre-announcement

If the applicant informs Swissmedic well in advance (five to eight months) of the date of filing the application for marketing authorisation, Swissmedic offers, under certain conditions, a 20 per cent faster process. The fees for the proceeding are then doubled.

Fast-track procedure

If there is no treatment, satisfactory or otherwise, against a perilous or heavily disabling disease, and if the medical preparation is of a high therapeutic value, a fast-track procedure is available at the applicant's request. The fast-track procedure must be applied for at least three months before the application for the marketing authorisation is filed. It enables registration to be completed within about four months. If Swissmedic has queries, the proceedings may take longer.

Simplified procedure

A simplified marketing authorisation procedure is available for certain types of medicinal products, such as:

- medicinal products with active substances that have already been authorised in Switzerland;
- parallel imports from a country with an equivalent marketing authorisation system;
- orphan drugs;
- radiopharmaceuticals and antidotes; and
- complementary and alternative medicinal products.

The procedure is mainly governed by the Ordinance on the Simplified Marketing Authorisation of Medicinal Products and Authorisation by Way of Notification and the Ordinance on the Simplified Marketing Authorisation of Complementary and Alternative Medicinal Products.

For certain medicinal products (eg, certain homeopathic and anthroposophical products), authorisation by way of a mere notification procedure is possible.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Article 16a of the LTP states that Swissmedic will withdraw the marketing authorisation of a medicinal product if it is not effectively brought into circulation within three years from the grant of the marketing authorisation or not marketed for three consecutive years. If a patent hinders the marketing of the medicinal product, the three-year period starts with the expiry of patent protection. Pharmaceuticals authorised in connection with an emergency situation and pharmaceuticals that are only exported are not subject to such withdrawal.

20 Which medicines may be marketed without authorisation?

The LTP provides for the following catalogues of human medicines that may be marketed without authorisation:

- (i) medicinal products manufactured by hospitals or public pharmacies based on a prescription by a physician for a specific person or a specific circle of persons (magistral formula) – the medicinal product can be manufactured ad hoc or for stockpiling, but only dispensed based on a prescription by a physician;

- (ii) medicinal products manufactured ad hoc or for stockpiling by hospitals, public pharmacies, drugstores or other establishments with a manufacturing licence based on a special monograph of the pharmacopoeia or another recognised dispensary for dispensation to their own clients (official formula);
- (iii) non-prescription medicinal products manufactured ad hoc or for stockpiling by hospitals, public pharmacies, drugstores or other establishments with a manufacturing licence based on their own formula or on a formula published in learned literature and within the dispensing competence of the person responsible for the manufacturing and for dispensation to his or her own clients;
- (iv) medicinal products for which no alternative equivalent medicinal product is authorised or available and that are manufactured for stockpiling by hospitals based on a hospital internal list of medicinal products and for dispensation to their own clients;
- (v) medicinal products for clinical trials; and
- (vi) medicinal products that cannot be standardised.

Manufacturing of the medicinal products listed under points (i) to (iv) can be delegated to an establishment with a manufacturing licence, and there are qualitative and quantitative limits for manufacture of these medicinal products.

Swissmedic may authorise the distribution or dispensation (for a limited period) of medicinal products against life-threatening or seriously disabling diseases if this is compatible with the protection of health, a significant therapeutic benefit can be expected from the administration of these products and no equivalent medicinal product is available in Switzerland ('compassionate use', according to articles 18 to 23 of the Ordinance on the Simplified Marketing Authorisation of Medicinal Products and Authorisation by Way of Notification).

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Apart from the regulations about clinical trials and the prohibition of advertising before a marketing authorisation is granted, there is no specific regulation on named patient programmes initiated by pharmaceutical manufacturers before a marketing authorisation is granted. Under certain conditions, physicians and pharmacists may import certain medicinal products that are not authorised for the treatment of named patients or for emergency situations (article 36 of the Ordinance on Establishment Licences). This right does not extend to pharmaceutical companies.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

Medicinal products that are reimbursed by the basic health insurance are subject to governmental price control. The prices of non-reimbursed products are free and are not government-controlled.

A finished medicinal product (whether prescription-only or non-prescription) must, in principle, be listed on the speciality list (SL) established by the Federal Office of Public Health in order to be reimbursed in the basic health insurance. When deciding on the admission of a medicinal product to the SL, the Federal Office of Public Health determines its list price. This price is the maximum price that can be invoiced by healthcare providers and that will be reimbursed by health insurance companies. About 80 per cent of the sales of pharmaceutical products in Switzerland relate to products listed on the SL.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

For reimbursed medicinal products, the SL established by the Federal Office of Public Health lists the maximum ex-factory price and the SL price. Healthcare providers can try to negotiate a lower price than the ex-factory price. Sometimes rebates are granted, namely to hospitals. For non-reimbursed products, prices can be negotiated.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

Under the basic health insurance, insurance companies pay or reimburse finished medicinal products prescribed by physicians (or, under certain circumstances, chiropractors) that are listed on the SL if they are

Update and trends

On 18 March 2016, Parliament decided a major revision of the LTP. The revision relates to several areas of the law, including regarding the extension of regulatory data protection, incentives for medicinal products for children and orphan drugs, obligations regarding the product information and the grant of financial advantages to healthcare professionals. Market access for complementary medicines and phytopharmaceuticals shall be facilitated, and the dispensation competences of pharmacists shall be extended. There is a trend to focus on security of supply for important pharmaceutical products. The implementing ordinances are currently drafted. The revised LTP and its ordinances may come into effect in two to three years.

The ordinances regulating the pricing for reimbursed medicinal products are also under revision. The revised rules have not yet been decided by the Federal Council. The new rules will come into effect in 2017 and place more importance on the therapeutic cross comparison.

used within their indication. The SL listing may be accompanied with limitations regarding reimbursement. In two exceptional situations, the costs of a product that is either not listed on the SL, or is listed on the SL but used off-label or outside a limitation of reimbursement, are taken over by the basic health insurance: in a compassionate-use situation if there is no effective and authorised treatment alternative, and in the situation of a 'treatment complex' (ie, when there is a very narrow connection between medical services that are reimbursed and services that are not or are only partially reimbursed when the non-reimbursed services are a necessary condition for the treatment, or are of considerable importance for the success of the treatment).

In both situations according to recent provisions in the relevant ordinances that are currently under revision, the physician of confidence of the respective health insurance company has to be consulted, and the health insurance company has to approve reimbursement in advance and determines the extent of reimbursement.

Optional additional private insurance usually also covers authorised medicinal products that are not listed in the SL.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The competent body is the Swiss Federal Office of Public Health. It decides on the admission of finished medicinal products to the SL. A medicinal product is only admitted to the SL if the applicant can show its efficacy, usefulness and economy. The relevant criteria for fixing the SL price of an original product are the prices of drugs having the same indication or a similar mode of action and the average price of the product in other countries. Currently, the prices in nine reference countries - Germany, Denmark, England, the Netherlands, France, Austria, Belgium, Finland and Sweden - are used for this comparison. There are detailed provisions about the weighing of the two criteria and the relevant prices in the comparison countries. For determining the SL price, the Federal Office of Public Health adds a distribution margin to the ex-factory price determined according to the criteria described above. The fulfilment of the conditions for admission to the SL is in principle reviewed every three years. A review of the conditions for admission to the SL also takes place immediately after the expiration of the patent protection, as well as in the following situations: authorisation of a new indication by Swissmedic, restriction of an indication by Swissmedic, request for changing a limitation and request for a price increase. The SL prices of generics are determined in function of the prices of their reference products. Several aspects of the pricing system are currently under judicial review and a revision of the ordinances is pending.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

There are no statutory rules obliging manufacturers or distributors to give certain discounts. Healthcare providers must pass on discounts that they have received on medicinal products or in relation to services reimbursed by the basic health insurance to the debtor of the healthcare product or service (insurance or patient).

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Swiss legislation provides for several means to combat the counterfeiting and illegal distribution of medicines. The LTP prohibits the distribution of medicinal products that are not authorised and provides for severe sanctions. The competences of Swissmedic and the customs authorities to block counterfeited or illegally traded medicinal products and to investigate breaches of the law are broad. Swissmedic has made combating the illegal trade of medicinal products a priority and is in close contact with foreign authorities.

Besides the LTP, the legislation on intellectual property also offers means to counter the counterfeiting and illegal distribution of medicines.

In 2011, Switzerland signed the Medicrime Convention of the Council of Europe. Changes to the law necessary for its ratification are currently being prepared.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

Advertising for prescription-only medicines to the general public is prohibited in Switzerland. The Swiss Federal Court has confirmed this prohibition in several decisions. In contrast, information on illnesses and treatment options is admissible. The product information for a prescription-only medicine (information for professionals and the patient leaflet) is not to be regarded as advertising and can be made freely available, including on the internet. Swissmedic makes it available on its website, www.swissmedicinfo.ch.

Since 1 June 2015, the Federal Office of Public Health for reimbursed products makes available a summary of the basis for the assessment of the efficacy, usefulness and economy of a product in case of admission on the SL and changes of the indication or limitation.

Pharmaceutical companies seem to be intensifying initiatives to make health-related information on illnesses and treatment options available to the general public, and also to advertise themselves as companies.

In its 'Gesundheit 2020' report of 2013, the federal government declared its goal to foster greater health literacy among the general public.

29 Outline major developments to the regime relating to safety monitoring of medicines.

A major development to the regime relating to the safety monitoring of medicines has been the implementation of the ICH guideline on pharmacovigilance planning (E2E) since 1 January 2007.

The revision of the LTP that was decided on 18 March 2016 (see the 'Update and trends' section) provides for an extension of the reporting obligations, the implementation of 'good vigilance practices' and pharmacovigilance planning, and for quality assurance measures in the medication process.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

There is no general obligation to vaccinate in Switzerland. Currently, the cantons can foresee such an obligation. Only very few cantons have imposed an obligation to vaccinate, for example, against diphtheria. The Act on Epidemics of 28 September 2012, which came into force on 1 January 2016, gives the Confederation the competence to impose an obligation to be vaccinated on certain groups of exposed persons if they want to continue their exposed activity. The importation and batch release of vaccines are in principle subject to authorisation by Swissmedic on an individual basis. The vast majority of vaccines are prescription-only medicinal products. The Federal Office of Public Health and the Federal Commission for Questions related to Vaccinations establish a vaccination plan each year. The vaccinations according to the vaccination plan and certain other vaccinations are reimbursed by the social health insurance.

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Taiwan

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

Taiwan has a national health insurance (NHI) system that covers nearly all of Taiwan's population. NHI is a mandatory, single-payer system for Taiwan citizens who have established at least six months of residency. Foreign nationals who meet the NHI's residency requirements are also insured, as are those hired by local employers.

The NHI system coverage provides access to over 20,000 hospitals, clinics, pharmacies and medical labs which provide in-patient and ambulatory care, dental services, vision, traditional Chinese medicine therapies, child delivery, physical therapy, home care and chronic mental illness care. The vast majority (93 per cent) of Taiwan's hospitals and clinics are NHI-contracted and most forms of treatment are covered, including general diagnoses, examinations, lab tests, anaesthesia, prescription and over-the-counter drugs, nursing care and hospital stays.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

NHI is funded and organised by the Taiwan government under the jurisdiction of the Ministry of Health and Welfare. The NHI is designed to be a financially self-sufficient pay-as-you-go system that is primarily funded by premiums paid by the insured, employers and subsidised by the government. Other sources of funding for the NHI include fines on overdue premiums, public welfare lottery contributions, and a surcharge on cigarettes. Premiums on the insured are based on income, taking into account various income sources such as wages, bonuses, stock dividends, interest and rental income. Co-payments for in-patient stays are typically 5-10 per cent of the cost, but a cap is set on in-patient co-payments to reduce in-patients' financial burden for lengthy stays.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

Generally, in Taiwan, the Pharmaceutical Affairs Act and its Enforcement Rules provides the necessary definitions for the key nomenclatures of the medical and healthcare industry; they also govern the principles for advertising aimed at healthcare professionals as well as advertising aimed at the general public.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

Articles 4, 24 and 65-69 of the Pharmaceutical Affairs Act and articles 44-47 of the Pharmaceutical Affairs Act Enforcement Rules provide the rules and regulations in terms of advertising medicinal products.

In general, all advertisements and commercials of medicinal products must be reviewed and approved by the government agency before publication and broadcasting. See Pharmaceutical Affairs Act, article 66. Only pharmaceutical dealers can advertise medicinal products. See id at article 65.

The advertisement and commercial of the medicinal products may not be presented in any of the following ways: (i) under another person's name; (ii) using journals or publications to support and endorse the product's performance and efficacy; (iii) publicising the products in

an interview or news story; and (iv) publicising the product by any other improper means. See id at article 68.

Article 45 of the Pharmaceutical Affairs Act Enforcement Rule provides rules and regulation governing the content requirements of a medicinal product. This article limits the texts and images that may be used in a drug advertisement and regulate the packaging inserts of the pharmaceutical products. Furthermore, the advertisement and commercial must include the pharmaceutical manufacturer's name, permit licence number and advertisement approval number. See article 46.

In addition, an advertisement and commercial may not include:

- content involving enhancing sexual intercourse;
- the methods of using the advertised medicinal products that would be likely to encourage drug abuse;
- any representation that any use of a drug will cure a particular disease or will improve a person's health or could be interpreted to guarantee certain results; or
- exaggeration of a drug's efficacy or safety. See article 47.

The same rules and regulations for advertisements and commercials apply to the general as to the healthcare professionals, except medicinal products that require prescriptions or have been identified in public notices of the government health agency. See Pharmaceutical Affairs Act, article 67.

5 What are the main rules and principles applying to advertising aimed at the general public?

See question 4. The main rules and principles for the advertisements and commercials to the general public are substantially similar to those to healthcare professionals, except that medicinal products that require prescriptions or have been identified in public notices of the government health agency may not be advertised to the general public. See Pharmaceutical Affairs Act, article 67.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The most common type of infringement by manufacturers in advertising is false or misleading statements or the overstatement of product efficacy.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

The provision of information regarding off-label use to healthcare professionals is not permitted.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

The Ethical Committee of the Department of Health published a 'code for the relationship between medical doctors and drug companies' (the Code), which provides guidelines for medical doctors. The Code provides specific guidelines for doctors when they attend medical meetings sponsored by drug companies; accept gifts from drug companies; conduct medical research sponsored by drug companies; and act as a consultant to drug companies. The Code is based on the following

principles in order to avoid conflicts of interest and to ensure patients' interests are always protected and independent of clinical judgement. The rules are as follows:

Rules for attending sponsored medical conferences

- Attendees spend at least two-thirds of the time on academic discussion;
- attendees can only accept sponsorship for the physician's registration fee, travel, lodging expenses and speakers' fees;
- full disclosure of the identity of the sponsor, the host, name of the speakers, the relationships, etc;
- presentation fully supported by clinical or patent data; and
- pharmaceutical companies should not bias the contents of any speakers' presentation.

Rules for accepting gifts from the pharmaceutical manufacturers

- Must be lawful and not in violation of industry guidelines;
- complies with industry customs, no expensive gifts are allowed;
- no cash, gift certificates, bonds, stocks; and
- cannot use gifts, cash or gift certificates to bind the physicians to prescribe certain types of pharmaceutical products.

Rules for sponsored research

In order to publish one's research result, a person must comply and work within the confine of legal, ethical regulations and the Helsinki doctrine. In addition:

- the research must be as neutral and as non-biased as possible;
- compensation for the research should be calculated based on time and effort spent on the project, not the result of the research;
- when publishing the research data, the direct and indirect supporters' identities must be simultaneously disclosed; and
- prior to the start of the research, one must fully communicate with the pharmaceutical manufacturer and the pharmaceutical manufacturer may not in any way try to influence or restrict the outcome of the research.

Rules for acting as a consultant for a pharmaceutical company

Any decision must be made independently and without any bearing of the fact that one is acting as a consultant for the pharmaceutical company.

