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PREFACE

Welcome to this second edition of *Global Legal Insights – Pricing & Reimbursement.*

This edition provides updates on the most significant developments in 22 jurisdictions around the world and aims to present a comprehensive market overview of the legal developments, policies, processes and issues affecting pricing and reimbursement for pharmaceuticals.

The authors were invited to offer their perspectives on the most recent developments in their own jurisdictions, explain significant changes, and highlight key trends in pharmaceutical pricing and reimbursement. Authors also discuss policy issues that affect pricing and reimbursement decisions, including efforts to address population growth, the increasing cost of healthcare delivery, the cost of research and development, and varying global strategies for balancing the financial investments needed to promote medical innovation with the high costs of making these new drugs and services broadly accessible to all who need them.

Each chapter explores these topics with reference to the issues that affect every jurisdiction, including global budgets, competition, fraud, and domestic and international politics. As a result, the guide provides a useful comparative analysis where policy and regulatory developments in one jurisdiction can inform understanding in another.

I would like to thank all of the authors for their invaluable contributions and I hope that you will find this book a stimulating read.

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Angola

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Angola does not yet have a Pricing and Reimbursement system in place. While there are encouraging signs that the country is willing to undertake legislative and administrative reform, general improvement of economic conditions must be achieved before an effective system can be implemented.

Market introduction/overview

The Republic of Angola is one of the largest countries on the African continent with a surface area of 1.2 million km^2, located on the west coast of sub-Saharan Africa. Recent population estimates are about 25 million inhabitants, comprising *ca*. 48% men and 52% women.

After almost four decades of conflict, ending in 2002, Angola experienced fast economic growth, mainly driven by its oil industry. The sharp decline in oil prices since mid-2014 and weak growth of the non-oil sector significantly impacted the economy and social services, resulting in a reduction of public revenues, severe tax and external imbalances (including forex shortages). Exports dropped by more than half, and the external accounts moved from surplus to deficit.

On top of this, there was the devaluation of the Angolan Kwanza. The state of Angola's economy is threatening the recent progress in terms of economic and social development, notably the long-term target of improving human development outcomes. Public spending on health has decreased since 2014 (however, this was already low compared to international standards), compromising previous increases in health expenditure by the public sector.

The National Health Service ("NHS") includes: (i) the Ministry of Health; (ii) Provincial Governments – with Provincial Health Directions and Provincial Hospitals; and (iii) Municipal Administrations – with Municipal Health Directions, Municipal Hospitals, Health Care Units and Posts. The Municipal Administrations have been assuming a progressively more dominant role in the primary healthcare network and basic healthcare activities, despite their limited administrative and technical know-how. Public expenditure at municipal level is high but struggles to achieve its goals.

Public health services provided by the NHS are free of charge and delivered through a three-layer pyramid: (a) first level – health centres and clinics, municipal hospitals, nursing stations and doctors' offices; (b) second level – general and monovalent hospitals; and (c) third level – central and specialised hospitals. The public health system also comprises the Army, the Ministry of Interior and public companies' health facilities. There are significant disparities in health facilities and access to care between urban and rural areas.

Pharmaceutical pricing and reimbursement

Regulatory classification

The regulation of medicinal products in Angola is still incipient and inconsistent.

The law establishes different types of medicines, but the system has not matured enough to associate a specific regime to each type.

Medicinal products are regulated by the Ministry of Health. Medicines are controlled and monitored by the General Health Inspection ("IGS"), which is responsible for inspecting pharmaceutical products. Among other aspects, IGS monitors the quality of imported pharmaceuticals.

The National Directorate of Health ("DNME") regulates pharmaceutical activity, and oversees the application of administrative and technical regulations to the sector. Medicines cannot be legally supplied and purchased without being registered in Angola through a procedure managed by the DNME. The registry is valid for five years and is renewable.

Generics and biosimilar medicines do not yet have a legal definition. However, the law does define "therapeutic equivalents" to the reference product. The law establishes that the Ministry of Health should promote generic substitution in pharmacies, and that medicines should be purchased at the best available price. Additionally, it is stated that generics should benefit from simpler and cheaper registration procedures. However, all these aspects reflect legal intentions; neither the law, nor any regulation, provides for any specific regime. Government plans also set out that the acquisition of generics is a priority.

An important feature of pharmaceutical regulation is inclusion in the National List of Essential Medicines ("List"). The List outlines the medicines that Angolan authorities deem necessary to treat the most pressing conditions from a public health perspective – and a significant share of the market concerns the sale and purchase of those medicines. The law provides that the List should contain medicines that are indicated for treatment of prevalent diseases, and are safe and efficacious. Given the abstract nature of these criteria, the inclusion of medicines in the List is rather subject to the Ministry of Health's discretion.

Most medicines are purchased by the State. Reimbursement of pharmaceutical products has not yet been regulated, despite several indications that this is a public policy priority that should advance soon. As for medical prescription, the foundation of the regime has been laid, but additional regulation is required to define which medicines are subject to medical prescription.

Indeed, while the law provides that suppliers of medicinal products can obtain a Marketing Authorisation after the request is assessed by the National Directorate of Medicines and approved by the Ministry of Health, specific marketing authorisation legislation is yet to be enacted. Subjection to medical prescription is typically assessed and decided in the Marketing Authorisation procedure. If such procedure is not legally provided for, subjection to medical prescription is not assessed by the authorities in a legally foreseen procedure.

Notwithstanding, the law does determine that medicines are subject to medical prescription if they fulfil one of the following requirements:

(i) raise direct or indirect risks when used without medical supervision;

(ii) are, or can be, widely used for a different purpose than intended, and such purpose poses a direct or indirect risk to public health;

(iii) contain substances, or combinations that include substances, with sensitive side effects; and

(iv) are prescribed by a doctor to be administered by a parent.

Medicines subject to medical prescription can be classified as: common (if they fulfil the requirements to be subject to medical prescription, and do not fall into other special categories); medicines subject to *renewable prescription* (that are intended for diseases with extended treatment, and where the prescription may be used more than once without raising safety concerns); medicines subject to *special prescription* (medicines that raise substance abuse, addiction, or misuse concerns); and medicines subject to *restricted medical concerns* (medicines that are exclusively used in a hospital or otherwise monitored setting because of their adverse effects).

A comprehensive list of prescription-only medicines in Angola is yet to be approved. The Ministry of Health has, however, issued an Order (731/17, of December 29), where it provides that the following medicines cannot be dispensed without medical prescription:

(i) antibiotics, including antituberculotic medicines and 3rd generation antibiotics;

(ii) Misoprostol;

(iii) Sildenafil, Tadalafil and Vardenafil; and

(iv) narcotic and psychotropic medicines.

Additional medicines can be included in such a list in the future or, alternatively, the Ministry of Health can decide on a general procedure whereby the medicine's subjection to medical prescription is assessed and decided.

The Ministry of Health recently appointed, through Order no. 56/18, of 6 March, a National Commission of Medicines and Health Products. The Commission works as an advisory body of the National Directorate of Medicines, and, among other tasks, is responsible for approving and updating the National List of Essential Medicines and for assessing the list of medicines that may be sold without medical prescription. While the Commission was appointed in March 2018, neither of these lists have been approved or updated since then.

Who is/Who are the payer(s)?

While a small private sector is gaining traction, the great majority of medicine purchases in the country are conducted by the State.

What is the process for securing reimbursement for a new pharmaceutical product?

There are indications that a pricing regime for pharmaceutical products – and, possibly, for reimbursement – is being prepared. However, the law does not currently provide for a process to secure reimbursement. Admittedly, reimbursement can be secured exceptionally, through an *ad hoc* decision of the Ministry of Health. However, at this stage, such a decision would not follow a predetermined legal procedure.

How is the reimbursement amount set? What methodology is used?

The law does not currently provide for a reimbursement procedure, and hence it does not provide a methodology to set the reimbursement amount.

How are drug prices set? What is the relationship between pricing and reimbursement?

The prices are not set linearly.

The General Framework for National Pharmaceutical Policy foresees the creation of a Commission for Price Regulation with the purpose of creating or changing the laws and regulations applicable to the pricing of pharmaceutical products. Even though the law dates from 2010, this Commission has not been created so far. Because of the delay in creating or changing these laws and regulations, a Law dating from 1974 is technically still in force,

but is considered inapplicable due to it being incompatible with inflation and overall market evolution.

Medicinal products are therefore, in practice, subject to the same regulation as any other product, pursuant to the National Pricing System. The National Pricing System is managed by the Pricing and Competition Institute which works under the supervision of the Ministry of Finance. Because no special regulation currently applies to medicinal products, they are bought and sold under a free pricing regime, where the margins are not administratively set.

No regulation is foreseen regarding hospital medicines. For this reason, prices are determined via public procurement procedures launched to purchase hospital medicines.

Tender award procedures for medicinal products are launched by a Centralized Medicine Purchase Authority ("CECOMA"). CECOMA is a public authority, working under the supervision of the Ministry of Health, charged with developing and managing the system of purchase, distribution and maintenance of goods for the National Health Service. In other words, CECOMA purchases and stores medicines and carries out their distribution to health facilities all over the country.

Prior to making a purchase, CECOMA submits an inventory with the available stock to said health facilities, who prepare an annual estimate of their needs. Based on the information provided, CECOMA then proceeds to contact local and international suppliers, and launches tender procedures to award supply contracts that correspond to the identified needs. Each healthcare facility provides their estimates within the budget that is allocated to them and allocated to each healthcare facility.

In the call for tenders, CECOMA determines the maximum price it is willing to pay for a certain product. While the maximum price will be decided by CECOMA, the product's final sale price should result from the tender procedure, and will depend on whether there is competition in the tender.

Private health institutions purchase directly from their suppliers or through their designated local distributors.

Issues that affect pricing

Lack of regulation and scarcity of medicines are the main problems. Medicines are dispensed for free in public healthcare facilities. However, the National Health System is clearly unable to meet demand, and hospitals are frequently out of stock. The National Health Services' insufficiency, together with structurally unregulated prices, cause private pharmacies to charge very high prices for medicinal products.

While it is difficult to assess, these conditions also foster a very active black market, with severe counterfeiting issues. The country's size and deficient health coverage further contribute to this outcome. Direct importation of products therefore remains a relevant concern.

The National Health Development Plan for 2012–2025 (the "Plan") sets out to increase the use of generic medicines. While this may contribute to decreasing medicine prices in the future, the country currently lacks the institutional framework to ensure or promote the substitution of branded medicines by generics.

Direct import is also a relevant concern. Even though CECOMA is the procurement agency in charge of the acquisition, storage and distribution of medicines for the public sector, some private actors and Provincial Governments may carry out procurement on their own, which also gives rise to price surges.

Policy issues that affect pricing and reimbursement

Children aged under five account for 15% of the population, and those under 15 account for 48%. In addition, 47% of inhabitants live in urban areas, while 49% are based in rural areas. Though significant improvements have occurred, the estimated average life expectancy in 2015 was only 51 years for men and 54 for women.

There is a clear need for improvement in the quality of primary healthcare service delivery, notably for underprivileged groups and rural areas. These quality failures are mainly due to a defective health system, e.g. dysfunctional health posts and hospitals, outdated classifications of healthcare professionals, lack of trained staff, a restricted number of individuals with appropriate academic background, lack of incentives linked to performance (outputs or service quality), work delays and absence, etc. In addition, the health system is exposed to disease outbreaks. Angola's epidemiological surveillance system has detected several epidemics since 2013, namely: yellow fever; malaria; measles; human and animal rabies; cholera diarrhea (bloody stool and viral); dengue fever; and chikungunya. Some of these occurrences are a sign of patchy vaccination coverage.