One's obligation to the patient cannot be compromised by his or her responsibilities to the pharmaceutical manufacturer; and

When giving speeches, or publishing one's work, full disclosure must be made when it comes to the relationship between the author and the pharmaceutical company.

Although the Code was officially published by the government, it is only an ethical guideline. However, healthcare professionals could be indicted if found to receive illegal 'profits' from a company. Those working in governmental hospitals or institutes could be more harshly punished according to laws regulating the conduct of governmental employees. Generally speaking, any collaboration without official approval from the institute could be considered illegal.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

See question 8.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

The most common violation is the financial consideration or other benefit to healthcare professionals provided by the pharmaceutical manufacturers.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

See question 8.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes, violations of the Fair Trade Act can be pursued, upon complaints or ex officio, by the Taiwanese Fair Trade Commission, and certain provisions can be enforced by the central competent authority. Any enterprise violating the Fair Trade Act can be ordered to cease or rectify its conduct, and can be subject to fine or imprisonment or both. Additionally, municipal or county (city) governments may investigate violations of the Consumer Protection Act and take prescribed actions where the goods or services rendered have caused or will cause injury or damage to consumers. Where a violation is found, the competent authority may impose an administrative fine or suspend operations of the violating entity or both, and request a civil suit or criminal investigation.

13 Is follow-on private antitrust litigation against manufacturers possible?

A person injured by the conduct of an enterprise in violation of the Fair Trade Act can bring a claim for damages. Pursuant to the Consumer Protection Act, consumers may file a complaint and, if not adequately resolved, participate in mediation concerning the consumer dispute. In addition, under certain conditions, a consumer advocacy group may initiate litigation for damages or seeking an injunction to discontinue the wrongful act.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

General anti-corruption

Anti-corruption laws in Taiwan are governed by three entities: (i) the Anti-Corruption Act; (ii) the Criminal Code; and (iii) the Organic Statute for Anti-Corruption Administration.

Public bribery (pharmaceutical manufacturer bribing a public official)

- Bribery of public officials is regulated under Taiwan's Anti-Corruption Act, articles 4, 5, 6 and 11; and the Criminal Code, articles 121, 122, 123 and 131. The provisions in the Criminal Code dealing with anti-corruption and the defences thereof are similar to those contained in the Anti-Corruption Act;
- the penalties or consequences of bribery are limited to the individual responsible, the Anti-Corruption Act and the Criminal Code do not provide for any corporate offence against the company or legal entity (however, pharmaceutical manufacturers could violate other laws, which would depend on the specific corrupt activity or case-by-case analysis); and
- any facilitation payment, even low-level gratuities, could be viewed as a bribe by Taiwanese courts.

Private bribery (pharmaceutical manufacturer bribing a physician)

- Private bribery is regulated under the Criminal Code, article 342, and the Securities and Exchange Act, article 171, paragraphs 1 and 2;
- the Criminal Code and the Securities and Exchange Act do provide penalties for individual parties, but do not provide for any corporate offence (however, pharmaceutical manufacturers could violate other laws, which would depend on the specific corrupt activity or case-by-case analysis).

Transparency rules

Disclosure, guidance and transparency rules for listed companies (relevant for pharmaceutical manufacturers) can be found in the Securities and Exchange Act (www.selaw.com.tw).

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Yes, the advertising of medical devices and collaboration of manufacturers of medical devices with healthcare professionals and patient organisations is regulated as rigorously as advertising and collaboration

in the pharmaceuticals sector. Relevant medical device regulations are listed in the Pharmaceutical Affairs Act, Regulations Governing Management of Medical Devices and the Guidelines for Registration of Medical Devices. Medical device registration and approval must also comply with requirements set forth by the Taiwan Food and Drug Administration (TFDA) prior to market entry.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The framework for granting marketing authorisations and placing medicines on the market is laid out in the Pharmaceutical Affairs Act (amended 11 December 2013) and the Pharmaceutical Affairs Act Enforcement Rules (amended 7 December 2012) through the Ministry of Health and Welfare. Additional rules are set out in the Regulations for Registration of Medicinal Products, which were amended on 7 May 2015.

17 Which authorities may grant marketing authorisation in your jurisdiction?

In the central government, the Department of Health of the Executive Yuan is tasked with granting marketing authorisation. In municipalities, the municipal government grants marketing authorisation, and county and city governments grant such authorisations as well. Throughout the Pharmaceutical Affairs Act and Enforcement Rules, each of these authorities is referred to as the 'competent health authority'. Each competent health authority may engage a health foundation or similar organisation to review academic research, safety and clinical trials, and other technical materials in connection with the market approval of drugs. Approval by the specific agency, the TFDA, under the Ministry of Health and Welfare, is required for the marketing of new drugs.

18 What are the relevant procedures?

A drug may not be manufactured or imported until a drug permit licence is approved and issued. The specific application criteria, review procedure, and approval criteria are established in the Criteria Governing the Review for Registration and Market Approval of Drugs by each respective competent health authority.

Certain information is required for the registration and market approval of a drug, including, but not limited to: (i) the Chinese and foreign-language name of the drug; (ii) the prescription and dosage form; (iii) the labelling, usage instructions and packaging; (iv) the indications, efficacy, properties, method of use, amount used and type of the drug; (v) the manufacturing method, test specifications and method of testing; and (vi) the name of the pharmaceutical firm and name and address of the factory that produces the drug.

Appendix 1 to the Regulations for Registration of Medicinal Products details the Maximum Unit Package Sizes for various dosages including, but not limited to, tablets, oral liquids, injections and ointments. Appendices 2 and 3 detail each and every document necessary for the Application for Drug Review and Registration of New Drugs, New Dosage Forms, New Administration Doses and New Unit Strengths. Appendices 4 and 5 detail the same information with particular respect to generic drugs, and Appendices 6-7, 8-9, and 10-11 do the same with respect to biopharmaceutical products, API and radiopharmaceutical drugs, respectively.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Within five years after a licence is issued for a new drug, no other pharmaceutical firm may apply for evaluation and registration of the same items by citing the data submitted by the licensee (without that licensee's authorisation). Three years after a drug's approval for marketing, however, another pharmaceutical firm may apply for registration of drugs of the same substance, the same dosage form, the same dose, and the same dose unit. A drug licence may be issued to another firm on the day following the expiration of five years after the issuance of the original licence.

Manufacturing and import permit licences are valid for five years. Where it is necessary to continue manufacturing or importing a medicine after a permit licence expires, the permit licence may be

extended for no more than five years with approval of the competent health authority.

If an application for drug registration and market approval is denied, an applicant has four months within which to submit an application for re-examination. Only one application for re-examination is allowed.

20 Which medicines may be marketed without authorisation?

There appear to be no medicines that may be marketed in Taiwan without at least some form of authorisation. For example, even forms of traditional Chinese medicine and natural medicinal products, such as extracts from plant, animal or mineral materials, must be approved by the China Food and Drug Administration. Additionally, the Committee on Chinese Medicine and Pharmacy funds and oversees clinical trials of herbal medicine in Taiwan.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Generally speaking there are no named patient programmes in place. However, there are some exceptions:

- a drug for the treatment of severe malaria that is manufactured in China and not otherwise approved or offered for sale in Taiwan can be obtained under special circumstances. This life-saving drug may be secured by hospitals upon special request from the government's Centre for Disease Control in order to treat patients suffering from life-threatening cases of malaria;
- in 2016, the Elotuzumab (BMS-901608) Named Patient Program was accepting request forms from Taiwan (found on Bristol-Myers Squibb);
- in 2015, the Lomitapide Named Patient Program was permitted by the TFDA (Aegerion Pharmaceuticals); and
- in 2013, the Boceprevir Named Patient Program was permitted (Merck Sharpe and Dohme).

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

Taiwan follows a drug pricing reimbursement system by which certain drugs are approved for listing on the NHI's Pharmaceutical Benefits and Reimbursement Schedule. Listed drugs are reimbursed by the government at preset reimbursement prices, whereas drugs not listed are paid for by patients out-of-pocket. Once a new drug is listed, it can then be prescribed by any healthcare facility in Taiwan. Drugs approved for listing are priced according to the median price of that drug in 10 reference countries. New drugs first introduced in Taiwan can be priced based on drugs with similar effects, or based on costs.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

No. See question 22.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

Drugs submitted for listing must first have been approved and registered with the TFDA. Certain classes of drugs are excluded from listing, including vaccines, non-essential drugs (eg, contraceptives, hair tonics, dark spot detergents, smoking patches, shampoo), as well as other drugs deemed by the government to be non-reimbursable. In 2014, there were around 1,400 behind-the-counter products reimbursed by NHIA (eg, gastrointestinal drugs, antihistamines, antitussive agents), however, delisting in the future is likely because of the pressure to contain costs.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

Decisions regarding reimbursement of new drugs are made by the Bureau of National Health Insurance (BNHI). In 1996, the BNHI established the Drug Benefit Committee - consisting of government personnel, physicians and economists - to make recommendations on whether to list a new drug, whether to impose restrictions on coverage, and the reimbursement price.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

Yes, as prices for listed drugs are set by the government. See question 22.

Medicine quality and access to information**27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?**

The Pharmaceutical Affairs Act and the Pharmaceutical Affairs Act Enforcement Rules outline rules targeting the counterfeiting and illegal distribution of medicines and medical devices. The competent health authority of each municipality, county or county-level city is tasked with addressing these issues, and each is empowered to establish an investigating centre to take enforcement action against counterfeit drugs.

Once counterfeit or misbranded drugs are seized, the competent health authority may issue a reward based on the point system discussed in article 39 of the Pharmaceutical Affairs Act, under which points correlate to monetary amounts. Greater awards are given in exchange for reports of the manufacture or importation of counterfeit drugs. Fewer points are awarded for reports of the wholesale resale, shipment, storage, or manufacture of misbranded drugs or defective medical devices. Rewards are collected jointly where a case is reported by two or more persons at the same time. If two or more persons separately report the same case, the reward is issued to the first person who makes the report. The name of any informant or person who assists in the seizure of counterfeit drugs must remain confidential.

The competent health authority should confine and take samples of any seized counterfeit drugs. Drugs that pose a health hazard should be confiscated and destroyed. Once the counterfeit drugs are linked to a business, the original authority that issued a drug permit licence, pharmaceutical firm business permit licence, and medicament manufacture licence may revoke any such licences from the business. Similarly, the competent health authority must publicly announce the name, address and responsible person, the name of the drugs involved, and the details of the violation of any firm that sells or displays counterfeit drugs. If a further violation occurs, subsequent to the initial counterfeiting violation, that firm's business operations may be suspended.

In the case of domestically produced, misbranded drugs, or defective medical devices that are tested and determined to be usable through remodification, the competent health authority must assign an official to supervise the original manufacturer to remodify the drug or device. Drugs or devices that cannot be reused must be destroyed. If the drugs are approved imports, the drugs must be confined and returned to the foreign suppliers.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

The TFDA maintains a website for the general public that provides various updated information on prescription drugs, food, cosmetic, and medical instruments are provided.

29 Outline major developments to the regime relating to safety monitoring of medicines.

The TFDA operates a web-based reporting system for adverse drug reaction (ADR). Anyone can report a suspected ADR to the TFDA.

In addition, drug companies are required to present safety report of their products on a regular basis to the TFDA. The TFDA also actively solicits domestic and international information on ADRs and makes public announcements. Pursuant to the Pharmaceutical Affairs Act article 45, medical institutions, drug stores and drug companies also have an obligation to report ADRs. For serious ADRs, such as death, life-threatening reactions, permanent disability, congenital deformity in babies and the need for hospitalisation or prolong hospitalisation, medical institutes and drug stores must submit a report within seven days, and drug companies within 15 days, to the governmental health authority.

Vaccination**30 Outline your jurisdiction's vaccination regime for humans.**

The vaccination timetable for children requires hepatitis B, BCG and five-in-one (diphtheria, pertussis, tetanus, polio, haemophilus), measles, German measles, chickenpox, Japanese encephalitis B and pneumococcal vaccines, all of which are free.

Adults are able to receive the flu vaccine for free every year for those over the age of 65, and single shot of pneumococcal vaccine for those over 75.

A vaccination register is maintained and regularly monitored by health authorities, particularly for children. For adults, it is recorded in the hospital file.

Under the supervision of a medical doctor, nurses can administer vaccines.

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The healthcare system is governed principally by the Fundamental Law on Healthcare Services No. 3,359, which furnishes the Ministry of Health (MoH) with the authority to issue healthcare related regulations and establish a healthcare system enabling each and every person living in Turkey to have equal, equitable access to the healthcare system. The regulatory authority is the MoH and its subsidiaries.

The MoH is responsible for establishing hospitals and public health institutions to provide healthcare services to the public. In addition to public hospitals and healthcare institutions, universities with medical faculties may also establish hospitals under the authority granted to universities by the Higher Education Law No. 2,547, and this system is also quite common in Turkey. Private hospitals and healthcare institutions are also common in places where the purchasing power of the population is high.

There has been a fundamental change in the structure of the MoH in 2011. The authorities of the General Directorate of Pharmaceuticals and Pharmacy of the MoH have been transferred to the Turkish Pharmaceutical and Medical Device Institution (the Institution), which was established by Decree Law No. 663. In line with the amendment, the Institution undertakes the following duties in general:

- granting licences or authorisations, monitoring and imposing sanctions where necessary and setting forth the standards for licensing, pricing, manufacturing, storing, sales, import, export, marketing, distribution, promotion, monitoring, recall and usage-related activities regarding the products falling under the authority of the Institution (pharmaceuticals, medical devices, cosmetics, traditional herbal medicinal products, all other products marketed with a health claim);
- regulating, approving and controlling clinical trials with regard to the products falling under its authority; and
- taking the necessary precautions to maintain the accessibility of pharmaceuticals, medical devices and other products that are of vital importance.

Moreover, the Turkey Public Hospitals Institution has been established as a subordinate body of the MoH in accordance with Decree Law No. 663. The Turkey Public Hospitals Institution is responsible for the following:

- opening and operating the hospitals, oral and dental health institutions, and any other institutions dedicated to providing second and third-step health services. Province-based public hospitals unions have been established for the operation of the above-mentioned health institutions;
- monitoring, evaluating and auditing the activities of such institutions; and
- ensuring that any services related to diagnosis, treatment and rehabilitation are provided in such institutions.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The active population, retirees and their dependants are covered by the health insurance provided by the Social Security Institution (SSI). Employers must pay monthly contributions for their employees, who

automatically become covered by the health insurance provided by the SSI; the self-employed may also benefit from this insurance coverage by voluntarily paying monthly contributions. The health insurance provided by the SSI covers practically every physical exam, test and treatment option (both outpatient and in-patient) conducted at public healthcare institutions and university hospitals, apart from those that are not necessary for the health of the insured person, such as cosmetic operations. The SSI also covers emergency services given to the insured at private health institutions.

A big proportion of the public is covered by the SSI health insurance, while only a small proportion benefits from private insurance coverage by paying monthly contributions.

A new plan, the General Health Insurance, has been in place since January 2012, and accordingly every citizen in Turkey is now under SSI health insurance coverage. The aim is that all citizens who were not covered by the SSI health insurance packages now benefit from public health insurance.

Compliance - pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

In Turkey, advertising of medicinal products is governed by Pharmaceutical and Medical Preparation Law No. 1262, and the Regulation on Promotional Activities of Medicinal Products for Human Use (Promotion Regulation), which is based on the former. The Promotion Regulation was published and came into effect on 3 July 2015. For further information about the important amendments, see question 9.

Further, the Act on Protection of Consumers, Regulation on Principles and Fundamentals of Practices regarding Commercial Advertisements and Announcements, and Code of Obligations are applicable where a matter is not regulated under Law No. 1262 or the Promotion Regulation. Additionally, the Supreme Council of Radio and Television (RTUK) is authorised to conduct examinations for radio and television broadcasts regarding the determination of advertisements that breach the principles set out in the Law on Establishment and Broadcasting of Radio and Television Institutions No. 6112 (RTUK Law). As per article 11/2 of the RTUK Law, no advertisements for prescribed medical products or treatments can be broadcast. There are also three industry-based associations in Turkey: the Turkey Pharmaceuticals Industry Association (TISD), the Association of Research-Based Pharmaceutical Companies (AIFD) and the Pharmaceuticals Manufacturers Association (IEIS), which have their own codes of promotional practices.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

The fundamental rule is that marketing authorisation or marketing authorisation holders and their representatives may not provide, offer or promise benefits to healthcare professionals by way of promotional activities, as explained in further detail in question 9. According to the Promotion Regulation, products that are not granted permits or authorisation in Turkey cannot be promoted (off-label promotion is strictly forbidden), and that advertisements directed at healthcare

professionals must contain information consistent with the products approved, and an updated summary of product characteristics (SmPC).

Promotion must be aimed at healthcare professionals, and shall include objective, informative and factual medical data to enable the healthcare professionals to form their own opinion about the product. The promotional activities shall not be used to encourage unnecessary use of a product, and the promotion must be made by certified representatives.

The mandatory certification of the sales team is a requirement that was foreseen by the former regulation as well. All promotion representatives shall receive certificates if they are successful in the examination or upon submission of diplomas from the departments of universities educating medical sales representatives. The examinations required for such certification will be conducted according to Guidelines published by the MoH and based on the Promotion Regulation. To date, the MoH has only authorised a single university in Turkey to conduct the vocational education and examinations, although assurances have been made that this number may be extended depending on the demands of the industry regarding said certification. The effective date of the provision coming into force has been delayed until 1 January 2019 in order to establish the implementation system. Once this date has passed, individuals without the aforementioned certification will not be able to work as promotion representatives for medicinal companies.

5 What are the main rules and principles applying to advertising aimed at the general public?

According to the Pharmaceutical and Medical Preparations Law No. 1262 and the Promotion Regulation, it is strictly forbidden to promote medicinal products for human use to the general public. Over-the-counter products are categorised as non-prescribed products and are subject to the same promotion principles as prescribed products. The need for a new law governing over-the-counter products has been under discussion for a long time; however, no official draft has been submitted for comment, and it is therefore unlikely that we will see a new law in the near future.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The Promotion Regulation forbids pharmaceutical companies from making promotional materials available to the public, either intentionally or unintentionally. However, examples of illegal advertising of products can be found, such as in display windows of pharmacies. The other common type of infringement concerns advertisements aimed at healthcare professionals that are not supported with sufficient scientific data. Other than these infringements, occasionally healthcare professionals may be found not to be fully in line with the applicable legislation.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

According to the Promotion Regulation, off-label promotion is strictly forbidden in Turkey. The only exceptions to this rule are the provision of off-label information during international congresses held in Turkey, or if a healthcare professional has asked for the provision of such information in writing. This prohibition does not prevent the provision of scientific material that contains off-label information to healthcare professionals. Upon the written request of a healthcare professional, the requested information must be delivered by a scientific service representative.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

The Promotion Regulation governs the relationship between pharmaceutical companies and healthcare professionals.

The ethical principles set out by medical associations of which the healthcare professional is a member also apply to this relationship.

If a service to be rendered by the healthcare professional for the pharmaceutical company is concerned, the Law on Public Officials No. 657 or the Higher Education Law No. 2547 may also be applied, since

the rules set forth in this legislation provide limitations regarding the working principles of healthcare professionals.

The Regulation on Ethical Principles of Conduct and Procedure and Principles of Application will also apply to the relationship between a healthcare professional who is a public official and a pharmaceutical company.

There is no difference in the rules that apply to physicians in the outpatient or in-patient sectors.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

The Promotion Regulation imposes limitations on the relationship between pharmaceutical companies and healthcare professionals. The fundamental rule is that marketing authorisation holders and their representatives cannot provide, offer or promise benefits to healthcare professionals by way of promotional activities. The marketing authorisation holder shall not encourage the prescription of its products by offering any kind of benefit to a healthcare professional. In this regard, the value of the reminder promotional materials, may not exceed 2.5 per cent of the applicable minimum wage per month. Moreover, with the amendment to the Promotion Regulation, the limitations regarding congress and symposium sponsorships are further extended. Namely, a healthcare professional may benefit from sponsorships only four times in one year, and at most twice from the same pharmaceutical company. In addition, only two out of these four sponsorships may be used abroad. However, organisations that healthcare professionals attend as a speaker are not limited by the above rule.

With regard to the seasons, as per article 5 of the Promotion Guidelines, congresses and symposia cannot be organised at certain periods during the year in ski centres or at seaside holiday resorts. All organisations have to be notified to the MoH. Furthermore, healthcare professionals have to state the support that they have been given by the pharmaceutical companies at the beginning of their presentations and at the end of their articles, as per the amended version of the Promotion Regulation.

Regarding services to be rendered by healthcare professionals to a pharmaceutical company, a law that was published in January 2014 had banned physicians working in state or university hospitals from working privately, and a transitional period was granted to those physicians that held private clinics to close those clinics by 18 April 2014. Just before the expiry of the transitional period, the Constitutional Court stayed the execution of the law ordering physicians to close their private clinics by 18 April and recently cancelled the article granting this transitional period. However, the provision banning state and university physicians from having private practices remains in force.

As a result of this court decision, physicians with private clinics founded before the publication of the said law, do not have to close those clinics. However, it has stated that the provision banning state and university physicians from private practice is still in force.

The most important change introduced by the Regulation is the obligation of disclosure. Together with article 11/7 of the Promotion Regulation, value transfers (in cash or in kind) that are provided to healthcare professionals, healthcare institutions and organisations, universities, unions, associations and foundations active in the field of healthcare and NGOs established for the purpose of the protection and the advancement of health, by the marketing authorisation holders, exceeding 10 per cent of the applicable gross monthly minimum wage in terms of its monetary value shall be disclosed to the Institution. The disclosure of value transfers for a calendar year shall be submitted within the first six months of the subsequent year. The system of disclosure introduced by the Promotion Regulation only necessitates the disclosure of information by the marketing authorisation holders to the Institution, without providing for an additional mechanism for disclosure to the public.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

The most common infringement with regard to collaboration with healthcare professionals is seen in congress-symposium sponsorship relations. These congresses and symposia, which at times have only a

minimal scientific purpose, have sometimes been used as a way to offer holidays or extra benefits to healthcare professionals.

Together with the new Promotion Regulation, marketing authorisation holders may organise or sponsor scientific meetings held abroad on the condition that the meeting is international, or a majority of the participants are healthcare professionals not working in Turkey. These conditions are in fact implemented owing to some cases that the Institution faced in the recent years. This provision will avoid the global companies to be the sponsor for the organisation of these meetings and Turkish companies affiliated to these global companies to be the sponsor to all of the participant healthcare professionals working in Turkey.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

There are no official regulations regarding the collaboration of the pharmaceutical industry with patient organisations. However, industry associations such as TISD, AIFD and IEIS have their own codes of practice that govern relations with patient organisations. According to the AIFD Code of Ethics, if a pharmaceutical company decides to provide support to a patient organisation, either financially or through rendering services, a written agreement shall be signed between the parties. Pharmaceutical companies shall not have an influence on the content of the printed or visual materials of a patient organisation to gain commercial advantages, and cannot stipulate being the sole supporter of a patient organisation or a project.

12 Are manufacturers' infringements of competition law pursued by national authorities?

The Turkish Competition Law is applicable to the sale of goods and services in Turkey; the sale of goods and services outside Turkey that do not have any effect on Turkish market are not covered by the Competition Law. The Turkish Competition Authority is the body authorised to monitor competition in the market.

Manufacturers' infringements of competition law are pursued by the Turkish Competition Authority as investigations initiated by the authority itself or upon complaints that can be made by anyone (in most cases by competitors).

The Turkish Competition Authority can impose sanctions including heavy administrative fines on companies and board members, and may invalidate the relevant contract or transaction in cases of infringement of competition.

13 Is follow-on private antitrust litigation against manufacturers possible?

According to article 57 of the Competition Law, anyone who prevents, distorts or restricts competition through practices, decisions, contracts or agreements contrary to this law, or abuses a dominant position in a particular market for goods or services, is obliged to compensate any damages to injured parties. Parties who claim that they have suffered damages and loss arising from anticompetitive acts of manufacturers may claim compensation by filing a lawsuit before the courts. Accordingly, the injured party may ask for an amount equal to three times the actual loss incurred.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

Under Turkish law, there is no umbrella legislation that covers all types of anti-corruption issues. Crimes such as bribery and official misconduct are punishable according to Turkish Criminal Code No. 5237, regardless of the sector in which they are committed. In terms of bribery regulated under article 252 of the Turkish Criminal Code No. 5237, any kind of benefit provided for executing a legal transaction, which should be executed or vice versa, is prohibited with a zero-tolerance approach. In addition to the Turkish Criminal Code, the Regulation on the Code of Ethics of Public Officials and Application Procedures and Principles is establishing the basic principle for public officials not to receive or give gifts and not to derive interest as a result of their duty. This Regulation also defines a black list of all sorts of goods and benefits that public officials cannot receive.

In order to guide pharmaceutical companies interacting with healthcare professionals, the MoH defined sector-specific rules. In this sense, provisions regarding promotional interactions like congress sponsorship of healthcare professionals, donations made to healthcare organisations, as well as all kinds of promotional materials that can be given to healthcare professionals are regulated under the Promotion Regulation.

As explained in question 9, on July 3 2015, the MoH introduced a requirement to disclose to the Institution, transfers of value made to healthcare professionals by pharmaceutical companies. Companies started documenting transfers of value made in 2016 and are preparing for their disclosure submissions within the first six months of 2017. This data will not be disclosed to the public, but will be reviewed and retained by the MoH.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

The long-awaited Regulation on the Sale, Advertisement and Promotion of Medical Devices came into force on 15 May 2014 and was amended on 25 July 2015. The advertisement and promotion of medical devices were previously unregulated, leading to a lack of uniformity in practice across the Turkish medical device market. A distinction that has been introduced specifically for the medical device regulatory regime is a provision that distinguishes between medical devices that can be advertised to the public and those that are prohibited from being advertised. Medical devices that must be used or administered exclusively by healthcare professionals and medical devices within the scope of reimbursement cannot be advertised to the public, either directly or indirectly. However, the advertisement of devices intended for personal use and that do not fall within the scope of reimbursement is allowed. Regarding this distinction, the Regulation on the Sale, Advertisement and Promotion of Medical Devices finds a balance between the severe restrictions applied to pharmaceutical products and a more variable approach that is better suited to the medical devices industry, which encompasses thousands of very different products.

The term 'promotional activities for medical devices' covers the promotion of medical devices that fall within the scope of the Regulation on the Sale, Advertisement and Promotion of Medical Devices to healthcare professionals and technical staff working in the medical device field who are employed by healthcare institutions and organisations, and activities intended to inform these people on subjects such as operating manuals. Technical support services and clinical support services are not regarded as being within the scope of promotional activities. The Regulation on the Sale, Advertisement and Promotion of Medical Devices introduces rules and principles that relate to promotion to and relationships with healthcare professionals (eg, promotional materials, scientific and educational activities, sponsorships, free samples and donations) that are similar to the established rules and principles applied to the pharmaceuticals sector. Consequently, medical devices are now also subject to provisions that have been modelled on pharmaceutical practice and that are unique to Turkey, including the maximum monetary value applied to reminder promotions directed at healthcare professionals, quotas relating to the amount of congress sponsorships that healthcare professionals can make use of each year, and transparency and notification obligations.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The regulatory framework for granting marketing authorisations is governed by the Regulation on Licensing of Medicinal Products for Human Use (Licensing Regulation). As for placing a pharmaceutical product on the market, additional regulations, such as the Regulation on Labelling and Packaging of Medicinal Products for Human Use and the Regulation on Safety of Medicines, also apply.

17 Which authorities may grant marketing authorisation in your jurisdiction?

The MoH is the sole authority entitled to grant marketing authorisations for pharmaceutical products in Turkey. The MoH fulfils this duty through the Institution.

18 What are the relevant procedures?

No medicinal product for human use can be marketed unless it is granted a marketing authorisation (licensed) by the MoH pursuant to the provisions of the Licensing Regulation. According to the Licensing Regulation, the eligibility criteria for the persons who may apply for pharmaceutical product licence are as follows:

- natural persons should have a degree from a university providing education in the branches of pharmacy, medicine or chemical sciences and should avail of the authority to practise their profession in Turkey. In line with the related laws, pharmacists should be Turkish citizens able to perform their profession in Turkey. There is no such requirement for chemists. Until quite recently (before the passing of Decree Law No. 663 dated 2 November 2011) only Turkish citizens were allowed to practise as physicians in Turkey; however, foreign physicians may currently conduct their profession in Turkey, under some conditions. This recent amendment is still under discussion; and
- legal persons should employ someone with an 'authorised person' title who has the qualities specified in the above bullet point, and who has sufficient information and experience with regard to the concerned product for which an application is submitted.

The following documents, in general, shall be submitted to the MoH along with the application for the pharmaceutical product licence:

- a notarised copy of the diploma indicating that the applicant may practise one of the professions specified above;
- a certified document indicating that the applicant is authorised to submit an application;
- in the event of the applicant being a legal person, the original version or a copy of the commercial registry gazette indicating the objectives for the establishment of the company, the relevant members, duties and titles of the persons responsible;
- the name or corporate name, permanent address, email address, telephone and fax numbers of the applicant;
- the name, permanent address, telephone and fax number of the manufacturer;
- product-related information, such as:
 - the name of the product;
 - quantitative and qualitative particulars of all the components of the product (except for the empirical chemical formula) and its international non-proprietary name;
 - a description of its manufacturing method;
 - any therapeutic indications, contraindications and adverse reactions;
 - the dosage, pharmaceutical form, method and route of administration;
 - the shelf life and amount in the package;
 - an indication of the disposal method of waste products; and
 - a description of control methods used by the manufacturer (such as sterility tests, tests for measuring the presence of heavy metals, stability tests, biological and toxicity tests);
 - results of physico-chemical or microbiological tests, toxicological and pharmacological tests and clinical trials;
 - a good manufacturing practice (GMP) certificate, issued to the manufacturer by the MoH; and
 - the summary of product characteristics specified in the Regulation on Packaging and Labelling and the patient information leaflet prepared accordingly; the immediate and outer packaging samples with the dimensions and design to be used in the market; and in the case of products authorised abroad and imported or manufactured on licence, the originals of summary of product characteristics, and patient information leaflets from other countries along with their Turkish or English translations, which are declared to have been recently updated;
- in the context of pharmacovigilance practices, the curriculum vitae, address, telephone and fax numbers and job description of the person responsible for product safety; and

- in the context of the Promotion Regulation, the document defining the scientific service and its address, telephone and fax numbers.

In the case of imported products or products manufactured under licence, additional documents are requested from the applicant.

Abridged applications are also possible in Turkey under the conditions set forth in the Licensing Regulation.

The MoH follows the European CTD format (including five modules) for the application files.

The Licensing Regulation envisages a 210-day period for the evaluation of the licence application by the MoH following the preparation of all required documents. In practice, however, this may go up to two years or more due to the GMP certification rules of the MoH, which require that each manufacturing facility be audited by Ministry personnel.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

According to the Licensing Regulation, if the concerned product is not actually placed on the market within three years of the issuance of the licence, the licence may be suspended by the MoH. No exception to this rule is set out in the related regulations. However, the licence is not automatically suspended after the lapse of this three-year period, and the MoH shall issue a decision in this regard in order to suspend the licence.

20 Which medicines may be marketed without authorisation?

Medicines that may be marketed without authorisation are those provided to the patient in the scope of 'compassionate use' or 'named patient use'. The details of these programmes are outlined in question 21.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

The Compassionate Use Programme is regulated under the Guideline on Compassionate Use Programme and is defined as the provision, free of charge, of a pharmaceutical to a patient by the manufacturer or supplier company for humane reasons, where the drug has no marketing authorisation in Turkey. The Compassionate Use Programme is a patient-based programme. The physician applies to the MoH if he or she feels that a product without marketing authorisation in Turkey is necessary for a patient who is suffering from a life-threatening disease, and that they cannot be healed with any authorised product or be included in clinical trials. According to the Guideline, it is not important whether the pharmaceutical product used in the programme is licensed abroad or not. Ideally, at least phase II trials will have been completed; however, this is not a requirement. During the Programme, only the costs of routine tests may be covered by the patient or reimbursed by the SSI; other than that, no cost can be imposed on the patient or the SSI.