Due to the lack of a strict testing mechanism, the quality of pharmaceutical products is worrying. The country does not have a national quality-control laboratory: 10 small-sized laboratories screen the quality of medicines at entry points and are not enough to cover the whole supply of imported pharmaceuticals. Storage conditions are often deficient, notably for products which require temperature control.

Communicable diseases account for over 50% of deaths recorded within the population. Even with the improvements attained in the past decade, the child mortality rate, neonatal and maternal mortality, estimated at 48/1000 and 477/1000 live births respectively (2017), remain high. Malaria endures as a major public health concern, being the main cause of death, disease and absenteeism. Tuberculosis also has a negative impact on public health and development, affecting mainly individuals in the labour force. Despite a relatively low HIV/Aids prevalence rate of 2.2%, the situation varies within the country, with some provinces more affected than others, the province with the highest prevalence being Bié.

Emerging trends

Angola has not enacted a coherent and comprehensive regulatory system. The existing legal framework is clearly insufficient and is not applicable in numerous aspects. Legal and administrative reforms are patently necessary. However, even though several plans and legal instruments have been approved, implementation remains a challenge.

While it is difficult to anticipate where the regulatory system is headed, it is nevertheless bound to become more sophisticated and predictable.

The National Health Development Plan for 2012–2025 (the "Plan") outlines the following priorities:

(i) rehabilitating and expanding public healthcare infrastructure and capacity, especially for rural and underserved urban populations;

(ii) expanding the training of healthcare professionals; and

(iii) preventing disease.

The Plan also foresees the transition of the health system from a government-financed model to a system with recourse to diversified revenue streams. However, considering the country's current stage of development, and according to the World Health Organization

(WHO), primary healthcare will continue to rely on public and external financial resources.

The Plan acknowledges that the medicinal products market lacks a global approach to address its most significant challenges, namely:

(i) supporting local production of medicines;

(ii) building a National Laboratory for Quality Control;

(iii) further developing the List (the National List of Essential Medicines);

(iv) preparing a National Form of Medicines and Therapeutic Guides, as an important tool to support the rational use of medicines; and

(v) developing the legal and technical framework of traditional medicines.

Presidential Decrees of 2010 establish an increase in local manufacturing of basic primary pharmaceuticals as a government priority. The self-sufficiency of the national market is deemed as the ideal scenario, and thus as the ultimate goal.

In the Plan, the State undertakes to guarantee the availability of "physical resources" – such as infrastructure, medicines, medical equipment, and human resources – of the health system, to the extent of its capacity.

The Government further intends to develop legislation and technical rules regarding the manufacture, acquisition, storage, distribution and rational usage of medicines, as well as pharmacovigilance, in order to ensure that the medicines are safe and accessible to the Angolan population.

Reimbursement of medicines is also mentioned as a priority. At the current stage of development, the Government considers that reimbursement is a "human rights" issue, which materialises the principle of the State bearing a significant share of the burden of health costs.

The Government further undertakes to develop the NHS. The Plan sets out the following guidelines for its reform:

(i) definition and reorganisation of the national health system and the National Health Service;

(ii) increased coverage and rational organisation of healthcare services (with a reference system between health centres, hospitals, and polyvalent hospitals);

(iii) lowering mother and child mortality rates;

(iv) lowering the death rate for chronic and most prevalent diseases (malaria, tuberculosis, trypanosomiasis, measles, tetanus, meningitis and poliomyelitis);

(v) coordination of the public and private sectors and traditional medicine;

(vi) standardisation, organisation and financing of healthcare services; and

(vii) promotion of scientific investigation.

Successful market access

Considering the structural lack of regulation and the unpredictability of the market, cooperation with the competent authorities plays a significant role. Interested parties have to try to anticipate market and regulatory trends and ensure their products are approved and placed on the market according to the authorities' interpretation of applicable laws. Interested parties would also do well to consider adjusting their portfolios or business plans to cater to the most pressing needs of the Angolan population.

Given the scarcity of resources and the Angolan system's level of maturity, it is natural that

successful market access will depend on the product being used to treat or prevent a disease whose treatment or prevention is deemed as a priority. Local collaboration can also help to accelerate or clarify procedures, which can be particularly lengthy or bureaucratic if they are managed remotely.

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Australia

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Abstract

The primary mechanism governing the pricing and reimbursement of prescription pharmaceutical products in Australia is the Pharmaceutical Benefits Scheme (**PBS**). The PBS is a scheme by which the Commonwealth (Federal) Government subsidises access to medicines. Because of the impact on the Commonwealth budget, funding of the PBS is often a politically charged issue, and the subject of regular attention by Parliament and among pharmaceutical sponsors.

Market introduction/overview

Australia is a nation with a population of approximately 25 million people.[1] It is a generally healthy nation, with life expectancies in the top 10 of OECD nations. Australians have access to a Government-subsidised system of universal healthcare, which includes subsidised access to many medicines through the PBS.

Like many western countries, Australia is experiencing an ageing population. The median age of the Australian population, as at June 2018, was 37.3 years, compared to 34.8 years in June 1998. The Australian population is also growing – population growth in the 12 months leading up to September 2017 was 1.6%, a slightly higher rate of growth than the average for the previous three years. Roughly two-thirds of the population growth is attributable to immigration and one-third to natural increases.

While Australia is a generally healthy nation, it faces many of the problems typical of western countries in which life expectancy has been extended and diet and lifestyle factors play a significant role in affecting health. The following snapshot of Australian health is taken from the Australian Institute for Health and Welfare's report on Australia's Health for 2018:[2]

- in 2018 around 10 million Australians were estimated to be aged 45 or older;
- the life expectancy of a person born in 2016 is 80.4 years for a male and 84.6 years for a female (which has been rising steadily over time);
- in 2016 the leading cause of death in Australia was coronary heart disease for men, and dementia and Alzheimers disease for women (replacing heart disease);
- chronic disease is becoming increasingly common. This is attributable to a combination of the ageing of the population and a change in lifestyle factors which contribute to chronic disease. The five risk factors which make the highest contribution to chronic disease in Australia are tobacco use, high body mass, high alcohol use, physical inactivity and high blood pressure. In 2014–2015, 63% of Australian adults were estimated to be overweight or obese; and

- persons in rural and remote areas of Australia achieve significantly worse health outcomes than those in urban areas. Aboriginal and Torres Strait Islanders have still worse health outcomes. The life expectancy of a Aboriginal or Torres Strait Islander person is approximately 10 years less than that of the average Australian.

Australia is a federation comprising six states and two territories. The Australian Constitution defines the powers of the Federal Government (called the "Commonwealth"). In particular, section 51(xxiiiA) of the Constitution provides that the Commonwealth Parliament may make laws with respect to:

> "*the provision of maternity allowances, widows' pensions, child endowment, unemployment, pharmaceutical, sickness and hospital benefits, medical and dental services (but not so as to authorize any form of civil conscription), benefits to students and family allowances*".

The Commonwealth has used this power to establish the PBS, which will be the main subject of this chapter.

However, in reality, the funding of the health system in Australia is much more complicated and relies on a combination of Commonwealth, State and private funding. The essential elements of the system are:

- the Commonwealth has established the Medicare system pursuant to which Australian citizens and permanent residents receive access to universal healthcare. Any eligible person may be admitted to a public hospital and receive care free of charge, prioritised on the basis of need. Furthermore, outside the public hospital system the cost of services listed on the Medicare Benefits Schedule, which are provided by doctors, is subsidised by the Commonwealth. In practice, this means that most eligible persons pay little or nothing for routine visits to the doctor;
- the public hospital system is, with very limited exceptions, operated by the State and Territory Governments, who received funding from the Commonwealth in exchange for agreeing to provide the care required by the Medicare system;
- the cost of prescription medicines is subsidised by the Commonwealth pursuant to the PBS; and
- there is a private hospital system which runs alongside the public hospital system. Private hospitals are used by patients for elective surgery, or who wish to choose their doctors or avoid waiting lists in public hospitals. Private health insurance is available to meet the hospital costs of private hospitals. However, fees charged by doctors for services provided in a private hospital setting are still subsidised by Medicare. Any gap between the subsidised amount and the doctor's fee must generally be paid by the patient (although health insurers are now permitted to make arrangements with individual doctors to make gap payments).

The total Commonwealth budget for health, aged care and sport for 2018–2019 was approximately AU$99.1 billion. On top of the approximately AU$11 billion allocated to the PBS in the 2017–2018 budget, the 2018–2019 budget saw additional investment of $2.4 billion for new medicine listings, including a $1 billion provision for future listings from improved payment administration.[3] The PBS is the third-largest item in the health budget after Medicare (more than AU$ 24 billion, with a commitment to grow to $28.8 billion in 2021–2022) and aged care (AU$ 11.5 billion, with an additional AU$5.0 billion investment in 2018–2019). However, it should be noted that the budget allocation for the PBS overstates net expenditure on the Scheme because it does not take into account the significant rebates

paid to the Commonwealth by sponsors of high-cost prescription pharmaceuticals. Those rebates, which are discussed in greater detail in section "Policy issues that affect pricing and reimbursement" below, are currently estimated to be worth AU$3 billion.[4]

Pharmaceutical pricing and reimbursement

Regulatory classification

In Australia, therapeutic goods (including prescription medicines, over-the-counter medicines, complementary medicines, medical devices, and certain blood and blood products) are regulated by the Commonwealth regulator, the Therapeutic Goods Administration (**TGA**), in accordance with the Therapeutic Goods Act 1989 (Cth) and its delegated legislation. The TGA is responsible for evaluating, assessing and monitoring goods which are manufactured or supplied in, exported from or imported into Australia.

The PBS is established by Part VII of the National Health Act 1953 (Cth). It is an extremely long-lived scheme, having begun in 1948 as a Government-subsidised scheme to provide free medicines for pensioners and a list of 139 life-saving and disease-preventing medicines free of charge for others.[5] It has evolved over time, with changes in recent years designed to manage the cost of the scheme for the Government and, in conjunction with industry (in particular, arising from agreement between the Department of Health and the industry body for prescription medicine sponsors, Medicines Australia, in 2010 (memorandum of understanding) and 2017 (strategic agreement)).

The PBS subsidises drugs or medicinal products, where a medicine is a therapeutic good that is represented to achieve, or is likely to achieve, its principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human.[6]

The regime under the National Health Act requires (except under very limited circumstances) that a pharmaceutical benefit may only be supplied by an approved pharmacist on presentation of and in accordance with a prescription written by a PBS prescriber as permitted by the legislation. Depending on the particular item in question, a PBS prescriber may be a medical practitioner, a participating dental practitioner, an authorised optometrist, an authorised midwife or an authorised nurse practitioner.[7]

As such, the Government does not subsidise medical devices, animal health products, blood or blood products, over-the-counter or complementary medicines via the PBS.

It is also worth mentioning that the Australian Repatriation System provides defined benefits for eligible veterans and their dependants, which include subsidising certain medications and dressings via the Repatriation Pharmaceutical Benefits Scheme (**RPBS**). This chapter focuses on the general PBS.

A further separate programme is the Life Saving Drugs Program (**LSDP**), which is a programme through which the Government subsidises high-cost transformational therapies for rare diseases which do not meet the usual expectations of the PBS for cost-effectiveness. The LSDP sits outside the PBS and is managed through individual agreements between the sponsors of such products and the Commonwealth. There are currently 14 medicines available to eligible patients for the treatment of nine rare conditions.[8]

In January 2018, the Commonwealth released the report of a review in relation to the LSDP which proposed certain changes to the criteria for inclusion in that programme and the way it is managed. The Australian Government and Medicines Australia (on behalf of sponsors of medicines on the LSDP) entered into an agreement on 8 May 2018, which operates from 1 July 2018 to 30 June 2022 in respect of the commitments of each party to implement

reforms outlined therein. These include the establishment of an Expert Panel to provide advice and assistance to the Commonwealth Chief Medical Officer in assessing rare disease medicines seeking listing on the LSDP, and Medicines Australia's support for reviews of LSDP medicines, including assessment of usage, financial costs and other relevant information associated with a medicine's listing.[9]

There are eight criteria which must be satisfied in order for a medicine to be listed on the LSDP which relate to the characteristics of the disease being treated, the availability of therapies and the cost of the medicine in question.[10]

Who is/Who are the payer(s)?