The Guideline explicitly states that compassionate use and off-label use cannot be conducted at the same time.

Another alternative is the 'special importation' of pharmaceuticals that have no marketing authorisation in Turkey, or that have a marketing authorisation but are not marketed in Turkey for various reasons. These products are imported from abroad on a named patient basis. The MoH published in May 2016 a new Guideline regarding the Supply from Abroad and the Use of Pharmaceuticals. The recent amendments to the guidelines were intended to return to the previous practice, under which only the Turkish Pharmacists' Association (TEB) could import pharmaceuticals from abroad within the scope of the NPP. The former guidelines allowed 20 pharmaceutical warehouses authorised by the Institution to import pharmaceuticals from abroad on a named patient basis, as well as the TEB. The TEB shall import only in the order defined below:

- products that have an authorisation from the US Food and Drug Administration or the European Medicines Agency and are put on the market; or
- products manufactured, authorised and put on the market in a country that is a member of the Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Cooperation Scheme.

The physician of a patient who needs to use such product for his or her treatment under a prescription may apply for its special importation if the physician believes that there is a scientific advantage to importing

the pharmaceutical without Turkish marketing authorisation. The results of these applications are collected in a pharmaceuticals list that is published on the Institution's website every Friday.

If the relevant product cannot be found in or supplied from these countries, the commercial name of the product manufactured and used in another country can be added to the Foreign Pharmaceutical List following an opinion from the Scientific Commission and approval of the president of the Institution.

The SSI and TEB signed a protocol in April 2007, which covers the reimbursement conditions for NPP pharmaceuticals imported by the TEB and that is still valid, allowing the reimbursement of NPP products.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

The principles for determining pharmaceutical prices are set by the Council of Ministers in the Pricing Decree, and in the Pricing Communiqué published by the MoH based on the Pricing Decree. These regulations have recently been republished. The MoH is still applying the reference price system. The maximum sales prices of pharmaceutical products are determined by taking into account the lowest price of the product available on the market respectively in the reference countries (France, Greece, Italy, Portugal and Spain) and the countries of batch release and import; where this is not available, the lowest price of the product available in the EU countries; and where this is not available, the ex-factory price (sale price to wholesalers) of the product available on the market in any country across the world. The reference price takes the active substance into consideration for each product. Then it determines the price of different forms and dosages of this active substance by using a proportioning method.

The price of an original pharmaceutical is revised and becomes maximum 60 per cent of the reference price upon the launch on the market of its first generic.

One of the most discussed topics related to the pricing of pharmaceuticals in Turkey is the euro and Turkish lira currency rate (Fx rate) determined by the Price Assessment Commission competent for calculating the price of a product. According to the Pricing Decree, the Fx rate should be adapted to the currency fluctuations. However, the Fx rate set to 1.95 in 2007 was still not amended until 2009. The industry formally requested from the MoH to change the Fx rate. Upon the rejection of this application, the industry associations filed an action against the MoH. The Council of State examining the case held its decision in favour of the industry and decided that the Pricing Assessment Commission should render a new decision with respect to the determination of the Fx rate. The Pricing Assessment Commission assembled and decided not to change the Fx rate. Although the administration bodies should comply with Court decision, as the Council of State's decision was indicating to take a decision regarding the matter, the Pricing Assessment Commission was, in theory, not in contradiction with the Court's decision. However, the industry associations filed a new action against the MoH, which was again accepted. During this process, the Pricing Assessment Commission set the Fx rate to 2 and then to 2.07 Turkish lira. Finally, the Pricing Decree was amended in July 2015 and the Fx rate was accepted as 70 per cent of the average annual euro value.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

According to the reference price system, the maximum price of a pharmaceutical is automatically determined; therefore, there is no place for negotiation in the system. On the other hand, manufacturers are free to sell their products below the ceiling price determined through the reference price system. Public healthcare providers must follow the public tender procedures and, as a general rule, the participant company offering the lowest price in the tender is awarded the tender.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

The cost of a medicine is reimbursed provided that it is registered in the reimbursement list of the SSI.

Update and trends

We expect the Turkish Pharmaceutical and Medical Device Institution to make amendments to some of the substantial regulations regarding the authorisation of medicinal products. In fact, the Institution requested the industry associations' opinion and amendment requests with respect to the MA Regulation, Bioavailability and Bioequivalence Regulation and the Regulation on Variations to authorised medicinal products. We may see within 2017 a sequence of amendments made to the regulatory rules of a pharmaceutical's access to the market.

A new Law on the intellectual property, which includes specific provisions to patent law, is expected to enter into force by early 2017. The new law will mainly harmonise national law with EU law.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The MoH, through the Institution, is the competent authority regarding the pricing of medicinal products. The competent body for reimbursement decisions is the SSI. There are also two important committees: the Pricing Committee, which is coordinated under the authority of the MoH and involves the participation of delegates from the Ministry of Finance, the Secretariat of State Planning Organisation, the Secretariat of Treasury and the SSI; and the Reimbursement Committee, which is organised by the Ministry of Finance and includes delegates from the MoH, the Secretariat of State Planning Organisation, the Secretariat of the Treasury and the SSI. These Committees review the applications and approve their conformity in line with the related pricing and reimbursement legislation.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

According to the Health Implementation Communiqué, the discount rate that is applied to original pharmaceuticals where no generic version is on the market is 41 per cent in total (11 per cent base discount plus 30 per cent additional discount), and 28 per cent (11 per cent base discount plus 17 per cent additional discount) for original products where the generic version is on the market. Twenty-eight per cent (11 per cent base discount plus 17 per cent additional discount) of the discount is applied to generic products.

The applied discount rates may differ according to the type of product, for example pharmaceuticals that are over 20 years old, over-the-counter pharmaceuticals or blood-derivative products.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Under article 18 of Law No. 1262 (as amended in January 2014), the sale of counterfeit medicines is subject to an administrative fine ranging from a minimum of 100,000 Turkish lira up to a statutory maximum of five times the aggregate of the annual sale proceeds of the counterfeit medicine in question. If the infringing acts are repeated, an administrative fine of twice the amount of the original fine will be issued. In a situation where the counterfeit medicines are being sold or distributed online, access to the infringing website will be blocked.

The counterfeiting and illegal distribution of medicines is also subject to the Turkish Criminal Code. According to article 186, any person who sells, procures or stores decayed or transformed foodstuffs, beverages or drugs and thereby causing risk to another's life and health is punished with imprisonment for a period ranging from one to five years and faces a punitive fine up to 150,000 Turkish lira to be paid to the state. The punishment to be imposed is increased by one-third if the offence is committed by a person who is qualified as a professional in his or her business area (eg, if the concerned person is a pharmacist and sells decayed drugs, the punishment will be increased by one-third).

In addition to this, according to article 187 of the Turkish Criminal Code, any person who produces or sells drugs in such a way as to risk another's life and health is punished with imprisonment for a period ranging from one to five years. The punishment to be imposed is

increased by one-third if the offence is committed by a physician or pharmacist, or within the scope of a professional activity.

On the other hand, if the name of the medicine is registered as a trademark in Turkey, the use of the trademark on counterfeit products is subject to the general provisions of trademark law regulated under the Decree-Law No. 556 pertaining to the Protection of Trademarks. As per article 61 of the Decree-Law, the use of the same or confusingly similar trademarks without the consent of the proprietor of the trademark shall be considered an infringement of the trademark.

Furthermore, if counterfeit medicines are imported into Turkey without being subject to customs procedures, article 19 of Law No. 1262 stipulates that these products will be subject to the general provisions set forth in the Law to Counter Smuggling No. 5607.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

No measure has been taken by the relevant authorities to facilitate public access to information about prescription-only medicine.

29 Outline major developments to the regime relating to safety monitoring of medicines.

As a major development regarding the regime relating to safety monitoring of medicines, the Regulation on the Safety of Medicines (Regulation) came into force on 15 April 2014, and the Regulation now governs pharmacovigilance in Turkey. The Regulation sets forth rules and principles for enabling a systematic monitoring of adverse effects, as well as data collection, recording, assessment, archiving of adverse effects, taking necessary measures so as to minimise the harm caused by medicinal products for human use and to ensure their safe use.

The licence or marketing authorisation holder shall continuously employ an appropriately qualified physician or pharmacist responsible for pharmacovigilance who shall be appointed as the officer responsible for the safety of the products, and this person shall be notified to the MoH along with the licence application. According to the Regulation, the Turkish Pharmacovigilance Centre (TUFAM) is the competent authority to follow the pharmacovigilance reports regarding pharmaceutical products. TUFAM has close connections with those foreign authorities that follow up pharmacovigilance reports, and constantly updates its database.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

In Turkey, there is no general obligation to vaccinate. However, there is an exception to this principle where article 72 of Public Health Law No. 1593 authorises the MoH to take relevant measures, including administering vaccines, when an illness specified under article 57 of Law No. 1593 (cholera, plague, prulente meningitis, typhus, etc) threatens public health.

In addition, according to Decree Law No. 663 on the Organisation and Duties of the MoH and its Affiliates, the MoH is entitled to regulate the services to be rendered in terms of vaccination in Turkey. Within this scope, the MoH has a routine vaccination regime called the Extended Immunisation Programme (the Programme). With regards to the Programme, the MoH published Circular 2009/17 dated 13 March 2009. The Circular regulates the procedures and principles regarding administration of vaccines, regulating which vaccines are to be administered as well as their times of administration. It also sets forth the registration and notification principles of the vaccines that are administered. To this end, there are printed forms attached to the circular for use by health professionals authorised to administer vaccines. The circular also determines teams responsible for the execution, monitoring, supervision, evaluation and logistics of the Programme. The managers of these teams are the province health directors in each province. They are primarily responsible for execution of the Programme at provincial level. Similarly, in the districts, the managers of the teams are health group managers, who are responsible primarily at district level. There are also supervisors and assistants who provide support in the provinces and districts. Other than that, family physicians and community health centres have direct duties and responsibilities under the Programme.

In terms of the costs incurred, vaccines are within the scope of social insurance coverage. The SSI pays for the vaccines according to article 2(4)(3) of the Health Implication Communiqué.

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The United Kingdom (UK) healthcare system comprises both public and private services.

Since 1999, the UK provision of healthcare has been devolved to the administrations of each of the UK's four constituent countries. Public healthcare is provided through the National Health Service (NHS) in England and by equivalent bodies in Northern Ireland, Scotland and Wales. The NHS was founded in 1948 with the aim of providing free healthcare at the point of use to the whole population. The Secretary of State for Health is ultimately responsible for the provision of medical services, but discharges this role through the hospitals, clinics and related institutions (some of which may be privately run) contracted by NHS Trusts and Health Authorities and statutory bodies called Clinical Commissioning Groups (CCGs) created under the Health and Social Care Act 2012. The Health and Social Care Act 2012 made fundamental changes to the core structure of the NHS so that, from 1 April 2013, CCGs within NHS England and local area teams share the responsibilities of commissioning healthcare services for patients. CCGs in turn contract to obtain the services of general practitioners (GPs) for use in the community and pharmacy services, and will tender for the supply of certain medicines and clinical services. NHS England is an independent body, at arm's length to the government. Its main role is to set the priorities and direction of the NHS and to improve health and care outcomes for people in England.

Private healthcare may be provided for those individuals who take out such cover in parallel to the NHS. It is generally used as a complement to NHS services, in particular with respect to non-emergency services or elective procedures.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

Publicly funded healthcare accounts for approximately 83 per cent of total healthcare expenditure in the UK, with the remaining 17 per cent of UK healthcare expenditure funded privately.

With the exception of some charges (including low-cost fees for prescriptions, optical services and dental services for non-exempt patients) the UK public health system offers in-patient and outpatient services that are free at the point of use for all UK residents.

Public healthcare expenditure in Northern Ireland, Scotland and Wales is decided by their respective devolved governments, while NHS expenditure in England is determined by the UK government. For 2016/17, planned NHS expenditure amounts to approximately £118.3 billion. This expenditure (and its equivalents in the devolved jurisdictions) is funded by:

- general taxation (80 per cent);
- national insurance contributions, which are payments made by workers and employers towards the cost of certain state benefits (18.8 per cent); and
- user charges (1.2 per cent).

The private healthcare sector in the UK is funded largely by private insurance. It operates its own clinics and hospitals, and may sometimes subcontract its services to the NHS. Certain practitioners in specialist areas work in the NHS as well as in private hospitals and clinics.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

The advertising of medicinal products in the UK is controlled by a combination of legislation and self-regulation through industry associations' codes of practice.

Part 14 of the Human Medicines Regulations 2012 (the UK Regulations) contains the key statutory provisions relating to medicines advertising, and serves to implement Titles VIII and VIIIa of EU Directive 2001/83/EC on the advertising of medicines for human use. Minor amendments to the UK Regulations were made by the Human Medicines (Amendment No. 2) Regulations 2014. In addition to the UK Regulations, the following legislation regulates particular aspects of medicines advertising in the UK:

- the Bribery Act 2010 contains certain provisions that are relevant to interactions between industry and healthcare professionals (HCPs), government officials and other stakeholders;
- the Enterprise Act 2002 implements certain provisions on the enforcement of Title VIII of Directive 2001/83/EC;
- the Cancer Act 1939 prohibits certain advertisements for cancer treatments; and
- the Trades Descriptions Act 1968, the Business Protection from Misleading Marketing Regulations 2008/1276 and the Consumer Protection from Unfair Trading Regulations 2008/1277 contain provisions governing advertising practices generally.

Supplemental guidance to the UK Regulations has been issued by the Medicines and Healthcare Products Regulatory Agency (MHRA) in its 'Blue Guide'. Part 14 of the UK Regulations and the Blue Guide set out different requirements depending on whether the advertising in question is aimed at the general public or to HCPs.

In addition to the legislative framework, a self-regulatory system for medicinal product advertising is operated by the Association of the British Pharmaceutical Industry (ABPI) and the Proprietary Association of Great Britain (PAGB). The ABPI's Code of Practice and the PAGB's Consumer Code regulate the advertising of prescription-only medicines (POMs) and the advertising of over-the-counter medicines respectively. The MHRA works with the Advertising Standards Authority, the UK's independent regulator on matters relating to general advertising across all media, and the Committee of Advertising Practice, the body responsible for writing and maintaining the UK advertising codes.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

Consistent with EU pharmaceutical law, as a general rule, advertising of an unlicensed medicine is prohibited and a medicine cannot be promoted outside its licensed indication(s). All medicines advertising must be consistent with the approved summary of product characteristics (SmPC) of the product.

Insofar as the advertising of medicines to HCPs who are persons qualified to prescribe or supply (PQPS) medicines is concerned, regulations 294 to 300 of the UK Regulations set out requirements relating to a variety of activities including internet advertising, the provision of samples and the conduct of medical sales representatives.

The advertising of POMs to PQPS must be accurate, balanced, fair, objective and unambiguous. It must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. It must not mislead, either directly or by implication, and must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine.

All advertisements of medicinal products aimed at PQPS must contain the essential information set out in regulation 294 and Schedule 30 of the UK Regulations. These requirements include an obligation of the marketing authorisation holder to:

- state one or more of the licensed indications in the advertisement;
- list the active ingredients;
- summarise the main points in the SmPC relating to dosage, method of use, adverse reactions, precautions, relevant contraindications and, where it is not obvious, method of administration;
- state the actual product name, active ingredients, licence number, name and address of the licence holder and cost of the product; and
- refrain from stating or implying that a medicine is 'safe' or 'new' (except in certain specified circumstances).

Regulation 300(1) of the UK Regulations moreover prohibits the supply, offer or promise of any gift, pecuniary advantage or benefit to HCPs in connection with the promotion of medicinal products, unless it is inexpensive and relevant to medical practice. Breach of regulation 300(1) is a criminal offence.

5 What are the main rules and principles applying to advertising aimed at the general public?

Regulations 282 to 293 of the UK Regulations govern advertising aimed at the general public.

The advertising of POMs to the general public is prohibited. Factual and non-promotional press releases relating to POMs are permitted, as long as their content is newsworthy and they provide an appropriate context relative to the use of the medicine and the population for which it is authorised.

Over-the-counter and general sales list medicines may be advertised to the public subject to certain requirements set out in regulation 291 of the UK Regulations and the guidance provided in Annex 3 of the Blue Guide, including that the advertisements:

- are consistent with the SmPC of the medicines concerned and are not misleading;
- refrain from suggesting that the medicine will enhance the health of a person not suffering from a disease or injury, or that the effects of the medicine are guaranteed or the same as or better than another identifiable treatment;
- refrain from implying that medical consultation is unnecessary or quote recommendations by HCPs or celebrities; and
- are not directed principally at persons aged under 16.

The UK Regulations also set out rules concerning the form and content of advertisements aimed at the public. Products must be clearly identified as medicinal products, and information regarding the correct use of the product and an express invitation to read the SmPC must be included. Pursuant to regulation 293 of the UK Regulations, the sale or supply of medicinal products to the public for promotional purposes is also prohibited.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The MHRA Advertising Standards and Outreach Unit's latest annual report notes that 170 complaints were received by the MHRA in 2015. This is a reduction from the number of complaints received in 2014 (193) and reflects an ongoing downward trend. Consistent with previous years, over 80 per cent of complaints received by the MHRA concerned advertising of POMs to the public. Complaints regarding advertisements of botulinum toxin products (eg, Botox, which featured particularly prominently). An increase was also observed in the number of complaints received about advertising on social media such as Facebook and Twitter.

The issues reported to the Prescriptions Medicines Code of Practice Authority (PMCPA) are of a more varied nature. These complaints relate to various forms of interactions between pharmaceutical

companies and other stakeholders, including advisory board and other meeting arrangements, the provision of hospitality to HCPs, journal advertisements and discount schemes.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

It is a breach of the UK Regulations to issue promotional material for a licensable medicine before the licence is granted, or for the off-label use of a licensed product that goes beyond the scope of its licence.

In exceptional circumstances, limited factual information regarding new treatments that are expected to give rise to significant changes in costs (compared to the costs of currently available treatments) may be disseminated by manufacturers to persons with responsibility for health budgetary decisions, such as health authorities. Manufacturers may also provide relevant factual information concerning unlicensed medicines or off-label use where this is required by certain national public advisory bodies.

The general prohibition on advertising of unlicensed medicines does not prevent the communication of a factual answer to an unsolicited question about an unlicensed medicine or off-label use. However, manufacturers must take care not to engage in activities that appear to be designed to solicit such questions, which would likely be regarded as promotion and therefore in breach of the UK Regulations.

Under the UK Regulations, licensed manufacturers and suppliers of unlicensed medicines (specials) may send out price lists to HCPs to whom the price of specials may be relevant. No product claims should be included in the price list. Typically, a price list would include the active ingredient, strength, dosage form, pack size and price for each product listed.

Companies may promote the service they provide but any proactive display of information about specials, for example at a conference stand, is likely to be seen as promotional.

The ABPI Code (Supplementary Information to Clause 3) recognises that the promotion of medicines at international meetings held in the UK may sometimes pose problems with regard to medicines or indications for medicines that are not licensed in the UK although they are licensed in another major industrialised country. The display and provision of promotional material for such medicines is permitted, subject to certain conditions being met.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sector?

The pharmaceutical industry's collaboration with HCPs is governed by a combination of UK domestic law (implementing EU law) and industry self-regulatory regime. The self-regulatory regime is provided in guidance notes and codes of practice. The governing regulatory framework does not distinguish between the outpatient and in-patient sectors and therefore apply equally to all practising physicians.

In addition to the UK Regulations (see question 3), the instruments (statutory or otherwise) that are particularly relevant to guiding collaborations between the pharmaceutical industry and HCPs in the UK include:

- the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), which govern the conduct of clinical trials;
- the Data Protection Act 1998, which ensures the protection of patients' and clinical trial subjects' personal data;
- the Bribery Act 2010;
- ABPI Code of Practice and guidance notes:
 - Clause 20 of the 2016 ABPI Code, which addresses joint working between pharmaceutical companies and the NHS;
 - the ABPI Guidance Notes on Joint Working Between Pharmaceutical Companies and the NHS and Others for the Benefit of Patients (2009)
 - ABPI Quick Start Reference Guide for NHS and Pharmaceutical Industry Partners (2012); and
 - the ABPI guidance Joint Working with the Pharmaceutical Industry, guide and case studies (2013);
- the General Medical Council's 'Good Medical Practice' guidance (2013), which provides guidance to doctors on standards of professional conduct and medical ethics;

- the General Pharmaceutical Council Standards of Conduct, Ethics and Performance (2012); and
- the Department of Health and NHS Best Practice Guidance on Joint Working between the NHS and Pharmaceutical Industry and Other Relevant Commercial Organisations (2008).

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

All collaborations between the pharmaceutical industry and HCPs must, in principle, be for the benefit of patients, although the arrangement may also benefit the parties to the collaboration. Collaborations should typically take place at an organisational level rather than with individual HCPs.

The ABPI Code sets out rules regarding gifts, inducements, promotional aids and hospitality provided to members of the UK health professions. There must never be any benefit provided to such persons by way of an inducement to prescribe, supply or recommend a medicine. Hospitality must also be strictly limited to the main purpose of any event in connection with which the hospitality is offered, and the level of subsistence offered must not exceed the level that the recipients would normally pay for themselves.

Sponsorships by pharmaceutical companies must be disclosed, and declarations of sponsorships made in publications must be sufficiently prominent to ensure that readers are aware of it at the outset.

The UK Regulations do not include a requirement for companies to make publicly available information about payments or other transfers of value provided to HCPs, patient organisations or healthcare organisations. These requirements have been agreed by the industry on a voluntary basis under the ABPI self-regulatory system.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

As indicated in question 6, complaints received by the PMCPA concern a variety of interactions between manufacturers and HCPs. The PMCPA's published case reports confirm that complaints commonly involve the arrangements and conduct of meetings with HCPs, such as advisory board meetings, misleading promotional materials or promotional events which are disguised as educational seminars.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

Regulations 280 to 293 set out the restrictions on advertising aimed at and interactions with the general public, which includes patients and patient organisations. Clause 27 of the ABPI Code (enforced by the PMCPA) sets out the conditions under which pharmaceutical companies may collaborate with patient organisations.

When working with patient organisations, pharmaceutical companies must ensure that its involvement is documented by a written agreement between the parties and that all of the arrangements comply with the ABPI Code. This includes the need to declare sponsorship and the prohibition on advertising POMs to the public. Pharmaceutical companies that are members of the ABPI must make publicly available, at a national or European level and on an annual basis, a list of patient organisations to which they provide financial support or significant non-financial support or both.

Restrictions apply with respect to the use of a patient organisations' logo or proprietary material. Companies must also not seek to influence the text of patient organisation material in a manner favourable to its own commercial interests. However, this does not preclude a company from correcting factual inaccuracies.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes. Alleged infringements of UK or EU competition law may be the subject of complaints to the Competition and Markets Authority (CMA), a body established under the Enterprise and Regulatory Reform Act 2013. The CMA may also investigate a matter of its own volition.

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes. Actions for civil remedies may be brought in the High Court by anyone with sufficient interest, such as a competitor, supplier or customer who has suffered loss or damage as a result of an alleged infringement of UK or EU competition law. These actions may be stand-alone or follow-on, and the available remedies include damages or an injunction or both.

In addition, any person who has suffered loss or damage as a result of an infringement of UK or EU competition law may bring a damages action before the Competition Appeal Tribunal (CAT). These are follow-on actions only. Claims on behalf of individuals may also be made to the CAT by certain recognised representative bodies acting on behalf of identified consumers.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

As indicated in question 8, interactions and arrangements involving the provision of hospitality, gifts and inducements to prescribe to HCPs (or other decision makers within healthcare organisations) are also subject to the Bribery Act 2010. Three particular offences thereunder should be borne in mind, namely:

- bribing or accepting a bribe from another person (sections 1 and 2);
- failing to prevent bribery (only corporate bodies) (section 7); or
- bribing a foreign public official (section 6).

The Bribery Act 2010 is enforced by the Serious Fraud Office (SFO). The SFO has issued a memorandum of understanding with the ABPI and the PMCPA, which confirms that the SFO sees self-regulation under the ABPI Code as the first means of dealing with complaints relating to the issues under the scope of the ABPI Code. Although both bodies deal with complaints whatever their source, the SFO focuses is on dealing with complaints not covered by the ABPI Code and that meet its criteria of serious fraud.

Closely interlinked with the Bribery Act is the Procurement Directive 2004/18/EC, which provides for a sanction of debarment from public procurement to any candidate who has been convicted of an offence of which the authority is aware. In the UK, the debarment from public procurement is discretionary where a company is convicted of failing to prevent bribery by an associated person. However, it is mandatory if a company is convicted of active bribery.

Compliance - medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

The rules relating to medical devices are similar to, but less detailed and less onerous in some aspects, than those relating to the pharmaceuticals sector. It has been said that the reason for the seemingly more relaxed approach is presumably due to a lower risk of misuse as compared to medicines.

Similar to the pharmaceuticals sector, the rules applicable to medical devices also derive from a combination of legislation and self-regulation. The Medical Devices Regulations 2002 implement the EU Medical Devices Directives and although they address issues of labelling, display, information to be supplied and the CE mark, they do not regulate advertising material per se. The current Medical Devices Directives are subject to a legislative amendment, which was approved by the European Parliament Committee on Environment, Public Health and Food Safety on 15 June 2016. The European Parliament is expected to agree the new Regulation this year, allowing it to come into effect by the end of 2016 or early 2017. The advertising of medical devices is therefore primarily governed by general consumer legislation, such as the Sales of Goods Act 1979, the Consumer Protection from Unfair Trading Regulations 2008 and the Business Protection from Misleading Marketing Regulations 2008.

The self-regulatory regime for the medical technology or devices sector is primarily controlled by the Association of British Healthcare Industries (ABHI) in accordance with the principles set out in its Code

of Business Practice, which requires any advertising of medical devices to be accurate, balanced, fair, objective and unambiguous. The ABHI Code, along with the Eucomed Code of Ethical Business Practice, govern collaborations and other interactions between medical device manufacturers and HCPs. The Bribery Act 2010 is also applicable to this industry sector.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The granting of marketing authorisations and the placing of medicines on the UK market is governed by the UK Regulations. The UK Regulations implement the relevant EU law concerning granting of marketing authorisations. The relevant procedures are set out in Title III of Directive 2001/83/EC and Title II of Regulation (EC) No. 726/2004 (as amended). In addition, Regulation (EC) No. 1901/2006 addresses the authorisation of medicinal products for paediatric use, while Regulation (EC) No. 1394/2007 contains specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

17 Which authorities may grant marketing authorisation in your jurisdiction?

In the UK, the MHRA is the competent authority for granting national marketing authorisations. It is responsible for applications made through the national, mutual recognition or decentralised procedures (see question 18).

The European Medicines Agency (EMA), established by Regulation (EC) No. 726/2004, is the European executive agency responsible for evaluating marketing authorisations submitted through the centralised procedure. It is currently based in London. The EMA advises the European Commission and EU and European Economic Area (EEA) member states on all matters concerning supervision of medicinal products.

18 What are the relevant procedures?

A medicine can be authorised for marketing in the UK through the following alternative regulatory routes:

- the centralised procedure (CP);
- the decentralised procedure (DCP);
- the mutual recognition procedure (MRP); and
- the national procedure.

CP, DCP and MRP are regulatory procedures created under EU pharmaceutical law that seek to achieve harmonisation and coherence of the regulatory decision on granting and supervision of a marketing authorisation.

A successful CP application results in a single marketing authorisation that is valid in all EEA countries. Applications through the CP are submitted directly to the EMA for scientific evaluation. The scientific evaluation is assisted by the EMA's relevant scientific committees resulting in adoption of an opinion, which will form the basis for the European Commission to issue a binding Commission decision. The European Commission serves as the EU licensing authority to grant marketing authorisations through CP in the EU.

The CP is the mandatory procedure where the application concerns a medicinal product that falls within the scope of the Annex to Regulation 726/2004, namely:

- advanced therapy medicinal product (ATMPs) such as gene therapy, cell therapy and tissue-engineered products;
- medicines derived from biotechnological processes;
- orphan medicines (medicines intended to treat rare human diseases); and
- new active substances with particular therapeutic indications (for example, cancer or HIV/AIDS).

Where a product does not fall within one of the above categories, companies may nevertheless use the CP provided that: (i) the new medicine concerned represents a significant therapeutic, scientific or technical innovation; (ii) if its authorisation would be in the interest of public or

animal health; or (iii) if the medicine is a generic version of a medicine previously authorised through the CP.

Pharmaceutical companies may apply for the authorisation of a medicine through the DCP that has not yet been authorised in any EEA country to be simultaneously authorised in multiple EEA countries (provided that the medicine does not fall within the mandatory scope of the CP). A reference member state leads the assessment of the DCP application and provides the other member states with a draft assessment report and a SmPC. The reference member state liaises with the member states where the applicant wishes to market the product. When an agreement is reached, the application is approved by the individual member states concerned resulting in the grant of national marketing authorisations. If an agreement to approve the application is not reached within 210 days, the matter is referred to the Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) (if the medicine is intended for human use) and potentially to the Committee for Medicinal Products for Human Use (CHMP).

The MRP is used in cases where a marketing authorisation has already been granted in one EEA country (this country would become the reference member state for MRP purposes) and an additional marketing authorisation is progressively granted in one or more other EEA countries. Similar to the DCP, the reference member state produces an assessment report and a SmPC for review and approval by the concerned member states. Provided there is no objection, the existing marketing authorisation is recognised and additional marketing authorisations are granted on that basis. If there is disagreement, the matter is referred to the CMDh and then the CHMP.

Provided that the product does not fall within the scope of the mandatory CP and that there is no commercial interest for the product to be marketed in the other EEA countries, an application for marketing authorisation may be submitted nationally to the competent authority. In the UK, the competent authority is the MHRA. In practice, the national procedure is of limited application for new innovative products.

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Other than in exceptional cases where the MHRA has granted an exemption on grounds of public health, a UK marketing authorisation will cease to be in force if the product to which it relates is not placed on the market in the UK within the first three years following the date on which it was granted (see regulation 67 of the UK Regulations). A marketing authorisation will also be invalidated if the product to which it relates has been placed on the market but has not been sold or supplied for a period of three consecutive years.

20 Which medicines may be marketed without authorisation?

Part 10 of the UK Regulations specify exemptions to the general requirement for a marketing authorisation. A medicine may be marketed, notwithstanding that a marketing authorisation has not been granted, in limited circumstances including:

- if the product is supplied in response to an order from an HCP for use by his or her individual patient on a special-needs basis (specials) (see question 21);
- if the medicine is manufactured and assembled in accordance with the instructions of an HCP; or
- if the product is manufactured by mixing authorised medicinal products with other authorised medicinal products, or with substances that are not medicinal products, provided that any authorised medicinal products used are subject to general sale.

There are also exemptions in relation to ATMPs prepared on a non-routine basis, and certain radiopharmaceuticals.

Products supplied under these exemptions cannot be advertised and must be manufactured and controlled according to specific requirements including proper record-keeping in relation to their supply.

The UK also operates a parallel import licensing scheme, which allows medicines authorised in other EEA countries to be marketed in the UK provided that the imported products have no therapeutic difference from equivalent products authorised in the UK. Companies wishing to import medicinal products must submit a parallel import licence application to the MHRA's Parallel Import Section (unless they are products authorised through the CP, in which case the application for parallel distribution should be made to the EMA).