Under the PBS, the Commonwealth Government subsidises the cost of medicines listed on the Schedule of Pharmaceutical Benefits (**Schedule**).

All Australian residents holding a current Medicare card, and certain overseas visitors with which Australia has a Reciprocal Health Care Agreement[11] are eligible to access the PBS. The National Health Act provides that an eligible person receiving applicable treatment is entitled to receive pharmaceutical benefits without paying money or any other consideration[12] except as follows:

- A patient co-payment which, from 1 January 2019, is up to AU$40.30 or AU$6.50 if the patient has a concession card for most PBS medicines. Pharmacists may (voluntarily) choose to discount the PBS patient co-payment by up to AU$1.00 for some medicines. The amount of the co-payment is adjusted annually on 1 January in accordance with the Consumer Price Index (**CPI**).[13]
- Two other fees may be payable by a general (not concessional) patient if the cost of the medicine is less than the current co-payment: an allowable additional patient charge (currently AU$4.53) and an additional fee for ready-prepared items (currently AU$1.23). Neither of these fees can be added to increase the amount payable by the patient above the co-payment amount.
- Some brands of medicines have a price premium or brand premium. This is an additional amount which represents the difference between the price at which the sponsor is prepared to sell and the price which the Government is prepared to subsidise. Government policy is to only allow such arrangements in limited circumstances, typically where an innovator medicine and one or more generic brands of the same drug are listed on the Schedule.

The legislation also provides for a "Safety Net". If a patient's prescriptions exceed the relevant Safety Net Threshold for a calendar year, general patients pay for further PBS prescriptions at the concessional co-payment rate, and concessional patients will receive PBS prescriptions at no additional charge for the remainder of the year. Current Safety Net thresholds (as at 1 January 2018) are AU$390 for concession card holders and AU$1,550.70 for general patients.

What is the process for securing reimbursement for a new pharmaceutical product?

Registration/listing and decision-making

Unless a medicine is proceeding along a parallel TGA and PBS track, it must be approved for supply in Australia before it can be listed on the Schedule. For prescription medicines, this requires registration on the Australian Register of Therapeutic Goods (**ARTG**).

The Commonwealth Minister for Health is empowered by the National Health Act to list medicines as pharmaceutical benefits on the Schedule.[14] The Commonwealth Minister will make a determination, set out in a legislative instrument, that a particular drug, in a particular

brand, form and manner of administration, is to be listed on the Schedule.

The Pharmaceutical Benefits Advisory Committee (**PBAC**) is established by the National Health Act to act as an advisor to the Department of Health and Minister for Health in relation to the listing and pricing of pharmaceutical items on the PBS. The PBAC's functions include making recommendations to the Minister as to the drugs which it considers should be made available as pharmaceutical benefits on the PBS, as well as providing advice on issues relating to the administration of the PBS more generally.[15] The Minister may not list a pharmaceutical item on the Schedule unless the PBAC has recommended that the Minister do so.

In deciding whether to recommend to the Minister that a particular drug or medicinal preparation (or class of drugs or preparations) be available as a pharmaceutical benefit on the PBS, the National Health Act requires the PBAC to give consideration to the effectiveness and cost of the therapy involving use of the drug, preparation or class, including by comparing this with alternative therapies.[16] Furthermore, if a medicine is substantially more costly than alternative therapies, the PBAC may not recommend its listing unless the PBAC is satisfied that, for some patients, the medicine provides a significant improvement in efficacy or reduction in toxicity of the alternative therapies.[17]

The PBAC publishes a detailed set of guidelines (current version 5.0, September 2016) which are the "Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee" (**PBAC Guidelines**).[18] The PBAC Guidelines identify five quantitative factors which influence PBAC decision-making:[19]

(a) comparative health gain – including magnitude and clinical importance of effect;

(b) comparative cost-effectiveness – including on a cost-effectiveness or cost-minimisation basis; as well as a consideration of comparative costs including healthcare resources not limited to cost of the drug;

(c) patient affordability in the absence of PBS subsidy;

(d) predicted use in practice and financial implications for the PBS (projected annual net cost); and

(e) predicted use in practice and financial implications for the Australian Government health budget (projected annual net cost).

The Department of Health has also published a "Procedure guidance for listing medicines on the Pharmaceutical Benefits Scheme" (version 1.4, February 2019),[20] which provides further detailed information about the processes, procedures, timelines and documents required. A further draft procedure guidance, and forms for listing medicines on the PBS, were available for consultation between 5 and 20 March 2019; it is likely that further resources will be published in the course of 2019.

In practice, at a high level, for listing a new medicine on the PBS, the process involves: the making of a detailed submission to the PBAC; consideration by two subcommittees – the Drug Utilisation Sub-Committee (**DUSC**) and the Economic Sub-Committee (**ESC**); consideration by the PBAC itself; recommendation by the PBAC to make or not make the requested listing and (if positive), negotiation and agreement on the price between the sponsor and the Department; and formalisation of the listing by the Minister signing the relevant legislative instrument.

Formulary placement

Amendments to the legislation in 2007 introduced two formularies called F1 and F2. The Minister may determine that a particular listed drug is on F1 or F2.[21] There is no requirement

(including as to timing) as to when this must occur; however, in practice, it is proximate to the initial listing (or change of circumstances necessitating a move between formularies), since the formulary also influences the pricing mechanisms which may apply.

The Minister may only determine that a drug is on F2 if it does not satisfy one or more of the criteria for F1. The criteria for F1 require that there are no brands of pharmaceutical items that have the drug, are bioequivalent or biosimilar, which are listed on the PBS, or if there are no brands of pharmaceutical items having another listed drug in the same therapeutic group. Generally speaking, F1 drugs are "innovator" or "single brand" drugs, which are still on patent and for which there is no suitable alternative for patients. Drugs on F2 are drugs for which there are multiple brands; that is, drugs that are off patent and operating in a competitive market with generic or biosimilar brands available.

Appeals

The powers of the PBAC and the Minister (intentionally) give wide scope for judgment and for rejection. This has also been confirmed in legal proceedings: *Pfizer Pty Ltd v Birkett* (2001) 112 FCR 305 at [36] – the purpose of the words in section 101(3) of the National Health Act is to give the PBAC "the widest scope for judgment and indeed for rejection".

There are no statutory rights to appeal or review decisions for the listing or pricing of items on the PBS. The alternatives open to an applicant who wishes to challenge such a decision include:

(a) resubmission to the PBAC (where a sponsor intends to challenge a decision made by the PBAC);

(b) independent review (a form of merits review); or

(c) judicial review.

The timing and likelihood of success will depend on which option is taken, what decision is subject to challenge, and the facts of the particular case.

Independent review may be an option where a submission to PBAC has not resulted in a recommendation to list a drug on the PBS or where PBAC has declined to recommend an extension of the listing of an already listed drug. Independent review involves an independent reviewer looking at all the evidence that was before the PBAC to determine whether the correct decision was made, and making a recommendation accordingly.[22]

The reviewer's findings are not binding on the PBAC.

Judicial review is the review of Government decision-making by a Court, under the *Administrative Decisions (Judicial Review) Act* 1977 (Cth) or sections 39B(1) and 39B(1A) of the Judiciary Act 1903 (Cth). Judicial review looks at the way in which a decision was made (which may include acts or steps preparatory to the decision). Relevant factors may include procedural impropriety (e.g. lack of procedural fairness), irrationality (e.g. failure to take into account a relevant consideration or taking into account irrelevant considerations), or illegality (decision-maker acting beyond power).

How is the reimbursement amount set? What methodology is used?

Once a pharmaceutical benefit is listed on the PBS, a set of quite complex arrangements set out the way in which the reimbursement is paid. In general terms, the Schedule specifies the price which may be charged by the sponsor for the medicine (the Approved Ex-Manufacturer Price, or AEMP). However, the Commonwealth subsidy is paid to the pharmacist who dispenses the medicine. The subsidy (called the Commonwealth price) is therefore the AEMP plus mark-ups and associated fees charged by the wholesaler and

pharmacist. Those mark-ups and fees are controlled. For community pharmacy, the current Sixth Community Pharmacy Agreement between the Commonwealth and The Pharmacy Guild of Australia set out how the Commonwealth price is set.[23] For private hospitals, the *National Health (Pharmaceutical benefits supplied by private hospitals) Determination* 2010 (Cth) applies. For public hospitals, *National Health (Commonwealth Price – Pharmaceutical Benefits Supplied By Public Hospitals) Determination* 2017 (Cth) applies.

How are drug prices set? What is the relationship between pricing and reimbursement?

A positive recommendation by the PBAC to list a drug on the PBS will trigger further steps to be taken by the Department of Health and the drug sponsor. Importantly, the Minister and the drug sponsor seek to negotiate the price for the new listing, having regard to the PBAC's advice to the Minister. The parties should seek to agree the appropriate maximum price of the brand for the pharmaceutical item, by reference to the pricing quantity of the brand of the pharmaceutical item.[24] Once negotiated, the sponsor provides the Department with a completed "PB11a" form – a request for an approved ex-manufacturer price.

The Government adopts a reference pricing policy whereby it will subsidise medicines which are therapeutically equivalent up to the lowest-priced such medicine.

For the first listing of a new drug, the economic evaluation to be adopted will depend on the clinical performance and cost-effectiveness of the new medicine compared with the main comparator. A cost-effectiveness analysis is appropriate where the proposed medicine is therapeutically superior to the main comparator but likely to result in additional costs to the healthcare system, or therapeutically inferior but likely to result in lower costs. If such a submission demonstrates therapeutic superiority, the sponsor will be able to negotiate a premium price over alternatives. A cost-minimisation approach is used where there is a therapeutic claim of non-inferiority (or superiority), the safety profile is equivalent or superior (nature and magnitude), and use of the proposed medicine is anticipated to result in equivalent or lesser costs to the health system.[25] In such circumstances, the sponsor will only be able to obtain a price equivalent to or lower than relevant comparators.

If there are no comparators for a medicine, the PBAC will examine the economic analysis provided by the sponsor and reach a view as to whether the economic analysis (which must assume a cost to Government and therefore a price) justifies a recommendation for listing. The tool used by the PBAC to do this is typically the incremental cost-effectiveness ratio (**ICER**) which measures the cost to the Commonwealth of each quality-adjusted life year the medicine generates. The PBAC does not have any formal policy as to what represents an acceptable ICER. However, it is widely assumed that the PBAC does apply informal standards about the ICERs it regards as acceptable (which vary depending on the therapeutic area).

It is quite common for high-cost drugs to be subject to a risk-sharing deed pursuant to which the sponsor agrees to rebate some part of the Commonwealth price to the government.[26] The formula is sometimes a simple percentage of the Commonwealth price and in other cases may involve a rebate applying once the Commonwealth payment moves above a certain level. There are also examples of differential rebates being paid for different uses of a medicine. These arrangements all create a difference between the AEMP and the effective price of the medicine.

The relationship between the price agreed between Minister and sponsor and reimbursement is described in section "How is the reimbursement amount set? What methodology is used?" above.

The legislation includes three types of mechanisms which operate to reduce the AEMP agreed between Minister and sponsor. They are as follows:

- automatic price reductions which apply on the 5th, 10th and 15th anniversary of listing for drugs on the F1 formulary (5%, 10% and 5%, respectively),[27] subject to a Ministerial discretion;
- statutory price reductions on the first listing of a bioequivalent or biosimilar brand of a pharmaceutical item (currently 25%, in place during the term of the Strategic Agreement with Medicines Australia, until June 2022), subject to a Ministerial discretion, as well as certain exemptions for new pharmaceutical items which are new presentations of existing medicines;[28] and
- for medicines on F2 price-disclosure-driven price reductions. These require sponsors to provide the Commonwealth with periodic data about the discounts and other benefits which they provide in association with the supply of the medicine. The Commonwealth then uses a formula set out in regulations[29] to calculate the weighted average effective price for a medicine and the AEMP for each brand of that medicine is reduced accordingly. As a result, once a medicine is on F2, its AEMP reduces over time to the minimum price at which sponsors are prepared to sell it.

Issues that affect pricing

In addition to the issues flagged in the sections above, an interesting issue in this space in recent years has been the Government's approach to biosimilar medicines and interchangeability of those medicines at a pharmacy level.

In Australia, there is no mandatory substitution of generic or biosimilar medicines (or "cheaper" medicines) instead of the innovator product. In fact, under the National Health Act, it is an offence for a pharmacist to supply anything other than the pharmaceutical benefit specified in a prescription, except under certain prescribed circumstances.[30]

A pharmacist may supply another substitute benefit if:

(a) the prescriber did not indicate that only that benefit was to be supplied (in practice, by checking a box or writing "substitution not permitted" on the script);

(b) the Schedule of Pharmaceutical Benefits states that the specified benefit and the substitute benefit are equivalent;

(c) the substitute benefit is a listed brand of a pharmaceutical item; and

(d) the supply of the substitute benefit is not otherwise prohibited by State or Territory law.[31]

Products which the Department has determined are "Schedule equivalent" are marked on the Schedule of Pharmaceutical Benefits with what is colloquially known as an "a" flag. The "a" flag has been relatively uncontroversial in the context of generic (bioequivalent) medicines. However, in the newer area of biological (biosimilar) medicines, the use of the "a" flag has been a cause for some concern within the medical community and industry. It has led to the Department's Biosimilar Awareness Initiative, directed at prescribers, pharmacists and consumers.

Policy issues that affect pricing and reimbursement

Most policy issues in relation to pricing and reimbursement arise from the tension between the desire to list new medicines on the PBS and the need to manage the Government's health budget.

The underlying philosophy of the PBS is not to choose particular products or brands for preferential treatment for reimbursement, but rather to allow any product which can demonstrate appropriate clinical efficacy and safety to be listed. Cost to Government is then managed in two ways:

- the role played by the PBAC as a gateway to the listing of new products unless they are either cost-effective or cost-minimised to existing therapeutically equivalent products. The way in which the PBAC discharges its role as an independent Health Technology Assessment body, its composition and its relationship with both Government and industry is a constant issue of interest to stakeholders; and
- a legislative and policy measure described above designed to ensure that the Government pays the same price for all products which have similar clinical effectiveness (and that price always moves to the lowest price available for a therapeutically equivalent product).

This approach has, in general, made the PBS a successful and cost-effective Government programme. However, it faces constant policy challenges as a result of a desire on the part of the Government to limit the growth of the PBS budget.

Within that framework, three policy issues which are of particular present interest and importance are as follows:

Statutory price reductions and Strategic Agreements

Since 2007, the Commonwealth has sought to manage the PBS budget by legislation and policy which seeks to reduce the AEMP for products on the Schedule over time. This occurs through the use of the reference pricing policy and the statutory price reduction mechanisms described in section "Pharmaceutical Pricing and Reimbursement", "How are drug prices set? What is the relationship between pricing and reimbursement?" above.

There has been a consistent level of concern within industry about the tendency of the Commonwealth to introduce new price-reduction policies (including new interpretations of the reference pricing policy) and new legislation without sufficient warning, thereby eroding the ability of the industry to predict and manage the future prices of their products.

The response from the industry and the Commonwealth has been to enter into agreements whereby industry agrees to certain price-control measures being introduced in exchange for the Commonwealth promising a degree of policy certainty and consultation and due process in relation to any future policy changes.

These agreements are reflected in agreements between the Commonwealth and industry representative bodies, in particular Medicines Australia representing the innovative medicines industry, and the Generic Medicines Industry Association for the generic medicines industry.

The first such agreement was a Memorandum of Understanding entered into between Medicines Australia and the Commonwealth in 2010 with a four-year term.[32] The Memorandum of Understanding was generally thought to have been effective in achieving cost control on PBS expenditure,[33] but questions were raised about whether it had been effective in providing industry with policy certainty.

In 2015, the Generic Medicines Industry Association entered into a Strategic Agreement with the Commonwealth with a five-year term,[34] the operation of which has now been extended until 30 June 2020.[35] This Agreement provided for certain changes to the price disclosure regime to accelerate the speed with which price disclosure reduced generic prices. In exchange, the Commonwealth promised not to introduce further price-related saving policies for medicines on the F2 Formulary and agreed to introduce policy measures to encourage increased use of biosimilars.

In 2017, Medicines Australia entered into a Strategic Agreement with the Commonwealth with a five-year term.[36] This Strategic Agreement provided for a substantial change to the

way in which the statutory price reduction regime operates (including increased price reductions). However, it also introduced for the first time Ministerial discretions not to apply statutory price reductions to medicines which have already been subject to significant reference-pricing-driven price reductions. In this agreement, the innovative medicine industry also agreed to a range of policy measures, including more expansive biosimilar uptake drivers.

Many of these changes were reflected in amendments to the Act which were passed into law in January and October 2018.

These effects of these two Strategic Agreements are still working their way through the system so it remains to be seen how effective they are in maintaining the balance required for a sustainable medicines policy.

Rebates

The last 20 years have seen dramatic growth in the use of risk-sharing agreements (described in section "Pharmaceutical Pricing and Reimbursement", "How are drug prices set? What is the relationship between pricing and reimbursement?") above to create a difference between the published price of a medicine (the AEMP) and the effective price paid by the Commonwealth for that medicine. Under these deeds, the difference between published price and effective price represents rebates paid by the sponsor to the Commonwealth. Almost all high-cost drugs are now listed on the Schedule with a confidential risk-sharing arrangement in place.

This has resulted in a dramatic growth in rebates over the last decade (see section "Market introduction/Overview" above) to the extent that the size of the rebates is about 25% of the total PBS budget and close to half of the amount of that budget attributable to the price charged by sponsors for their products. In recent years, the listing of non-interferon Hepatitis C medicines appears to have more than doubled the total value of rebates payable by industry.

For sponsors this creates a problem because the perceived cost of their products to Government is much greater than the actual cost. Medicines Australia has made submissions to the Commonwealth seeking explicit recognition of rebates in the way the PBS budget is presented.

For the Commonwealth, it has created an accounting problem because rebates are often paid months and sometimes more than a year after the supply has occurred.

For these reasons the Commonwealth has proposed restructuring the PBS payments system so that for high-cost drugs a net subsidy amount (the 'effective price') would be paid directly to the sponsor rather than to the pharmacist.

This apparent simple change gives rise to numerous complex legal, accounting and practical issues which are currently the subject of discussions between the Commonwealth and industry. It remains to be seen how those issues are resolved.

To that end, a Project Advisory Board (comprising representatives from the Department of Health and various industry associations) was established on 9 August 2018 to support, advise and assist the project, keep members and stakeholders informed, assist in resolving conflicts and disputes and make recommendations to the Department, as necessary. Technical working groups have also been established.[37]

The Department proposed to implement the first phase of the new payment arrangements from 1 July 2019 involving a subset of medicines with special pricing arrangements, and to progressively roll out new payment arrangements to all medicines with special pricing arrangements from 1 July 2020. There nevertheless remains significant uncertainty as to

whether the legal and practical difficulties associated with such an arrangement can be overcome. Representatives of the government have recently acknowledged that the implementation of the reforms is likely to be delayed. There is still no agreement as to which of five proposed models for a reformed payment system should be pursued.

In the meantime, the Government's approach to special pricing arrangements more generally appears to be under consideration, with reports of new criteria and, potentially, a substantial conceptual change to the circumstances in which the Government may agree to such an arrangement. The narrowing of the circumstances in which a special pricing arrangement may be agreed may have significant implications for decisions of innovator companies to list their drugs on the Australian PBS.

Timely access to medicines

The PBS is a very effective system in delivering access to subsidised medicines quickly once they are listed on the Schedule. However, there has been increasing criticism of the speed with which medicines are able to be listed on the PBAC.

For example, in the Fourth Edition of its Facts Book (July 2015), Medicines Australia reported that the success rate for submissions to the PBAC has been declining and that it took on average 22 months for a new medicine to be listed on the Schedule, with the success rate for initial submissions being just slightly more than 50%.[38] The PBAC's rigid meeting schedule exacerbates the problem because it means that if a submission is rejected by the PBAC it is usually a minimum of four months – and more commonly, eight months – before the medicine can return to the PBAC.

There are a number of policy reforms which have been made or are under consideration to address this issue, including the introduction of a parallel processing model whereby it is possible to lodge a submission for PBS listing before final TGA approval is obtained.

Emerging trends

As described in "Policy issues that affect pricing and reimbursement", "Statutory price reductions and Strategic Agreements" above, a Strategic Agreement was signed by Medicines Australia and the Commonwealth, with a five-year term. The purpose of that Strategic Agreement was to give some certainty to the prescription medicines industry and the Government. Since the pricing mechanisms were (necessarily) introduced into legislation, there have been some instances where expectations of the industry have not aligned with understanding of the role of the Strategic Agreement and the agreement reached with the Government. This means that there is still some uncertainty around the application of pricing policy and the interface with legislation. Of course, a change in the Government always has the potential to impact these arrangements. It is also clear that the general trend and focus for the Government is to control budgetary pressure and to appropriately manage the cost of the PBS in the future.

In addition, as described in "Policy issues that affect pricing and reimbursement", "Rebates" above, the widespread use of rebates and a potential new structure for the reimbursement of (at least) high-cost medicines continues to be a current focus for the Government, both in the context of the PBS and the LSDP.

Finally, the Government is in the process of introducing a cost recovery approach to the fees associated with listing a medicine on the PBS, which will likely result in a significant increase in those fees.

Successful market access

Critical to successful market access for an innovator prescription medicine sponsor is co-ordination between the company's clinical and pricing teams and a thorough knowledge of the competitive market for a particular drug and disease state. It is worth noting that the Government does not tend to be persuaded by comparative pricing in other international markets, although that may be a key driver for a particular sponsor. The Minister has broad discretion in relation to particular pricing decisions and those decisions may be difficult (and costly) to challenge.

New entrants to Australia sometimes underestimate the importance given to the role and independence of the PBAC and the principal Health Technology Assessment body. While the PBAC will be acutely aware of the broader political and market environment in which an application for listing is made, its approach is fundamentally data-driven. The PBAC will not recommend a product for listing unless the available data support its clinical efficacy and justify the price sought by the sponsor relative to the alternatives and in accordance with what the PBAC regards as acceptable cost-effectiveness.

A well-planned pricing strategy must give consideration to both the clinical needs of patients and the Government's budgetary pressures (and desire to focus upon lowest-cost comparators). If a sponsor wishes to seek a higher price for a medicine seeking listing, this must be justifiable by reference to the available alternatives and the advantages (whether clinical or economic) of the new product seeking listing compared to alternative therapies.