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Yes. Pursuant to the UK Regulations, an unlicensed medicine may be prescribed to an individual patient (often called 'named patient supply', although the patient does not, in fact, have to be named by the HCP seeking supply of the unlicensed product), subject to certain conditions in circumstances where a patient has a special need for the medicine and there is no existing alternative. This may be appropriate if the medicine is still undergoing clinical trials and a marketing authorisation has not yet been granted or, in respect of uncommon diseases, where there are no suitable medicines available. This provision implements article 5(1) of Directive 2001/83/EC.

In addition, the UK government launched the Early Access to Medicines Scheme (EAMS) in 2014. This is a voluntary, non-statutory scheme that runs in parallel to the UK Regulations, and is intended to allow patients to access innovative unlicensed or off-label medicines earlier than the current marketing authorisation procedures permit. The scheme applies to medicines that target life-threatening or seriously debilitating conditions for which there are no existing treatments, or where existing treatments are unsatisfactory. However, there must be sufficient quality, safety and efficacy data available to show that the risk or benefit profile of the product is positive, and that the medicine represents a significant advance in the treatment of an unmet need. As a result, products will normally be eligible for EAMS only after completion of Phase III clinical trials.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

The prices of branded health service medicines supplied for use in the UK (whether for use in the outpatient or in-patient sectors) are controlled through the Pharmaceutical Price Regulation Scheme (PPRS) or the parallel statutory scheme.

The PPRS is a voluntary scheme agreed between the Department of Health and the ABPI under section 261 of the National Health Service Act 2006 (the 2006 Act). The scheme is renegotiated about every five years; the current version of the PPRS is the 2014 scheme.

The PPRS is adhered to by members of the ABPI and non-members who have voluntarily agreed with the Department of Health to be subject to it. Scheme member companies are exempted from statutory price regulation by reason of their voluntary compliance with the PPRS. While companies are, in principle, free to set their own list prices, in practice the PPRS assumes that prices at product launch will be approximate to the product's anticipated value as assessed by National Institute for Health and Care Excellence (NICE) in England (and its equivalents in the devolved countries) pursuant to a technology appraisal recommendation. Price increases proposed by scheme member companies must be approved by the Department of Health and be compliant with the PPRS regime. Although the PPRS does not explicitly fix prices for branded medicines, companies with sales to the NHS that exceed a set value threshold are required to submit data on those sales from which a determination will be made as to the amount to be reimbursed. The PPRS requires manufacturers to make quarterly rebate payments at pre-agreed levels. These rebates are payable subject to certain conditions; for example, manufacturers with sales to the NHS of less than £5 million do not have to make rebates.

The statutory scheme, under sections 262-264 of the 2006 Act, is set out in the Health Service Branded Medicines (Control of Prices and Supply of Information) No. 2 Regulations 2008 (as amended). The statutory scheme is applicable only to POMs. All companies supplying branded health service medicines who are not members of the PPRS (representing about 10 per cent of branded medicines), are automatically subject to the statutory scheme. The Health Service Medical Supplies (Costs) Bill was presented to Parliament on 15 September 2016. The Bill has been prepared in recognition of the fact that the mechanism of controlling prices in the statutory scheme is less effective in terms of the level of saving it makes than the mechanism in the voluntary scheme, leading to some companies leaving the voluntary scheme in favour of the statutory scheme.

There is no price regulation of generic medicines. However, NHS services are reimbursed for medicines dispensed at nationally set prices, which has the effect of controlling prices.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

See question 22.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

There is no formal reimbursement step required before medicines may be prescribed for NHS patients. However, usage of medicinal products is controlled through inclusion in local formularies defined by CCGs or NHS Trusts. In England, NICE carries out appraisals of certain new products (and existing products in some cases) and issues recommendations based on health technology appraisals based upon an assessment of clinical and cost-effectiveness in order to determine whether such products should be used to treat NHS patients. Such recommendations are important for products to be adopted by CCGs or NHS Trust formularies. In practice, a medicinal product that is not included on the relevant formulary is unlikely to be used or its use is limited to very exceptional circumstances.

Pharmacies are reimbursed by the NHS for the actual cost of products they dispense, based on the published price of medicines as set out in the Drug Tariff (or, where no reimbursement price is set in the Drug Tariff, at the manufacturer's list price). This is the case in both the outpatient and in-patient sectors.

NHS Trusts are paid by their local CCGs, based on procedures actually performed, and the cost of the procedure is fixed in the 'national tariff', which includes standard medicines, but not many high-cost products (these are instead charged separately). The statutory basis for the national tariff is the Health and Social Care Act 2012.

HCPs can issue an NHS prescription for licensed and unlicensed products (in the case of 'specials' and any prescribed off-label use), except in respect of those that feature on the 'blacklist'. The blacklist can be found in Schedule 1 to the NHS (General Medical Services Contracts) (Prescription of Drugs, etc) Regulations 2004 and is reproduced in Part XVIII of the Drug Tariff. It primarily lists health supplements and cosmetic treatment that the patient must pay as the cost of dispensing is not reimbursed by the Department of Health.

24 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products

Overall responsibility for pricing and reimbursement matters lies with the Department of Health. However, as indicated in questions 22 and 24, NICE (and its equivalents in the devolved jurisdictions) conducts assessments that form the basis of recommendations to the NHS regarding the clinical and cost effectiveness of medicinal products.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

No, there is no statutory requirement for manufacturers or distributors to offer discounts on the medicinal products they supply.

However, as indicated in question 22, the PPRS and the various statutory powers under the National Health Service Act 2006 indirectly regulate the prices set by manufacturers for the supply of products to the NHS by regulating profits that pharmaceutical companies are allowed to make on their sales. Discounts by pharmaceutical manufacturers and distributors are, however, common practice in the UK.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

The Falsified Medicines Directive 2011/62/EU (FMD) came into force in the EU on 2 January 2013. It introduced harmonised, pan-European measures to ensure that medicines are safe and that the trade in medicines is rigorously controlled. The new rules include:

- obligatory safety features, comprising a unique identifier and an anti-tampering device, on the outer packaging of some medicines (these were detailed in Commission Delegated Regulation (EU) 2016/161 which was published in the Official Journal on 9 February 2016 and becomes directly applicable on 9 February 2009);
- a common, EU-wide logo to identify legal online pharmacies;

Update and trends

- The EU's General Data Protection Regulation (GDPR) was on track to come into effect on 25 May 2018. However, the Information Commissioner's Office has confirmed that the UK government needs to consider the impact of the result of the Brexit referendum on the GDPR. There is accordingly some uncertainty as to whether, and if so to what extent, the UK's current Data Protection Act 1998 will be overhauled by the GDPR.
- The EAMS (see question 21) has been in place since April 2014, and aims to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. Under the scheme, the MHRA will give a scientific opinion on the benefit or risk balance of the medicine, based on the data available when the EAMS submission was made. The process involves a two-stage evaluation, which requires applicants to first obtain a promising innovative medicine (PIM) designation, after which an EAMS opinion will be issued. By the end of September 2016, the MHRA had received a total of 32 applications for PIM designation and it had granted PIM designation to 20 of these.
- In November 2014, the UK government commissioned the Accelerated Access Review with the aim of speeding up access to innovative drugs, devices and diagnostics for NHS patients. The final report was published on 24 October 2016. It makes recommendations of establishing streamlined mechanisms for prioritising emerging technologies, working with innovators to accelerate approvals and aligning national organisations to enhance the NHS's ability to rapidly adopt the right innovations.
- The EU's new Clinical Trials Regulations (EU Regulation No. 536/2014) was published in the EU's Official Journal in May 2014, and will come into effect by October 2018. In the UK, the MHRA confirmed on 1 August 2016 that the UK is assessing the potential impact on its regulatory framework of the decision to leave the EU, but that the MHRA currently continues with its programme for implementing the Clinical Trials Regulations. A consultation on the MHRA's proposals for 'Risk proportionate approaches in clinical trials' was issued at the same time.
- As indicated in question 15, the existing medical devices legislation is in the process of being overhauled and it is likely that new EU legislation will come into effect by the end of 2016 or early 2017. In a position statement issued by the MHRA in the wake of the Brexit referendum on 27 June 2016, the MHRA confirmed that its preparations with respect to incorporating in the UK the new EU medical devices legislation will continue. More generally, the MHRA committed to continue to play a full and active role in European regulatory procedures for medicines.
- The new requirements, contained in industry self-regulation, concerning disclosure of transfers of value by pharmaceutical companies to HCPs (see question 9) have yielded its first year of published results. On 30 June 2016, the ABPI published details of payments or benefits in kind – made to HCPs and healthcare organisations in the UK – on a publicly accessible database. The new database (available at www.disclosureuk.org.uk) shows payments made by 109 pharmaceutical companies in the UK. The data shows that the pharmaceutical industry spent a total of £340.3 million on working with HCPs and healthcare organisations in 2015; the majority (67 per cent) of this amount related to activities connected with the research and development of new medicines.

- tougher rules on the controls and inspections of producers of active pharmaceutical ingredients; and
- strengthened record-keeping requirements for wholesale distributors.

The bulk of the FMD was transposed in the UK by the Human Medicines (Amendment) Regulations 2013, which became effective on 20 August 2013. However, provisions relating to safety features were carved out and do not have to be implemented until 9 February 2019.

Owners of certain intellectual property rights can impede the production and supply of counterfeit medicines by taking private civil actions against infringers, or by applying to restrict the importation of suspected counterfeit goods under Regulation (EU) No. 608/2013. The UK customs authority, HMRC, is responsible for reviewing applications and detaining suspected counterfeit products at the UK border. The owner of the intellectual property rights that the goods are alleged to infringe may then elect to commence proceedings.

More generally, the MHRA has powers under the UK Regulations to investigate cases and, where appropriate, bring criminal prosecutions in respect of the sale and supply of unlicensed medicines.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

As part of its 'Pharmaceutical Package', the European Commission aims to provide a clear framework for the dissemination of information by marketing authorisation holders about their POMs to the general public. In view of this aim, the European Commission published a legislative proposal in December 2008 concerning the provision of information to patients. However, following protracted but ultimately unsuccessful negotiations, the proposal was abandoned in May 2014. The UK authorities have not publicised any intention to take additional measures to facilitate the general public's access to information about POMs.

29 Outline major developments to the regime relating to safety monitoring of medicines

The EU legal framework of pharmacovigilance for medicinal products for human use is provided for in Directive 2001/83/EC for all medicinal products authorised under EU pharmaceutical law, and Regulation (EC) No. 726/2004 for centrally authorised products. The legislation was amended by Regulation (EU) No. 1235/2010 and Directive

2010/84/EU. The changes introduced by the Directive were transposed into UK law by the UK Regulations, while Regulation (EU) No. 1235/2010 is directly applicable.

The new pharmacovigilance legislative package has applied since July 2012 across all EEA countries. The regulatory tools made available under the revised legislation include risk-management plans, post-authorisation studies, signal detection and management at EU level, periodic safety update reports assessment and reviews of medicines through referrals. The legislation creates a Pharmacovigilance Risk Assessment Committee (PRAC), which is responsible for assessing and monitoring safety issues for human medicines.

Under the new legislative package, marketing authorisation holders are also required to maintain a pharmacovigilance system master file (PSMF) that is permanently available for submission or inspection by the national competent authority.

The process of reporting adverse drug reactions (ADRs) is in the process of being centralised through electronic submissions to the EudraVigilance database. Previously, reports were made via the individual national competent authority. Since September 2013, it has been mandatory to display a black inverted triangle on the product information of medicines that are being monitored particularly closely by regulatory authorities. With this measure, the European Commission aims to improve the safety of medicines and to highlight to patients the importance of reporting suspected ADRs.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

The Department of Health administers the UK's national immunisation programme, and has set out relevant considerations and guidance in its publication 'Immunisation against infectious disease' (also known as the Green Book).

Vaccination is not mandatory, and explicit consent must be obtained before any immunisations are administered. The NHS has issued a recommended vaccination schedule for children up to the age of 18, adults over the age of 65 and people who fall into certain risk groups (eg, pregnant women and healthcare workers). Certain travel vaccines are usually provided free of charge by the NHS (eg, hepatitis A, typhoid and cholera vaccines) whereas other travel vaccines must be arranged privately (eg, yellow fever vaccination).

GPs must maintain a record of patients' vaccination history, which may require them to draw on information from other healthcare bodies

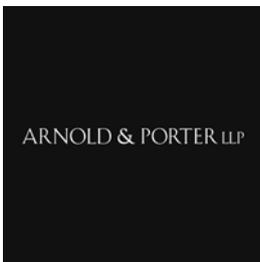
and institutions to produce a vaccination history. Individuals administering vaccinations must have received training in the management of anaphylaxis, and must have immediate access to appropriate equipment and to adrenaline (epinephrine).

The reimbursement regime surrounding vaccinations is governed by the General Medical Services Contract (GMS contract) made pursuant to the NHS (General Medical Services Contracts) Regulations 2004. This contract acts as the basis for arrangements between the NHS Commissioning Board and providers of general medical services in England. Under the GMS contract, vaccines and immunisations have been paid for through various mechanisms depending on which services a practice provides. Most payments are made through the 'global

sum', although certain directed enhanced services for patients at risk of infection are reimbursed separately. The global sum is a distribution of the NHS core funding to practices according to the needs of their registered list of patients and the costs of providing services defined as 'essential' and 'additional' services in the GMS contract.

NHS statistics indicate that, in 2014/15, roughly 92 per cent of children in the UK completed the recommended immunisations by the age of two years, with little variation between the four nations across all vaccines.

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Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

The United States operates a public-private system, with major public healthcare programmes such as Medicaid and Medicare. Those programmes serve demographics such as senior citizens, children, veterans, the disabled and low-income families. The Affordable Care Act is now implemented, ensuring healthcare for a larger percentage of Americans, and providing important protections such as coverage of pre-existing conditions, but it is a complex system involving state exchanges, and insurance companies and employers remain central in healthcare coverage. Significant problems have arisen in the implementation of the law, with certain insurance companies now declining to offer plans. As a result of the new law, we are seeing more risk-sharing arrangements and collaborations between pharmaceutical and device manufacturers, seeking to foster efficient and quality care via financial incentives. However, the problems with the law has been a contributing factor in the current, intense focus on pharmaceutical pricing.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

It depends on the programme. Some systems are run by federal agencies through a mix of appropriations and premiums paid by qualifying patients. Other programmes, such as Medicaid, are financed by a mix of federal and state funding. There are subsidies available for certain demographics to obtain coverage at reduced cost. For much of the population, care is financed via group health insurance policies associated with employers and policies purchased under the Affordable Care Act.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

For prescription drugs, the Federal Food, Drug, and Cosmetic Act (FDCA) is the primary source of the Food and Drug Administration (FDA)'s authority over advertising, whether to payers, physicians or direct-to-consumer (DTC). The Federal Trade Commission (FTC) has a subsidiary role, but can still police certain aspects of advertising by prescription drug manufacturers. However, the FTC has primary jurisdiction over most over-the-counter drug advertising in accordance with the Federal Trade Commission Act. State laws also have a role, to the extent they are not pre-empted by the federal framework. There are also private rights of action for addressing competitor disputes, including under the Lanham Act. Industry associations also maintain codes of conduct focused on pharmaceutical marketing and sales, including payments to physicians.

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

There are a wide array of requirements for such advertising, including routine submission of promotional materials to FDA, and:

- avoiding any claims that are false or misleading, including by implication;
- not making claims beyond the approved indications and labelling; although such restrictions are now under scrutiny due to recent First Amendment case law recognising pharmaceutical free speech

rights pertaining to communication of off-label truthful and non-misleading information;

- ensuring appropriate support for product claims, including comparisons and claims of superiority;
- adequately communicating safety information and balancing the presentation of the benefits and risks generally; and
- providing contact information to enable the provision of full labelling, responses to questions and reporting of adverse events.

5 What are the main rules and principles applying to advertising aimed at the general public?

Similar rules apply to DTC advertising, but there is more of an emphasis on the appropriateness of claims, balance (including in visual representations), providing extensive and prominent safety information and providing methods to obtain the full labelling. Given the sensitivities, many companies seek advisory review by the FDA for broadcast DTC advertising. The FDA has also issued guidance on the application of the above principles in the context of the internet, and social media particularly. Finally, the pharmaceutical and medical device trade associations maintain codes of conduct relating to DTC advertising.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

FDA officials typically cite the following as more typical violations:

- making claims that go beyond the terms of the label;
- failure to adequately communicate safety information or to present safety and effectiveness information in balance;
- unsupported comparisons or claims of superiority; and
- unsupported claims regarding quality of life.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

The FDA's rules in this area are restrictive. While they allow some degree of 'scientific exchange' in scientific or medical meetings, via publication reprints, and in response to unsolicited questions, the FDA's current policies do not allow manufacturers to participate fully in communicating scientific information that is beyond the label, even though they are typically the best source of such data. This has become a major legal debate and there is a trend toward case law citing First Amendment speech protections as supporting much broader manufacturer dissemination of product information. However, this case law is still developing, and there remain risks associated with going beyond the label due to the Federal False Claims Act, under which 'relators' bringing suits and the government often seek huge penalties and corporate integrity agreements. Manufacturers are generally treading carefully and some are seeking FDA input on such communications prior to use.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

This is a complex area, but these relationships are governed largely by the Anti-Kickback Statute, which prevents 'kickbacks' to physicians that could influence the practice of medicine and prescribing. However, it is a very wide-ranging and ambiguous, statute and these relationships

need to be examined carefully and be well documented in agreements based on unclear 'safe harbours' developed over years of interpretation and advisory opinions. The setting of care and relevant payment framework will have an impact on such analyses. There is also the Stark Law, which prohibits physician self-referral arrangements, and the Physician Payment Sunshine Act requiring transparency in manufacturer payments to physicians and teaching hospitals.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

Areas of particular importance in such collaborations include:

- providing fair market value for bona fide services rendered;
- ensuring disclosure of conflicts of interest; and
- ensuring independence of decision-making in the practice of medicine and the safety of patients.

However, the documentation and monitoring of such collaborations is important to ensuring the defensibility of the activities in the event they are later examined in a government audit or investigation.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

Such cases typically involve allegations of inappropriate remuneration to healthcare professionals that are intended to influence prescribing practices. Another area of enforcement interest is the use of physician speakers to convey off-label or false and misleading information. The government has also focused on issues such as ghostwriting of articles and manipulation of scientific publications for commercial objectives.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

The general rules relating to promotion and scientific exchange are typically followed in collaborations between manufacturers and patient organisations so as to prevent allegations of marketing for off-label uses or inducement of claims for payment by providing services to patients that physicians should provide in the practice of medicine. However, manufacturers and patient organisations may collaborate in areas such as providing patient assistance and financing clinical research. The key issues that arise in these collaborations typically relate to ensuring independence of the organisation, maintaining transparency regarding the support provided and avoiding use of patient-related programmes or events to provide kickbacks to prescribers or otherwise induce prescribing. The terms of patient assistance programmes and, in particular, contributions by pharmaceutical companies to third-party patient assistance foundations have recently come under government investigative scrutiny. Of course, in all dealings with patients' issues of privacy are critically important.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes. There is a wide array of antitrust laws, largely administered and enforced by the FTC and the Antitrust Division at the Department of Justice. Either may bring cases under antitrust statutes or theories, or may take action through certain approval processes (eg, merger approvals).

13 Is follow-on private antitrust litigation against manufacturers possible?

Follow-on litigation is very common and there are a wide variety of antitrust causes of action available to competitors, as well as consumers alleging unfair trade practices.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

In addition to the Anti-Kickback Statute, which is intended to prevent undue remuneration to physicians that induce prescribing in the US, transfers of value to physicians and institutions outside of the US may come under scrutiny under the Foreign Corrupt Practices Act (FCPA).

Update and trends

Over the past two years, the US Congress has been considering legislation, known as 21st Century Cures, aimed at speeding the development and approval of drugs and devices for serious and life-threatening diseases and disorders, and precision medicine strategies in particular. The legislation has passed the House of Representatives, but remains under development in the Senate. In addition, over 2017 Congress will consider the reauthorisation of drug and device user fees. This legislation, which is often a vehicle for other legislative initiatives pertaining to FDA regulation of drugs and devices, must be enacted by September 2017 to avoid an interruption to drug and device review processes.

Another major trend is the developing case law on the First Amendment and pharmaceutical and medical device manufacturer speech relating to unapproved uses. In the short term, the impact of the recent decisions in the *Caronia* and *Amarin* cases, in which the court found off-label communications regarding approved drug products to be protected speech, remains modest pending further decisions in other courts. However, the FDA and the US Department of Justice have been treading much more carefully in pursuing manufacturer off-label communications, and additional court decisions – or legislation – could force the FDA to make significant changes to its current, highly restrictive policies relating to manufacturer communication of off-label data.

The FCPA prohibits bribery of foreign officials, including certain physicians and institutions affiliated with governments, and addresses accounting transparency requirements under the Securities Exchange Act of 1934. Payments to US physicians and teaching hospitals are subject to a reporting scheme under the Physician Payments Sunshine Act, under which such payments are routinely reported and posted on a government-run website in considerable detail. Also, information on most clinical trials must be posted to the ClinicalTrials.gov website run by the US National Institutes of Health.

Compliance – medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

Although manufacturers of medical devices are in certain respects subject to less constant and intense scrutiny than pharmaceutical manufacturers, most of the same principles apply and medical device manufacturers are often the subject of enforcement relating to off-label marketing or violative arrangements with physicians. In the area of advertising enforcement, medical device manufacturers are typically not required to file their advertising with the FDA or the FTC, and the resources devoted to device advertising enforcement and guidance are significantly less than are devoted to drug products. Some differences are also attributable to the fact that advertising for non-restricted medical devices is regulated primarily by the FTC rather than FDA, and the FTC has less expertise in evaluating complex physician-focused claims for medical devices and largely focuses on consumer device claims.

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The Federal Food, Drug, and Cosmetic Act is the primary statute for FDA approvals, with innovator drug products approved under the FDCA framework for new drug applications. Abbreviated new drug applications are submitted for generic products. Although largely regulated as drugs, biologics and biosimilars must be licensed under the provisions of the Public Health Service Act.

17 Which authorities may grant marketing authorisation in your jurisdiction?

The FDA grants approvals for human drugs and licences for human biologics. Controlled drug substances must also be scheduled by the Drug Enforcement Administration. Animal drugs are regulated by the

FDA under the FDCA, although animal biologics are licensed by the US Department of Agriculture. States may also impose registration and licensure requirements for medical product distribution, as well as restrictions and transparency requirements pertaining to certain product marketing and sales activities.

18 What are the relevant procedures?

Research is regulated via rules for submitting investigational new drug applications (INDs) to the FDA, institutional review board review, and adherence to good clinical practices. Once the data is sufficient, companies may then apply for approval via the new drug application or biologic licence application. The review period ranges from eight to 12 months, including an initial 60-day filing period. For generic products, an abbreviated new drug application is filed with the FDA, and is based upon a showing of bioequivalence to a reference listed drug previously approved under an NDA that is not subject to a listed patent or exclusivity period. Biosimilars are licensed based upon an application under the Public Health Service Act demonstrating that the product is highly similar to, or interchangeable with, a referenced biologic product

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Typically not, although information filed with the FDA may need to be updated, and reinspections may be needed. There are exceptions if products are actually withdrawn for safety or effectiveness reasons, and for orphan drugs for rare diseases.

20 Which medicines may be marketed without authorisation?

Various 'unapproved' prescription drugs remain on the market due to years of grandfathered status. However, in recent years the FDA has sought to ensure that most such products either exit the market or obtain approval. There are also FDA monographs providing terms for permissible over-the-counter drug uses in various therapeutic categories. Companies complying with such monographs can market their products without obtaining a specific approval, although establishment registration, product listing and compliance with current good manufacturing practices are required.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Yes, FDA regulations provide for expanded access programmes under INDs, including both broad programmes run in conjunction or in parallel with controlled clinical trials, as well as compassionate-use INDs, which permit an individual patient to obtain access to an investigational product. Typically, such programmes must balance the risks and costs of expanded patient access with the uncertain-patient benefit and the potential impact on enrolment in controlled trials. The FDA has recently focused on streamlining the process for review of proposed expanded access programmes due to intense pressure under state laws purporting to establish a patient 'Right to Try' drugs for life-threatening illnesses.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

There are complex systems governing issues such as providing best price and rebates on pricing in certain government programmes, such as Medicaid. In certain areas negotiations over pricing may occur, but the US typically affords manufacturers greater flexibility in setting the market price of pharmaceuticals. Drug pricing is currently an area of intense scrutiny in the US, with several hearings in Congress focusing on manufacturer pricing practices and major price increases for certain drug products. A continued focus on this area is likely in the future.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

In most public programmes a negotiation does not occur, although issues such as coding for reimbursement and payment systems may influence the actual level of reimbursement, rebates may be required under statute, and pricing is influenced by factors such as formulary status. In the coming years there will be significant efforts to enact legislation establishing new mechanisms for negotiation of drug prices for public healthcare programmes.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

In general, most drugs approved by the FDA are considered 'covered drugs' under federal healthcare programmes. However, the actual payment for such drugs may be limited by various factors, such as bundling of payment for a drug with a general procedure. There are also statutory exceptions to the generally broad coverage rules and formulary decision-making can greatly influence when product coverage is actually available. Although some public programmes pay for certain off-label uses, investigational uses, such as under compassionate-use INDs, are generally not covered.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

The primary body regulating public healthcare programmes is the Centers for Medicare & Medicaid Services, which is part of the Department of Health and Human Services. However, there are other healthcare payor agencies, such as the Veterans' Health Administration and state Medicaid agencies.

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

Yes, in certain payment programmes this is required. For example, under Medicaid rebates by pharmaceutical manufacturers are required by statute.

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Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

The FDA administers the FDCA, which prohibits the ‘adulteration’ of drug products, including counterfeits, and maintains an Office of Criminal Investigation focused in part on this area. Under the 2013 Drug Quality and Security Act, a track-and-trace system has been implemented that requires that a pedigree is passed with each drug product in commerce and suspect product identified and reported, and ultimately drug distribution will be tracked via an interoperable electronic system. Various law enforcement agencies also play an important role in pursuing those engaging in drug counterfeiting or diversion, including the Federal Bureau of Investigation and US attorneys’ offices.

28 What recent measures have been taken to facilitate the general public’s access to information about prescription-only medicines?

Various associations have taken action to enhance the transparency of clinical data on drug products and the National Institutes of Health maintains – and recently finalised a rule to greatly expand – the ClinicalTrials.gov database, which requires the registration and posting of results information from clinical trials. Agencies are also required to comply with the Freedom of Information Act and release certain non-proprietary information to the public upon request.

29 Outline major developments to the regime relating to safety monitoring of medicines.

The FDA maintains detailed regulations and guidance governing drug safety reporting. Companies closely monitor events, and the FDA often takes action to require safety-related labelling changes. For certain drugs, risk evaluation and mitigation strategies may be required, including elements to assure safe use such as registries and training requirements for prescribing physicians, pharmacists and patients. The FDA also inspects companies for pharmacovigilance compliance, and is working with various stakeholders on a major effort – known as the Sentinel Initiative – to aggregate and analyse data on patient safety.

Vaccination

30 Outline your jurisdiction’s vaccination regime for humans.

In general, the federal government develops guidelines for vaccination, but there is no national register maintained. Many vaccines are paid for in whole or part by government and private healthcare programmes. State public health laws may attempt to require vaccination by tying such measures to public school access. States rules also govern who may administer vaccines. Unfortunately, vaccination rates in the US have been falling in certain areas owing to myths about vaccine safety.

Venezuela

Luis E López-Durán and Rosa Virginia Superlano

Hoet Pelaez Castillo & Duque

Organisation and financing of healthcare

1 How is healthcare in your jurisdiction organised?

In Venezuela, healthcare is a constitutional right. The administration and control of healthcare are tasked to the Ministry of Health. Healthcare in the outpatient and in-patient sectors is provided through public and private healthcare centres.

Public healthcare must cover any citizen that is in need of healthcare, and it must be free in hospitals, clinics and ambulatories that administer first, second and third-grade healthcare according to the institution. Public healthcare centres are administered by the central government through the Ministry of Health, the Venezuelan Social Security Institute (IVSS) and by regional and municipal governments. There are special assistance centres belonging to the central government outpatient programme, called 'Into the Slums Mission', which offer diverse levels of services: integrated diagnostic centres, rehabilitation centres and high-tech centres.

Private healthcare is administered in care centres and private hospitals run by private companies. These require prior authorisation by the Ministry of Health to commence their activities, and are subject to the supervision and control of this authority. Their services are paid for by patients directly or indirectly when they have hospital, surgery and maternity insurance policies. They are obliged to provide emergency assistance to any patient who enters their facilities, without checking whether the patient has private insurance; when the patient does have private insurance, they must treat the patient without waiting for authorisation to proceed from the insurance company.

Medications are imported, manufactured, distributed and sold by private companies. The Ministry of Health and the IVSS, through their integrated health system, acquires medication for a no-cost provision to patients being treated in their health centres. The IVSS provides free 'high-cost' medications (eg, cancer treatment) without evaluating the place where the patient is treated.

2 How is the healthcare system financed in the outpatient and in-patient sectors?

The outpatient and in-patient sectors in the public health system are financed with public funding from the national budget for the health sector, with state and municipal allocations, as well as any other special allocation or donations from the private sector. It also receives funding from obligatory contributions that workers and employees make to the IVSS, as well as contributions in virtue of the concept of social responsibility made by companies that contract with hospitals and healthcare centres.

The national budget for the health sector has a higher priority than any other sector, and it is integrated based on the health objectives in each territory, demographic level, epidemiology in terms of damage and risk, social status of the population and other variables or situations based on each locality.

The private health sector is financed through payments that are made by users or private insurers for treatment received, as well as donations made by individuals. Private centres do not receive national or regional government funds. Some private centres, in virtue of their social responsibility commitments, offer special free or financed medical treatments through foundations to low-income patients.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertising of medicinal products to the general public and healthcare professionals?

Advertising and promotion of medications are regulated by the Venezuelan Medications Law (2000) and by the Venezuelan Standards for Advertisement and Promotion of Medications issued by the Ministry of Health (2004).

4 What are the main rules and principles applying to advertising aimed at healthcare professionals?

Only medicinal products duly approved and registered for market purposes in Venezuela may be advertised. Advertising of medications may be aimed at healthcare professionals, including products whose sale depends on prescription. The handing out of medical samples is also permitted, but only to allow healthcare professionals to gain knowledge about them.

All medical advertising must be approved by the Ministry of Health before disclosure.

Advertisements must encourage the correct use of pharmaceutical products, and present them in an objective manner without exaggerating their properties.

Comparing products and product prices is permitted, but only mentioning the generic denominations and not the brands of the medication.

Public health centres (those run by the government) require prior authorisation from the Ministry of Health to receive free medical samples, and such samples should only be of essential medicaments.

Scientific and technical information contained in medical advertisements must be supported by corresponding literature with a correct description of the product duly approved by the science director and pharmacist sponsor of the manufacturer or importer company.

The use of publicity on the label or container and in any other leaflet that accompanies the medication is not permitted.

5 What are the main rules and principles applying to advertising aimed at the general public?

Only medicinal products duly approved and registered for market purposes in Venezuela may be advertised.

All medical advertising must be approved by the Ministry of Health before disclosure.

Advertising that targets the general public is limited to over-the-counter products. It is forbidden for medicinal products that require prescriptions from a physician or a pharmacist.

Any medical advertising, whether oral, audiovisual or written, must be informative, educative, true, up to date and testable; it must be in Spanish, and must contain the following warning: 'If ailment does not get better with treatment, stop using and consult a doctor.'