* * *

Endnotes

1. Unless otherwise indicated, data presented in this introduction and overview are sourced from the Australian Bureau of Statistics (www.abs.gov.au).
2. https://www.aihw.gov.au/reports/australias-health/australias-health-2018/contents/table-of-contents.
3. Health Portfolio Budget Statements 2018-2019, Budget Related Paper No 1.9, May 2018; http://www.health.gov.au/internet/budget/publishing.nsf/Content/2018-2019_Health_PBS_sup1/$File/2018-19_Health_PBS_1.00_Complete.pdf.
4. 2018–2019 Medicines Australia Federal Budget Submission (https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/02/2018-2019-MA-Federal-Budget-Submission.pdf).
5. http://www.pbs.gov.au/info/about-the-pbs.
6. Section 3, Therapeutic Goods Act 1989 (Cth) – "Medicine".
7. Sections 84 "PBS prescriber", 88–90 of the National Health Act. The Schedule of Pharmaceutical Benefits identifies which items are able to be prescribed by which type of PBS prescriber (e.g. dentists and optometrists cannot prescribe general PBS items but have access to a separate Dental Schedule or Optometrical Schedule (respectively)).
8. http://www.health.gov.au/LSDP.
9. http://www.health.gov.au/internet/main/publishing.nsf/content/FD13E541FA14735CCA257BF0001B0AC0/$File/LSDP-compact-with-Medicines-Australia.pdf.
10. http://www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-applications.
11. Currently, Belgium, Finland, Ireland, Italy, Malta, the Netherlands, New Zealand, Norway, Slovenia, Sweden and the United Kingdom.

12. Includes medical treatment by a medical practitioner, dental treatment by a participating dental practitioner, optometrical treatment by an authorised optometrist, midwifery treatment by an authorised midwife or nurse practitioner treatment by an authorised nurse practitioner (section 86 of the National Health Act).
13. http://www.pbs.gov.au/info/about-the-pbs#What_are_the_current_patient_fees_and_charges.
14. Section 85 of the National Health Act.
15. Section 101 of the National Health Act sets out the functions of the PBAC.
16. Section 101(3A) of the National Health Act.
17. Section 101(3B) of the National Health Act. Section 100 of the National Health Act also empowers the Minister to make special arrangements for, or in relation to, providing that an adequate supply of pharmaceutical benefits will be available to persons living in isolated areas, who are receiving treatment in circumstances where pharmaceutical benefits are inadequate for that treatment or if the pharmaceutical benefits can be more conveniently or efficiently supplied under those arrangements. Examples include the Efficient Funding of Chemotherapy program, Highly Specialised Drugs Program and IVF Program (https://www.pbs.gov.au/browse/section100).
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19. Page 4, PBAC Guidelines.
20. http://www.pbs.gov.au/industry/listing/procedure-guidance/files/procedure-guidance-listing-medicines-on-the-pbs.pdf.
21. Section 85AB of the National Health Act.
22. http://www.pbs.gov.au/info/general/independent-review/independent-review-pbs-info-for-applicants.
23. https://www.guild.org.au/resources/6cpa.
24. Section 85AD of the National Health Act.
25. Page 60, PBAC Guidelines.
26. Section 85E of the National Health Act empowers the Minister to enter into such deeds on behalf of the Commonwealth.
27. Sections 99ACF, 99ACHA, 99ACJ, 99ACK of the National Health Act.
28. Section 99ACB of the National Health Act.
29. Part 7, Division 2 – Subdivision B (sections 71–81) of the National Health (Pharmaceutical Benefits) Regulations 2017 (Cth).
30. Section 103(2)(a) of the National Health Act.
31. Section 103(2A) of the National Health Act.
32. http://www.pbs.gov.au/info/industry/useful-resources/memorandum.
33. See, for example, https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/01/20130515-rep-The-Impact-of-Further-PBS-Reforms-Final-report-from-CSES.pdf.
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Belgium

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Abstract

Belgium has adopted a broad social security system, which includes the compulsory health insurance managed by the Belgian National Institute for Health and Disability Insurance (the "NIHDI") (*Rijksinstituut voor ziekte- en invaliditeitsverzekering (RIZIV)/Institut national d'assurance maladie-invalidité (INAMI)*). This social security system is mainly funded by social security contributions from employers, employees, self-employed individuals and civil servants and through governmental subsidies and taxes.

The Belgian legislator has adopted a positive reimbursement list-system which entails that the compulsory health insurance shall only reimburse medicinal products that are included on the list of reimbursable products. To be included on the list and obtain reimbursement of a medicinal product, pharmaceutical companies must submit a reimbursement application with the NIHDI that will assess the application on the basis of several reimbursement criteria. The final reimbursement decision is taken by the Minister of Social Affairs and Public Health on the advice of the NIHDI.

The pricing procedure and the reimbursement procedure run in parallel; the reimbursement application must be submitted simultaneously with the pricing application. The pricing procedure falls under the responsibility of the Minister of Economic Affairs. The Minister of Economic Affairs determines the maximum ex-factory price, which forms part of the maximum price charged to the patients, which is referred to as the "maximum public price". The maximum public price is the sum of the ex-factory price, the margin for the wholesalers and the pharmacists, the pharmacist fee for delivery of the reimbursable product and 6% VAT.

In Belgium, approximately 75% of all healthcare expenses are covered by compulsory health insurance. However, health expenditures are increasing fast (with an expected annual growth rate of 2.7%) and are forecast to reach €49.19 billion in 2021, putting pressure on the health budget. The Belgian government is also being pressured by the European Commission to make budget savings in order to meet its fiscal deficit target.[1] Cost-containment measures are therefore essential to keep expenditures within bounds. These cost-containment efforts inevitably have an impact on the reimbursement system.

Overview of the healthcare system in Belgium

Belgium applies a compulsory social security system, comprising three systems (for employees, the self-employed and civil servants) and seven different pillars. The compulsory health insurance is one of these seven pillars. The social security system is mainly funded through proportional social security contributions from employers,

employees, civil servants and self-employed individuals based on income and through governmental subsidies and taxes.

The NIHDI is a federal social security institution, responsible for the administrative organisation, the (financial) management and control of the compulsory health insurance. The NIHDI also organises consultations between the various actors in the health insurance sector (the sickness funds, representatives of persons active in the healthcare sector (for example, doctors, pharmacists and hospitals) and the representatives of trade unions and employers). The NIHDI operates under the supervision of the Minister of Social Affairs and Public Health.[2]

The compulsory health insurance is organised through six private, non-profit-making national associations of sickness funds and one public national association sickness fund. Everyone must register with an accredited sickness fund. These sickness funds finance the healthcare costs of their members within the budget that was allocated to them by the NIHDI.[3]

In addition to the compulsory health insurance, individuals may also register with private profit-making health insurance companies to ensure coverage of healthcare costs that are not covered by the compulsory health insurance. It is to be noted that 75% of all healthcare expenses are covered by compulsory health insurance.[4]

Pharmaceutical pricing and reimbursement

Regulatory classification

Original medicinal products vs. generic medicinal products and biosimilars

Original medicinal products (or reference medicinal products) are medicinal products that have been granted a marketing authorisation on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data.[5] Original medicinal products usually require comprehensive and expensive research and development activities in order to develop a new chemical entity or a new biological entity and, consequently, to introduce such medicinal product on the basis of a full dossier on the market.

Generic medicinal products are medicinal products with the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated on the basis of appropriate bioavailability studies. A generic product is therefore essentially equivalent to its reference product. Contrary to the original medicinal products, generic companies do not need to submit a full dossier in order to receive marketing authorisation. Generic companies can submit an abridged application, in which they can refer to already existing data (of the reference product) to establish the safety, quality and efficacy of the product. Given that the reference product has already received marketing authorisation, there is no need to (unnecessarily) repeat costly trials and experiments.[6]

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product. Similarity to the original medicinal product in terms of quality characteristics, biological activity, safety and efficacy, based on a comprehensive comparability exercise, need to be established.[7] It is to be noted that biosimilars cannot be considered generics of a biological medicinal product. While generic medicinal products have the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference product, the natural

variability and more complex manufacturing of biologicals do not allow an exact replication of the molecular microheterogeneity.[8] Just like generics, biosimilars are granted marketing authorisation via an abbreviated procedure to avoid repeating costly and unnecessary trials.[9] However, given the complexity of biologicals, more studies are needed to obtain marketing authorisation for biosimilars than for generics to ensure that minor differences with respect to the reference product do not affect safety or efficacy.[10]

Prescription-only vs. non-prescription medicinal products

Prescription-only medicinal products are medicinal products that may only be supplied on the basis of a prescription. Conversely, non-prescription medicinal products (or "over the counter" or "OTC" medicinal products) are not subject to a prescription and can be freely supplied by the pharmacist. The applicant for a marketing authorisation must indicate in its application the proposed classification of the medicinal product. However, the final classification decision is taken by the Minister of Social Affairs and Public Health. Once the product is classified as prescription-only, the product can be further divided into subcategories. For example, the Minister can decide that some prescription-only medicinal products may only be prescribed by certain groups of specialists, or, with respect to medicinal products intended exclusively for use in a hospital, that the supply of these medicinal products will be reserved for hospital pharmacists.[11]

Reimbursable vs. non-reimbursable medicinal products

Reimbursable medicinal products are prescription-only medicinal products for which reimbursement has been requested. While the majority of prescription-only medicinal products are currently being reimbursed, some prescription-only products are, on the basis of medical and budgetary concerns, only being reimbursed subject to certain reimbursement conditions.[12]

There are two categories of non-reimbursable medicinal products. The first category includes prescription-only medicinal products for which no reimbursement has been requested or for which the reimbursement application has been rejected. The second category includes non-prescription medicinal products (or OTC medicinal products).

Who is/are the payors?

Reimbursed medicinal products are paid for by the health insurance and, as the case may be, for an amount limited by law, by the patient.

A distinction is made between seven reimbursement categories (see below under "How is the reimbursement amount set? What methodology is used?" in "Pharmaceutical pricing and reimbursement"). Depending on the reimbursement category in which the medicinal product is included, the health insurance will either pay the full price of the product, or part of it. In the latter case, the patient will be required to contribute to the price of the product; such contribution is called the patient contribution and is capped by law.[13] In addition, it should be noted that the patient contribution for pharmaceutical specialties differs depending on whether the patient qualifies for preferential reimbursement or not, and whether the medicinal product is supplied in a public pharmacy or in a hospital pharmacy.

By way of example, if the medicinal product is included in reimbursement category A, which covers vital medicinal products, the product will be fully reimbursed by the health insurance. If the medicinal product is included in reimbursement category B, which relates to therapeutic essential medicinal products, the product will be reimbursed up to 75%–85%.

What is the process for securing reimbursement for a new pharmaceutical product?

The main legal framework on the reimbursement of medicinal products includes:

- the Law of 14 July 1994 concerning the compulsory insurance for medical care and benefits (the "**NIHDI Act**"); and
- the Royal Decree of 1 February 2018 concerning the procedures, terms and conditions for reimbursement by the compulsory insurance for medical care and benefits towards costs of pharmaceutical specialties (the "**RD Reimbursement**").[14]

The Belgian legislator has opted to work with a positive reimbursement list in accordance with Article 6 of the Transparency Directive.[15] This entails that the health insurance shall only reimburse medicinal products that are included on the list of reimbursable pharmaceutical specialties.

To obtain reimbursement of a medicinal product that is not yet included on the list of reimbursable pharmaceutical specialties, an application for reimbursement must be submitted to the Secretariat of the Commission for Reimbursement of Medicinal Products (the "**CRM**") (*Commissie Tegemoetkoming van Geneesmiddelen (CTG)/Commission de remboursement des médicaments (CRM)*) within the NIHDI.[16] The final reimbursement decision will be taken by the Minister of Social Affairs and Public Health on the advice of the CRM.[17] The reimbursement application must be submitted simultaneously with the separate pricing application.[18] Contrary to the reimbursement procedure – which is a competence of the Minister of Social Affairs and Public Health – the Minister of Economic Affairs is responsible for setting the maximum price of the medicinal product (see below, under section "How are drug prices set? What is the relationship between pricing and reimbursement?", "Pharmaceutical pricing and reimbursement").