Medical labels and containers must indicate the name of the product, the active substances, the concentration, the healthcare record number, the elaboration and expiry dates, and the name and address of the representative or pharmacist of the medicinal product. Dosage instructions and contraindications must also be indicated in the product.

Advertisement of the product must not induce irrational self-medication or medication abuse.

The handing out of free medical samples to the general public is prohibited.

The use of the words 'harmless' and 'quality' in the text of the warning is also prohibited.

Comparing products and product prices is permitted, but mention must be made of the generic denominations and not the brands of the medications.

6 What are the most common infringements committed by manufacturers with regard to the advertising rules?

The most common infringements committed by manufacturers include:

- advertising prescription medications by indirect means;
- advertising over-the-counter products without obtaining previous authorisation from regulatory authorities;
- handing over to public health system institutions medical samples of non-essential medications or without previous authorisation from the Ministry of Health; and
- offering payment to a healthcare professional in exchange for prescription, dispensing or administration of products or the continuation of such conduct.

7 Under what circumstances is the provision of information regarding off-label use to healthcare professionals allowed?

There is no specific legislation concerning this issue. Information regarding off-label use to healthcare professionals may be allowed upon request and special authorisation from authorities.

8 Which legislation governs the collaboration of the pharmaceutical industry with healthcare professionals? Do different rules apply regarding physicians in the outpatient and in-patient sectors?

Specific regulation does not exist; in practice, the same principles that govern medical advertising for healthcare professionals apply (see question 4).

A Code of Conduct issued by the Venezuelan Chamber of Medicines (CAVEME) contains general guidelines about the behaviour of members in their relations with other healthcare professionals.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with healthcare professionals?

Even though there is no specific legislation, the principles from advertising legislation (see question 4) should be taken into consideration:

- prescription or consumption of medications cannot be induced;
- the manufacturer's advocacy for participation of healthcare professionals in scientific or educative activities, whether national or international, must not be conditioned to the advertisement, prescription or use of any medication or the compromise of continued participation; and
- the handing out of medical samples is limited to the amount necessary to allow the healthcare professional to get to know the product, and can only be handed out by the representatives of the manufacturer or distributor during the visit of their representatives. The handing out of free samples to public health institutions is permitted only when authorised by the Ministry of Health.

In addition, CAVEME's Code of Conduct establishes the following principles:

- relations of manufacturers with healthcare professionals must favour patients and improve the medical practice;
- the purpose of relations shall be to provide scientific, medical and pharmaceutical information on the products;
- no consideration in cash or kind shall be given to healthcare professionals for the prescription, administration or recommendation of a product;
- the criteria of the healthcare professional shall not be induced for the prescription, administration or recommendation of a product;
- the purpose of sponsorship of scientific and professional congresses and seminars for healthcare professionals shall be to provide scientific information. Providing information on products is allowed, as long as it is duly supported by the corresponding documents and

approved by the scientific director of the manufacturer or importer of the product;

- social events related to congresses or seminars must also abide by the referred principles; and
- sponsorship of attendance of healthcare professionals to scientific seminars or congresses, whether national or international, shall be restricted to covering transportation expenses, accommodation, meals and registration for the event.

10 What are the most common infringements committed by manufacturers with regard to collaboration with healthcare professionals?

The most common infringements committed by manufacturers include:

- handing out medical samples in excessive amounts to increase prescription of a product;
- giving or offering consideration to the healthcare professional that prescribes, recommends, acquires, dispenses or administers products or that commits to continue to do so; and
- inviting healthcare professionals to specialised conferences with expenses paid so as to have the medical product mentioned or advertised in return.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

No specific legislation or industry guidelines address this issue. Nevertheless, in practice, the principles governing drug advertising aimed at the general public apply (see question 5), as well as the general guidelines set in CAVEME's Code of Conduct.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes; the Antitrust Superintendency may oversee, control and impose sanctions on drug manufacturers and distributors that violate free competition practices. Actions by the Superintendency are executed either on its own initiative or may derive from a claim by the interested party.

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes. Individuals may turn to the relevant courts to claim payment of compensation for damages caused by anticompetitive practices after such conduct has been determined by the Superintendency, and following the corresponding administrative procedure.

14 What are the main mandatory anti-corruption and transparency rules applicable to pharmaceutical manufacturers?

The Decree with the status, validity and force of law amending the Law against Corruption was published in the Special Official Gazette No. 6.155 and dated 19 November 2014.

Compliance - medical device manufacturers

15 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with healthcare professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

There is no specific legislation covering this matter. The general principles governing advertising of over-the-counter medication apply (see question 5).

Pharmaceuticals regulation

16 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

The granting of sanitary registration certificates and marketing authorisations for medicines is governed by:

- the Law on Medicaments;
- the Pharmacy Practice Law;
- the Regulations of the Pharmacy Practice Law;

Update and trends

Further resolutions and technical regulations issued by Mercosur are expected to be incorporated into the Venezuelan legal system in connection with medications and commercialisation thereof. In addition, new norms are likely to be enacted for the amendment of the current system of allocation of foreign currency for importation of medications, equipment and health-related materials.

- the Rules enacted by the Review Board of the Rafael Rangel National Hygiene Institute (INHRR);
- the Manual of Good Manufacturing Practices for Making Pharmaceutical Products;
- the Venezuelan Standards of Bioavailability and Bioequivalence of Pharmaceutical Products;
- the Resolutions enacted by the Ministry of the People’s Power for Health and Administrative Rulings enacted by the Autonomous Service of Health Regulation;
- the Ministerial Joint Resolution, which creates the Drug Control System;
- the criteria for the Single Mobilisation Guide, Monitoring and Control of Medicines;
- Mercosur Technical Regulations on Good Distribution Practices for Pharmaceutical Products;
- Mercosur Technical Regulations on Good Sanitary Practices for Transportation of Goods and Pharmaceutical Products; and
- Mercosur Resolutions concerning narcotics and psychotropic substances.

17 Which authorities may grant marketing authorisation in your jurisdiction?

All medicaments, whether national or imported, require a sanitary registration certificate for their manufacture, distribution, holding, sale and dispensation. Such certificate is granted by the Ministry of Health after the technical and scientific evaluation of the product by the INHRR.

The authorisation for the mobilisation and distribution of drugs (Single Mobilisation Guide) must be processed before a state enterprise called Farmapatria.

18 What are the relevant procedures?

The registration procedure is initiated by filing the application form before the INHRR together with the corresponding legal, technical, scientific and clinical documents, as well as samples of the product and the prospective container and label of the product. The name identifying the product shall be specified and the following information, inter alia, must be provided: elaboration method, quali-quantitative formula, physicochemical properties of the active ingredients and excipients, clinical and preclinical studies, stability and bioequivalence protocols, package texts, labels and package insert for dosing and product samples.

After reviewing the corresponding documents and making the pharmacological, physicochemical and microbiological analysis of the product, the Review Board of the INHRR issues a report signalling the approved dosage, indications and contraindications of the product. This report is published in the Bulletin of the Review Board, and then the INHRR issues an official communication containing the sanitary registration certificate, which is later ratified by a resolution of the Ministry of Health and published in the Official Gazette (the instrument for publishing laws, regulations and main administrative authorisations in Venezuela).

19 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

Yes. The Rules of the INHRR Review Board provide for the possibility of revoking the sanitary registration certificate if the product is not marketed within the stipulated period that shall not exceed four years. However, such period could be increased according to the authorities’ criteria.

20 Which medicines may be marketed without authorisation?

Certain kinds of medications (those that treat rare diseases, low-incidence pathologies in the country or those required for special sanitary circumstances or epidemics) may be imported and sold without the sanitary registration certificate. Such medications can only be imported by institutions, manufacturers or distributors that have been authorised, and may only be marketed by the authorised institutions.

Medical samples required for processing the sanitary registration certificate of the product may also be imported without the certificate, as well as those necessary for conducting clinical investigation studies. An importation authorisation, however, must be previously obtained from the relevant authorities.

21 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

There are no named patient or expanded access programmes in Venezuela. The practice of supplying a doctor with unapproved medicine to treat a named patient or for compassionate use is not explicitly regulated in Venezuelan law. However, there are several provisions regarding medicine and pharmacy laws and regulations that may apply.

The Review Board of the INHRR may grant a special authorisation for the import of non-registered pharmaceutical products for specific cases where there is no available treatment. The Review Board will decide which cases are worth the authorisation. Such authorisation may be granted for a maximum period of six months. This procedure is considerably shorter than processing the sanitary registration certificate.

The following must be verified in the INHRR’s assessment:

- the pharmaceutical product to be imported under the above-mentioned circumstances is not available on the national market;
- the product is not intended for mass commercialisation. In the event that the importer’s intention is the mass commercialisation of the product, the sanitary registration certificate must be obtained;
- the specific health reasons of such importation; and
- any other fact that the Review Board may consider relevant.

Following the authorisation by the Review Board, the Ministry of Health will grant the importation permit of such pharmaceutical products without a sanitary registration certificate.

Regarding safety reporting obligations for the above-mentioned products, Venezuelan legislation is not explicit. However, the Venezuelan Law on Medicaments provides that healthcare professionals and pharmaceutical product manufacturers must inform the relevant authority of pharmacovigilance about any secondary or adverse effects caused by such products. Currently, the relevant authority of pharmacovigilance is the INHRR’s Review Board. Therefore, we consider that the opportunity will be at the time of submitting the aforementioned authorisation request.

Pricing and reimbursement of medicinal products

22 To what extent is the market price of a medicinal product governed by law or regulation?

Before 22 November 2011, the market price of a medicinal product had a dual regulation depending on its active ingredients; certain products’ prices were regulated by the Venezuelan authorities. Other products were not price-regulated, and Venezuelan authorities were given only 30 days’ notice of the new market prices prior to the sale of the products in the market with those new prices.

The Law on Fair Prices was amended on 8 November 2015 and published in the Special Official Gazette No. 6155 dated 8 November 2015. This Law applies to all those that, as a result of the performance of their activities within the territory of Venezuela, produce, import or commercialise goods or services for monetary compensation.

The Superintendent for the Defence of Socioeconomics Rights (SUNDDE) will set prices based on the information provided by traders, the information available to governmental agencies and public information, in accordance with direct costs structures, indirect costs structures, general costs, administrative costs, distribution and sale costs, when applicable; prices might have a profit margin of up to 30 per cent over its cost structure. The SUNDDE exercises a discretionary power to analyse prices on a product-by-product basis or on a product-basket basis.

23 Must pharmaceutical manufacturers negotiate the prices of their products with the public healthcare providers?

Public healthcare centres and hospitals shall purchase medicines from companies that are granted a sale contract upon an open or closed bid (contracts are usually granted to companies that offer the best sale conditions). If a drug is sold by a sole manufacturer or distributor, it shall be purchased through direct awarding.

24 In which circumstances will the national health insurance system reimburse the cost of medicines?

In Venezuela, there is no public policy to reimburse the cost of medicines; the IVSS and public hospitals hand out the medications for free. Private insurance companies do reimburse the cost of medicines, provided they are prescribed by a healthcare professional in connection with a condition covered by the insurance policy.

A programme entitled Pharmacy of High-Cost Medications was implemented in 2009. Under this programme, patients, whether affiliated to the IVSS or not, are given medications free of cost to treat the following diseases: cancer, multiple sclerosis, viral hepatitis, rheumatoid arthritis, hematologic diseases, transplants, attention-deficit and hyperactivity disorder, osteoporosis, schizophrenia, Gaucher's disease, Fabry disease, pulmonary hypertension and terminal chronic failure. To access these high-cost medications, the patient must file a medical certification confirming the presence of the disease, his or her identity document and the prescription. This programme is managed by the IVSS and currently comprises 73 pharmacies throughout Venezuela exclusively for this purpose.

25 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

There is no competent body in charge of reimbursability because Venezuela does not have a reimbursement programme. (See question 22.)

26 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

No. Manufacturers are only obliged to charge a lower price when they have an offer that entails a price reduction. Offers must be previously authorised by the SUNDDDE. Such obligation must be met during the time that the offer lasts. Prices set by the authorities must not be changed.

Medicine quality and access to information

27 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

Manufacture, importation, distribution, prescription and sale of medications are permitted only for those medications that are registered before the Ministry of Health.

Customs authorities verify that the imported medications are registered in the country. The consignee must be the holder of the sanitary registration certificate of such products.

Medications without a sanitary registration certificate, manufactured by unauthorised parties or under conditions that do not meet the Standards of Good Manufacturing Practices for Making Pharmaceutical Products shall be seized and destroyed by the authorities.

Manufacturers, importers and distributors must comply with the standards contained in the Good Manufacturing Practices for Distribution of Pharmaceutical Products regarding quality, preservation and transportation of medications.

Storage and transportation of medications are subject to compliance with strict conditions and vigilance.

Sale of medications is permitted only in pharmacies and stores duly authorised and supervised by regulating authorities.

In 2009, the Ministry of Health provided information to drug manufacturers on the general guidelines to denounce the existence of illegal medications (counterfeit, altered and those without a sanitary registration certificate). The Ministry of Health, private associations (such as CAVEME) and some patient organisations conduct institutional campaigns to warn the general public about the dangers of using counterfeit or altered medications and medications sold in unauthorised places.

Failure to comply with the sanitary legislation will result in administrative and criminal actions against the infringer.

28 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

No recent measures have been taken to facilitate the general public's access to information about prescription-only medicines. All information aimed at the general public regarding medications, sold with or without prescription, must be authorised by the regulating authorities on a case-by-case basis.

29 Outline major developments to the regime relating to safety monitoring of medicines.

The Ministry of Health issued the Standards of Good Manufacturing Practices for Pharmacovigilance (2010), which stipulate the duties of the National Centre of Pharmacovigilance (CENAVIF) and the procedure to notify the adverse effects or reactions to medications. It also obliges manufacturers or importers, and holders of sanitary registration certificates of medications, to:

- appoint a person who shall be responsible for pharmacovigilance;
- make a programme of initial and continuous training in pharmacovigilance available for their staff;
- evaluate, in a continuous manner, the risk/benefit ratio of each drug during the post-registration period;
- keep a detailed record of all suspected adverse effects produced in Venezuela;
- record and inform the CENAVIF of all suspected adverse effects occurring in Venezuela and that have been notified by sanitary services professionals;



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- ensure the management of data on adverse effects protects confidentiality regarding the identity of the persons involved;
- prepare and provide to the health authorities periodical safety reports of the products, including content, frequency and periods stipulated by current legislation; and
- cooperate with pharmacovigilance centres in matters involving medication safety.

Vaccination

30 Outline your jurisdiction's vaccination regime for humans.

It is mandatory for all the inhabitants of the country to undergo preventive immunisation against diseases preventable by vaccines.

There are two national systems of vaccination, which describe the vaccines, dose and frequency that apply to: children under one year and children from one to nine years; and adolescents, adults and seniors, men and women.

Mandatory vaccinations are required for:

- any child under 10 years of age (there are 10 mandatory vaccines);
- workers in health centres (both public and private);
- workers in agricultural facilities and slaughterhouses;

- workers in food-handling outlets;
- people in areas of risk, such as chronic disease patients exposed to viral or bacterial aetiology diseases preventable by vaccines;
- pregnant women;
- citizens serving under conscription; and
- special situations involving risk of epidemics.

There is no registry of vaccinations, but those who administer vaccines are required to issue a certificate of immunisation for minors under 10 years of age, in which the vaccines applied and their frequency should be recorded.

Vaccination programmes are administered by public bodies and private health facilities, and the administration of vaccines by health professionals authorised by the Ministry of Health.

Vaccinations ordered, performed and supervised by the health authorities as part of health programmes are free of charge.

According to indicators published by the Ministry of Health, up to April 2014, vaccinations were completed for 98.56 per cent of the population at risk. In June 2016, the management of the Extended Immunisation Programme announced that 6,000 free vaccination centres are available throughout the country for children and adults.

Getting the Deal Through

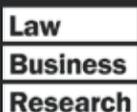
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