The RD Reimbursement includes specific timelines for the reimbursement advice by the CRM and the final decision by the Minister. The standard procedure may not take more than 180 calendar days (subject to suspension).[19]

The decision to reimburse a medicinal product will be taken after evaluation of the reimbursement criteria: (i) the therapeutic value of the medicinal product; (ii) the price and the proposed reimbursement basis; (iii) the importance of the medicinal product in the medical practice in relation to the therapeutic and social needs; (iv) the impact on healthcare expenditures; and (v) the relation between the healthcare cost and the therapeutic value of the medicinal product.[20]

The CRM will first assess and appraise the therapeutic value of the medicinal product, which is expressed in three classes, whereby classes 2 and 3 are further divided into three sub-classes (i.e. class 2A, 2B, 2C and class 3A, 3B and 3C):[21]

- class 1: includes medicinal products with proven therapeutic added value compared to existing therapeutic alternatives;
- class 2: includes medicinal products without proven therapeutic added value compared to existing therapeutic alternatives, and that are not included in class 3; and
- class 3: includes generic medicinal products and medicinal products approved on the basis of a bibliographic application.

Depending on the (sub-)class in which a medicinal product is ranked, different reimbursement procedures and timelines apply.[22] For example, for medicinal products ranked in sub-classes 2A or 3A, a simplified administrative reimbursement procedure exists

which does not require the involvement of the CRM, and under which a reimbursement decision must be taken by the Minister within 60 calendar days.[23] As for medicinal products ranked in sub-classes 2C, 3B or 3C, the procedure may not take more than 90 calendar days.[24] For all other medicinal products, the standard period of 180 calendar days will apply.[25] It is to be noted that the RD Reimbursement includes specific procedures with respect to parallel imported medicinal products, orphan medicinal products and biosimilars.[26]

Moreover, depending on the (sub-)class in which the medicinal product is ranked, the CRM will evaluate different reimbursement criteria to formulate a (positive or negative) reimbursement proposal. For example, when a medicinal product is ranked in class 1, all reimbursement criteria included in Article 4 of the RD Reimbursement must be weighed to formulate the reimbursement proposal. Otherwise, when a medicinal product is ranked in sub-class 2B, 2C, 3B or 3C only the reimbursement criteria (i)–(iv) as set out above must be evaluated.[27]

The CRM's reimbursement proposal not only sets forth the committee's position with regard to the class of added value, but also with regard to the reimbursement modalities (including the reimbursement category, the reimbursement group and the reimbursement conditions),[28] the reimbursement basis (see below under section "How is the reimbursement amount set? What methodology is used?", "Pharmaceutical pricing and reimbursement"), as well as whether the specialty will be subject to a periodic individual review.[29]

The Minister makes the final reimbursement decision on the basis of the reimbursement proposal made by the CRM and after having obtained the approval of the Minister of Budget. The Minister is allowed to deviate from the CRM's proposal, but only for social and/or budgetary reasons.[30] If the Minister takes a positive reimbursement decision, the medicinal product will be included on the list of reimbursable pharmaceutical specialties. The final decision of the Minister will be published on the website of the NIHDI.[31] Negative reimbursement decisions can be challenged by the applicant before the Council of State (*de Raad van State/le Conseil d'Etat*). If the Minister does not take a reimbursement decision within the period of 180 days (or any other period imposed by the RD Reimbursement), the reimbursement application shall be deemed approved by the Minister.[32]

Once the product is included on the list, the RD Reimbursement includes specific procedures to amend the reimbursement modalities or remove medicinal products from the list.[33]

How is the reimbursement amount set? What methodology is used?

If the application for reimbursement is assessed positively, the medicinal product will be included on the list of reimbursable pharmaceutical specialties. However, this does not entail that the product will be fully reimbursed by the health insurance. Based on the proposal of the CRM, the medicinal product will be attributed a reimbursement category. A distinction is made between seven reimbursement categories (A, B, C, Cs, Cx, Fa and Fb).[34] The reimbursement categories indicate to what extent the medicinal product will be reimbursed by the health insurance and what amount must be co-payed by the patient. Depending on the reimbursement category in which the medicinal product is ranked, the health insurance will either reimburse the complete cost of the medicinal product, or only a certain percentage thereof. As indicated above under section "Who is/are the payors", "Pharmaceutical pricing and reimbursement", the patient contribution is determined and limited by law.

Category A and Fa include vital medicinal products, such as medicinal products for the treatment of cancer or diabetes. Medicinal products included in category A and Fa shall be fully reimbursed and represent up to 15% of public expenditure on medicinal products. Categories B and Fb cover therapeutic essential medicinal products, such as antihypertensives and account for approximately 80–85% of public expenditure on medicinal products. Medicinal products that are ranked in category B and Fb shall be reimbursed at 75%–85% of the reimbursement base for non-hospitalised patients and at 100% for hospitalised patients. Medicinal products intended for symptomatic treatment are ranked in category C, which corresponds with a general reimbursement rate of 50%. Category C covers, for example, the influenza vaccine, providing a general reimbursement rate of 40%. Category Cx includes contraceptives with a general reimbursement rate of 20%. Categories C, Cs and Cx represent a minor percentage of public expenditure on medicinal products. Non-reimbursed medicinal products, such as sleeping pills or tranquilisers, are included in the so-called "category D".[35]

These reimbursement rates must be applied on the reimbursement basis. The reimbursement basis shall in principle be equal to the public price (see below under section "How are drug prices set? What is the relationship between pricing and reimbursement?", "Pharmaceutical pricing and reimbursement").[36] However, for example, for medicinal products containing the same active substance, a reference reimbursement system applies which reduces the reimbursement basis of the original medicinal products from the moment a generic version is introduced. This reference reimbursement system is also referred to as the "patent cliff". After application of the patent cliff, the reimbursement basis shall be lower than the public price initially determined by the Minister of Economic Affairs (see below, under section "How are drug prices set? What is the relationship between pricing and reimbursement?", "Pharmaceutical pricing and reimbursement").

From the moment a reimbursed generic version of the original medicinal product is introduced on the market, a so-called "reference cluster" is opened, including the original medicinal product and its generic version(s). The opening of such a reference cluster does not only have an impact on the reimbursement basis of the original medicinal product, but also on the public price of the original product.

Following the opening of a reference cluster, the reimbursement basis of the original product will automatically be reduced by a certain percentage. In principle, a reduction of 43.64% will occur. For medicinal products ranked in reimbursement category A, a reduction of 51.52% will occur. It should be noted that there are exceptions to the aforementioned percentages; for example, for injectable medicinal products, a reduction rate of 23.37% and 27.82% (if the medicinal product is ranked under reimbursement category A) will apply. This reduction rate shall be applied on the ex-factory price.

A lower reimbursement basis entails a lower contribution by the health insurance, which means that the original medicinal product will become more expensive for the patient. Following the reduction of the reimbursement basis, the applicant must therefore choose one the following options:

(i) decrease the public price (or in the absence thereof, the ex-factory price) of the original medicinal product to the level of the new reimbursement basis increased by a safety margin of 25% of the new reimbursement basis; the safety margin may, however, never exceed €5.00; or

(ii) decrease the public price (or in the absence thereof, the ex-factory price) of the original medicinal product to a level, higher than the new reimbursement basis, but lower than

the public price calculated under (i); or

(iii) decrease the public price (or in the absence thereof, the ex-factory price) to the level of the new reimbursement basis; or

(iv) remove the medicinal product from the list.

Pharmaceutical companies must decide themselves whether to lower the public price of the original medicinal product to the reimbursement basis or to pass on the safety margin to the patient. If the applicant does not choose between these four options, option (iii) will automatically be applied.[37]

It is to be noted that the Minister of Social Affairs and Public Health has recently introduced a new reimbursement system pursuant to which an original medicinal product shall no longer be reimbursed if that product continues to be more expensive compared to "the least costly" alternatives on the market, at least 21 months after the application of the patent cliff (see below under section "Policy issues that affect pricing and reimbursement").

How are drug prices set? What is the relationship between pricing and reimbursement?

The main pricing rules are included in:

- Book V, Section 2 of the Code of Economic Law;
- the Royal Decree of 10 April 2014 establishing the admissibility conditions, time frames and practical modalities concerning pricing and price increase requests, pricing notifications and (price)communications of medicinal products, objects, appliances, substances assimilated to medicinal products and raw materials, as referred to in Book V of the Code of Economic Law (the "**RD Pricing**"); and
- the Ministerial Decree of 17 June 2014 determining the objects, appliances and substances assimilated to medicinal products referred to in Book V of the Code of Economic Law, and determining the maximum prices and maximum margins for medicinal products, objects, appliances and substances assimilated to medicinal products (the "**MD Pricing**").

The prices of medicinal products are subject to a price control by the Price Department of the Federal Public Service ("**FPS**") for Economic Affairs.[38] Price determination and price increases are a competence of the Minister of Economic Affairs, which determines the maximum ex-factory price on the advice of the Price Department.[39] The applicant must submit its pricing dossier, justifying the requested ex-factory price, to the Price Department. This dossier must include, *inter alia*: the pharmaceutical form, indication and dosage of the product; the therapeutic improvements (if any) of the product; a copy of the marketing authorisation, the cost structure; a copy of the applicant's annual accounts for the past three years; and an overview of the market and the competition conditions (including a comparison with the prices applied in the EU Member States and the prices of comparable medicinal products marketed in Belgium).[40] The Minister of Economic Affairs determines the price on the basis of the scientific and economic information submitted by the applicant.

As mentioned above, the pricing procedure and the reimbursement procedure run in parallel. The pricing procedure differs depending on whether reimbursable or non-reimbursable medicinal products are involved.[41] After completion of the pricing procedure, the Minister of Economic Affairs will determine the maximum ex-factory price. The ex-factory price is the sales price, excluding VAT, which can be charged by the applicant to the wholesaler (or pharmacist). The ex-factory price will be communicated to the applicant via registered mail, in general, within a period of 90 calendar days.[42] The applicant may file an appeal against this pricing decision with the Council of State.

After determination of the maximum ex-factory price by the Minister of Economic Affairs, the applicant must inform the Price Department of the actual ex-factory price that will be applied. If afterwards, the applicant decides to reduce the ex-factory price communicated to the Price Department, the applicant must again give notice of such reduction to the Price Department. This reduced ex-factory price shall then be the new, admissible ex-factory price.[43] A specific procedure applies for increasing the ex-factory price; this procedure is similar to the procedure for obtaining the initial ex-factory price.[44]

The ex-factory price forms part of the maximum price charged to the patients, which is referred to as the "maximum public price". The maximum public price shall, on the request of the applicant, be calculated by the Price Department and communicated to the applicant.[45] The maximum public price is a sum of (i) the ex-factory price, (ii) the pre-defined profit margin for the wholesaler, (iii) the pre-defined profit margin for the pharmacist, (iv) a fee for the pharmacist (if reimbursable medicinal products are involved), and (v) the VAT (currently 6%).[46] The aforementioned pre-defined profit margins for wholesalers and pharmacists will always be maximum margins,[47] meaning that the wholesalers and pharmacists may not apply higher profit margins when selling the medicinal product, respectively, to the pharmacist or the patient.

Issues that affect pricing

The entering into the market of generics and biosimilars has an important impact on the price of the original medicinal product; competition with generics and biosimilars forces pharmaceutical companies to reduce their prices. Innovative pharmaceutical companies are therefore often looking for strategies and practices to maintain a competitive market share. Compliance of these practices with applicable competition laws should always be carefully scrutinised.

European competition law equally applies to marketing authorisation holders, wholesalers and pharmacists. Article 101 of the Treaty on the Functioning of the European Union (the "**TFEU**") prohibits business agreements, cartels or any other arrangements that prevent, restrict, or distort competition within the internal market and affect trade between the Member States. In addition, Article 102 of the TFEU is aimed at preventing undertakings who hold a dominant position in a market from abusing that position.

In 2008, the European Commission launched a sector inquiry aimed at uncovering the causes of low levels of competition in the pharmaceutical sector in the Member States. Following this inquiry, several pharmaceutical companies have been fined by the European Commission for performing certain anti-competitive practices including the conclusion of the so-called "pay-for-delay agreements" and the creation of patent clusters.[48] These anti-competitive practices prevent generic companies from entering the market, and therefore keep prices at a high level. In addition, as innovative pharmaceutical companies are often dominant companies, the granting of discounts and rebates may also lead to a violation of European competition law if these discounts and rebates result in the exclusion of competitors.

Policy issues that affect pricing and reimbursement

The Belgian government is under pressure from the European Commission to make budget savings in order to meet its fiscal deficit target. However, expenditure on medicinal products is increasing fast, resulting in great pressure on the health budget. In order to keep expenditure within a reasonable boundary, several cost-containment measures have been or are being taken.[49]

One of these measures is the introduction of the reference reimbursement system or the patent cliff. As mentioned above under section "How is the reimbursement amount set? What methodology is used?", "Pharmaceutical pricing and reimbursement", once a generic version enters the market, a reference reimbursement system applies, pursuant to which the reimbursement basis and the public price of the original medicinal product will automatically be reduced.

The purpose of this reference system is twofold. On the one hand, the reference system is intended to stimulate competition by encouraging innovative pharmaceutical companies to lower their prices. If the original product becomes more expensive for the patient, innovative pharmaceutical companies will be forced to lower the price of their product in order to stay competitive. On the other hand, the reference system is also an important means to keep expenditure on medicinal products within bounds, as its application results in a lower contribution by the health insurance. Physicians are also encouraged to prescribe products that are less expensive because of the need for budget control.[50]

In addition, the Minister of Social Affairs and Public Health has recently introduced a new reimbursement system, pursuant to which an innovative medicinal product shall no longer be reimbursed if that product continues to be more expensive compared to "the least costly"[51] alternatives on the market, at least 21 months after the application of the patent cliff. Only medicinal products included in the category "the least costly medicinal products" shall remain reimbursed.[52] This new regime should encourage innovative pharmaceutical companies to lower their prices faster, and at the latest within 21 months after the application of the patent cliff. The new regime should also allow the health insurance to free additional budget that can be invested in the reimbursement of innovative medicinal products.[53]

Emerging trends

There are a couple of noticeable emerging trends originating from the main fundamental challenge in pricing and reimbursement policies: in times of budget scarcity, how to ensure that patients have access to medicinal products that effectively positively impact their quality of life; in other words, in deciding on the price and reimbursement of a medicinal product, how to secure and enhance the cost-benefit balance ("cost-effectiveness").

First of all, there is an increased use of managed entry agreements. These agreements are often concluded for medicinal products whose therapeutic added value, impact on healthcare expenditure and cost-effectiveness are still uncertain, but for which patient access is preferred. Through these agreements, the payor tries to manage and monitor said uncertainties and the risks in relation thereto. In this respect, the product obtains a temporary reimbursement status for a period of minimum one and maximum three years, with the possibility of renewal.[54] The final reimbursement decision will be postponed to the end of the term of the agreement and can be linked to financial conditions (e.g. price discounts), the achievement of certain health outcomes ("performance criteria"), or the gathering of additional evidence.[55] The managed entry agreements are, therefore, also called "pay-for-performance" agreements.

These managed entry agreements were introduced in 2010 and have been frequently concluded since. However, these agreements came under fire when the Federal Knowledge Center (the "**KCE**") published a report in which these agreements were evaluated.[56] The KCE states that these agreements are often used to negotiate price discounts and that the additional evidence gathered – which is often a condition under the agreement – is rather poor. However, once the product is reimbursed through a managed entry agreement, it will be difficult for the Minister to come back on his/her decision; this does not encourage

pharmaceutical companies to meet the condition of gathering additional evidence. Further issues include the lack of transparency, given that the specific terms and details of these agreements are not publicly available. In its report, the KCE stresses that the conclusion of these agreements should stay exceptional and be limited to situations where they are clearly beneficial for the patients.

A second emerging trend is that authorities start to cooperate internationally to help each other in assessing the aforementioned cost-benefit ratio. This cooperation may take place through mutual recognition of assessments, sharing of (non-confidential) information and expertise, the joint negotiation of managed entry agreements, and the elaboration of common assessment reports. However, as the final decision is still taken by the competent national authority on the basis of its national system, decisions may still diverge from one participating country to another.

A third trend is that authorities clearly advocate a gradual shift from a so-called supply-driven reimbursement system ("industry proposes, payor disposes") to a more demand-driven system whereby only medicinal products that address an unmet medical need are eligible for reimbursement. Such unmet medical needs would be determined on the basis of field needs expressed by physicians, regulators and payors. The early temporary reimbursement procedure, which provides for reimbursement of medicines that have been granted early temporary access (e.g. through compassionate use approval, medical need programmes), could be seen as an example of such new approach which is entirely driven by the "unmet medical need" rationale.

Another important trend is the shift towards personalised healthcare solutions. Personalised or precision medicine allows for the development of healthcare solutions that are tailored to a specific (and smaller) sub patient population based on the patient's genetic profile and characteristics. Through personalised medicine, patients receive treatments that are adequate and effective for them, and as the European Parliament states in its briefing on personalised medicine of October 2015, "*the aim of personalised medicine is generally perceived to be the* '*right treatment for the right person at the right time*'".[57] The success of these innovative, personalised healthcare solutions largely depends on the use of companion diagnostics, however, which are key to delivering personalised medicine. Companion diagnostics are in vitro diagnostic tests (i.e. medical devices), and essentially biomarker tests, through which the effectiveness of a specific medicinal product for the patient taking the test can be determined. Consequently, companion diagnostics are very important tools in the context of precision medicine.

However, reimbursement pathways for medicinal products and their biomarker (companion diagnostic) are currently not synchronised. To facilitate access to personalised medicine, the INAMI proposed a new simultaneous reimbursement procedure for medicinal products and their biomarkers by introducing a new Chapter VIII in the RD Reimbursement. This new Chapter VIII will include all medicinal products for which reimbursement depends on the result of the biomarker test, as well as a list of the linked biomarkers. If the Minister decides to reimburse the medicinal product in Chapter VIII, the linked biomarker will simultaneously be included to the list, and reimbursed. This new procedure is expected to enter into force mid-2019.

Successful market access

While obtaining marketing authorisation is a prerequisite and a necessity, it is not the only determinant of successful market access. Obtaining an official price and reimbursement for

the medicinal product are also critical to ensure effective market access. Pharmaceutical companies must have a deep understanding of the market and develop a comprehensive market access strategy, which includes a pricing and reimbursement strategy.

To ensure successful market access at the level of pricing and reimbursement, early engagement and communications with the various actors that impact the pricing and reimbursement process (including the representatives of the Minister of Social Affairs and Public Health and the Minister of Economic Affairs, the NIHDI and persons active in the healthcare sector) are essential. In addition, successful reimbursement means starting early in order to prepare your dossier adequately; pharmaceutical companies must gather sufficient evidence to demonstrate, *inter alia*, the therapeutic value of the medicinal product, the importance of the product in practice and its cost-effectiveness.

A deep understanding of the evidentiary requirements combined with early and close interactions with stakeholders, is the ultimate key to increase the likelihood of success.

* * *

Endnotes

1. Belgium Pharmaceuticals & Healthcare Report Q4 2017.
2. https://socialsecurity.belgium.be/nl/netwerk/rijksinstituut-voor-ziekte-en-invaliditeitsverzekering-riziv.
3. KCE Report 138 – "The Belgian health system in 2010" (https://kce.fgov.be/sites/default/files/atoms/files/KCE_138C_The_belgian_health_system_second_print.pdf).
4. http://www.coopami.org/fr/coopami/realisation/2017/pdf/2017051103.pdf.
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6. Article 6*bis* of the Law of 25 March 1964 concerning the medicinal products (the "Medicines Act").
7. EMA – Guideline on similar biological medicinal products (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf).
8. EMA – Biosimilars in the EU: Information guide for healthcare professionals (http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf).
9. Article 6*bis* of the Medicines Act.
10. EMA – Biosimilars in the EU: Information guide for healthcare professionals (http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf).
11. Article 6, §1*bis* of the Medicines Act.
12. https://economie.fgov.be/nl/themas/verkoop/prijsbeleid/gereguleerde-prijzen/geneesmiddelen-voor-menselijk.
13. Article 2 of the Royal Decree of 7 May 1991 on the establishment of the patient contribution.
14. On 15 March 2018, the new RD Reimbursement has been published in the Belgian State Gazette. The RD Reimbursement repeals the Royal Decree of 2001 and applies

to all reimbursement applications submitted as from 1 April 2018. For applications submitted prior to 1 April 2018, the procedures and timelines included in the text of the Royal Decree of 2001, will apply. This contribution sets out the rules and procedures included in the new RD Reimbursement as applicable to applications submitted as from 1 April 2018.

15. Article 6 of the Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems (the "**Transparency Directive**"); Article 35*bis* of the NIHDI Act and Article 2 of the RD Reimbursement; the positive list is included in an appendix to the RD Reimbursement.
16. Article 10 of the RD Reimbursement.
17. Article 3, §1 of the RD Reimbursement; note that for some medicinal products a simplified administrative procedure exists which does not require the involvement of the CRM (see Articles 50–54 of the RD Reimbursement).
18. Article 10 of the RD Reimbursement.
19. Article 15, §1, 3rd paragraph of the RD Reimbursement.
20. Article 35*bis*, §2 of the NIHDI Act; Article 4 of the RD Reimbursement.
21. Article 35*bis*, §2 of the NIHDI Act; Article 5 of the RD Reimbursement.
22. Procedure class 1 medicinal products: see Articles 16–22 of the RD Reimbursement; Procedure class 2B medicinal products: see Articles 23–29 of the RD Reimbursement; Procedure class 2C medicinal products: see Articles 30–36 of the RD Reimbursement; Procedure class 3B and 3C medicinal products: see Articles 37–42 of the RD Reimbursement; Procedure class 2A and 3A medicinal products: see Articles 50–54 of the RD Reimbursement.
23. Article 15, §1, 1st paragraph of the RD Reimbursement.
24. Article 15, §1, 2nd paragraph of the RD Reimbursement.
25. Article 15, §1, 3rd paragraph of the RD Reimbursement.
26. Procedure parallel imported medicinal products: see Articles 43–49 of the RD Reimbursement; procedure orphan medicinal products: see Article 55 of the RD Reimbursement; procedure biosimilars: see Articles 56–58 of the RD Reimbursement.
27. Article 6 of the RD Reimbursement.
28. Note that medicinal products with similar reimbursement conditions are included in the same reimbursement group. For example, cardiovascular medicinal products are included in reimbursement group I. Some medicinal products reimbursement shall only be reimbursed upon certain conditions. These conditions can, for example, relate to the need for diagnostic examination, the maximum dosage, the age of the patients, etc.
29. Articles 20, 27, 34 and 40 of the RD Reimbursement.
30. Articles 20, 27, 34 and 40 of the RD Reimbursement.
31. Articles 3, §1 of the RD Reimbursement; see http://www.riziv.fgov.be.
32. Articles 22, 29, 36, 42 and 54 of the RD Reimbursement.
33. Articles 59–89 of the RD Reimbursement.
34. Article 2, §1 of the Royal Decree of 7 May 1991 on the establishment of the patient contribution.

35. Article 2, §1 of the Royal Decree of 7 May 1991 on the establishment of the patient contribution; Belgium Pharmaceuticals & Healthcare Report Q4 2017.
36. Article 35bis, §2*bis* of the NIHDI Act.
37. Article 35ter, §3 of the NIHDI Act.
38. Article 3, §1 of the RD Pricing.
39. Article V.10, §1 of the Code of Economic Law.
40. Article 3, §2 of the RD Pricing.
41. As specified in the RD Pricing.
42. Article 3, §6 of the RD Pricing.
43. Article 3, §9 and §10 of the RD Pricing.
44. Article 4 of the RD Pricing.
45. Article 3, §7 of the RD Pricing.
46. Article 35*octies*, §1 of the NIHDI Act.
47. As specified in the MD Pricing.
48. http://ec.europa.eu/competition/sectors/pharmaceuticals/antitrust_en.html.
49. Belgium Pharmaceuticals & Healthcare Report Q4 2017.
50. Articles 73 and 146*bis* of the NIHDI Act.
51. For the qualification of "least costly" see Article 73, §2 of the NIHDI Act.
52. Article 35*quater*/1 of the NIHDI Act.
53. http://www.deblock.belgium.be/nl/de-tijd-duur-medicijn-niet-altijd-meer-terugbetaald.
54. Article 116 of the RD Reimbursement.
55. KCE Report 288 – "How to improve the Belgian process for managed entry agreements? an analysis of the Belgian and international experience" (https://kce.fgov.be/sites/default/files/atoms/files/KCE_288_Improve_Belgian_process_managed_entry_agreements_Report.pdf).
56. KCE Report 288 – "How to improve the Belgian process for managed entry agreements? an analysis of the Belgian and international experience" (https://kce.fgov.be/sites/default/files/atoms/files/KCE_288_Improve_Belgian_process_managed_entry_agreements_Report.pdf).
57. http://www.europarl.europa.eu/RegData/etudes/BRIE/2015/569009/EPRS_BRI(2015)569009_EN.pdf.

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Brazil

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General considerations

In Brazil, pharmaceutical products are governed by a comprehensive and complex regime of legislation and regulations spanning many different areas of law. The legislative and regulatory landscapes are also very dynamic, as patent laws are constantly under review and government authorities constantly update regulatory processes and policies.

In the Brazilian health regulatory system, introduced by Law No. 6,360/76, any drug may be marketed only if: (i) it has been previously registered with the National Agency of Health Surveillance (ANVISA), according to Law No. 9,782/99; and (ii) its price has been established by the Drug Market Regulation Chamber (CMED), as per Law No. 10,742/03.

Concerning access to drugs, as the healthcare system is primarily public in Brazil, in many cases, patients do not have out-of-pocket expenses, inasmuch as drugs considered to be essential to public health are provided by the Government.

In the private healthcare system, health insurance companies must supply patients at least with drugs included in the List of Procedures issued by the National Agency of Supplementary Health – ANS.

Regulatory submission of drug application

In the Brazilian health regulatory system, Law No. 6.360/76 establishes that a drug may only be marketed if it has been previously registered with the Ministry of Health:[1]

> *Article 12— No product to which this Act refers, including the imported ones, may be manufactured, marketed or released before registration with the Ministry of Health.*[2]

The marketing approval, issued by ANVISA, is the effective authorisation for manufacturing and marketing of a drug in Brazil. ANVISA issues marketing approval for the following kinds of drugs: (i) non-biological drugs, which are divided into (a) reference drugs, (b) similar drugs, and (c) generic drugs; (ii) biological products, which are divided into (a) new biological products and (b) biological products; and (iii) herbal medicines.

Legal framework

There are three marketing approval categories for non-biological drugs: (i) reference drugs, (ii) branded generic drugs, and (iii) non-branded generic drugs.

A *reference drug*[3] is defined as the "innovative product registered with the Federal authority responsible for the health surveillance and marketed in the Country, whose efficacy, safety and quality were scientifically proven before the pertinent federal authority, by the time of the registration."

A *branded generic drug* is that which "contains the same active ingredient(s), has the same concentration, dosage form, administration route, dosage administration and therapeutic recommendation, it is equivalent to the drug registered with the federal authority responsible for the health surveillance, and it may differ only in characteristics relative to the product size and form, expiration term, packaging, labeling, excipients and vehicles, and it must always be identified by trade name or brand".[4]

A *non-branded generic drug* is a "drug similar to a reference or innovative product, that is intended to be interchangeable, usually manufactured after the expiration or waiver of the patent protection or other exclusivity rights, with proven efficacy, safety and quality, and assigned by DCB or DCI, when the first one is absent."[5] The similarity between the generic drug and reference drug is proven by pharmaceutical equivalence study results and relative bioavailability/bioequivalence study results.

Pharmaceutical equivalents[6] are drugs that contain the same dosage form, the same administration route and the same quantity of the same active ingredient; that is, the same salt or ester of the therapeutically active molecule, and may or may not contain identical excipients as long as well established for the intended function. They must comply with the same updated specifications of the Brazilian Pharmacopoeia, preferably, or with other codes authorised by ANVISA, or, in the absence of those, with other quality and performance standards. Pharmaceutical forms of modified release that use reservoir or excess systems may or may not contain the same amount of active ingredient, provided that they release identical amount of the same active ingredient in the same dosage interval.

Bioequivalent drugs[7] are those proven to have equivalent bioavailability under the same experimental conditions."[8]

The registration of biological products, on the other hand, is regulated by ANVISA´s Resolution RDC 55/2010. Biological products are defined as drugs that have, as their active ingredient: (i) molecules extracted directly from microorganisms, organs, or tissues of animal origin, or cells or fluids of human or animal origin ("biological origin"); or (ii) molecules produced by the process of genetic modification ("biotechnological origin").[9]

Drugs considered to be biological products are (i) vaccines; (ii) hyperimmune serum; (iii) blood derivatives; (iv) biodrugs, including (a) drugs obtained from biological fluids or animal tissues, and (b) drugs obtained from biotechnology procedures; (v) monoclonal antibodies; and (vi) drugs containing live, attenuated, or dead microorganisms.[10]

RDC 55/2010 makes a distinction between "new biological products", which are biological products that have not previously been registered in Brazil, and "biological products", which contain a molecule with known biological activity that has previously been registered in Brazil.

Only non-biological products are interchangeable – that is, the patient is able to choose whether he or she will acquire the reference or the generic (branded and non-branded) drug if the physician prescribes it by the reference brand or by its International Nonproprietary Name (INN). Although Resolution RDC 55/2010 does not address interchangeability, the Brazilian sanitary law states that only non-biological drugs (reference and generics) are interchangeable. Therefore, considering that a biological product cannot be considered a generic of a new biological product, both are not interchangeable.

Reference drugs

The registration of new drugs is regulated by Resolution RDC 200/2017. An applicant for a new drug must submit to ANVISA a dossier containing: information related to the

company; information related to the drug (composition of the drug, technical information regarding the active ingredient, shelf life, etc.); and reports of preclinical and Phase 1, 2 and 3 clinical trials, in order to prove the quality, safety, and efficacy of the new drug. The applicant must also present a copy of the Good Manufacturing Process (GMP) Certificate issued by ANVISA to the manufacturing facility and, if applicable, the local labelling site.

Generic drugs (Branded and non-branded)

The registration of non-branded and branded generics is regulated by ANVISA's Resolution RDC 200/2017.

It is not necessary to perform clinical trials in order to prove the safety and efficacy of branded or non-branded generics. The rationale is that clinical trials have already been performed on the reference drug.[11] Instead, the applicant must prove that its branded or non-branded generic drug is bioequivalent to the reference drug. If the applicant can prove bioequivalency, ANVISA will assume that the branded and/or non-branded generic drug is safe and effective by relying on the clinical data that was evaluated during the registration of the new drug.

An applicant seeking approval of a generic drug must therefore submit to ANVISA a dossier which includes information related to the company; details of the drug (composition of the drug, active ingredient, technical information, shelf life, etc.); and reports of relative bioavailability/bioequivalence studies. The applicant must also submit GMP Certificates for the manufacturing facility and local labelling site.

Biological products

The marketing approval of biological products in Brazil is regulated by ANVISA Resolution RDC 55/2010.

Biological products are defined as drugs that have as their active ingredient: (1) molecules extracted directly from microorganisms, organs, tissues of animal origin, or cells or fluids of human or animal origin ("biological origin"); or (2) molecules produced by the process of genetic modification ("biotechnological origin").[12]

Drugs considered to be biological products are: (1) vaccines; (2) hyperimmune serum; (3) blood derivatives; (4) biodrugs, including (a) drugs obtained from biological fluids or animal tissues, and (b) drugs obtained from biotechnology procedures; (5) monoclonal antibodies; and (6) drugs containing live, attenuated, or dead microorganisms.[13]

RDC 55/2010 makes a distinction between "new biological products", which are biological products that have not previously been registered in Brazil, and "biological products", which contain a molecule with known biological activity that has previously been registered in Brazil.

In order to apply for marketing approval in Brazil for biological drugs (either new or follow-on), it is necessary to submit a dossier to ANVISA proving that the product meets the standards for quality, safety, and efficacy as defined by sanitary laws.

In summary, the dossier must contain: (1) the name of the manufacturer; (2) the country of manufacture of the active ingredient(s), the bulk biological product, the biological product in its primary package, and the finished biological product; (3) the quality control tests conducted on the active ingredient, the bulk biological product, and the finished biological product batches; (4) the site where the respective quality control tests will be conducted; and (5) the product specifications.

The applicant must also indicate the name of the manufacturer of the active ingredient and of the biological product in its primary package, if the applicant is not the manufacturer.

As to the evidences of safety and efficacy, for *new biological* drugs, the applicant must submit to ANVISA a dossier containing reports of preclinical and clinical trials Phase I, II and III. Exceptionally, the application may be submitted with Phase III clinical trials still in progression, when it is proved that the product has high therapeutic or preventive efficacy, or there is no approved treatment for the disease intended to be treated by the new biological drug.

Marketing approval for *follow-on biological products*, on the other hand, may be obtained by either the individual development route or the comparability route.

By the individual development route, the applicant must submit reports of preclinical and clinical trials. The results of the Phase III clinical trial must be comparative (i.e., demonstrate noninferiority, clinical equivalence, or superiority), whereas Phases I and II clinical trials need not be comparative.

By the comparability route, the applicant must provide a report proving that its product is comparable to the comparator product. This report must provide a comparative analysis between the two products at all stages of development, including the manufacturing of the molecule as well as a comparison of the products' stability, purity, impurity profile, and so on. The applicant must also provide nonclinical trial reports designed to detect significant differences between the biological product and the comparator product. The applicant must file reports of: (1) pharmacokinetics studies; (2) pharmacodynamic studies; and (3) pivotal studies regarding safety and efficacy. Such studies must also be compared with the comparator product.

Biological drugs that have been manufactured in other countries will only be registered in Brazil if the products have marketing approval in those other countries.

Finally, ANVISA allows the follow-on biological product to be identified by the very same nonproprietary name of active pharmaceutical ingredient of the new biological product, even though there is no interchangeability between such products, since they are not considered therapeutic equivalents by the legislation in force.

Simplified procedure for marketing approval

Since May 2014, with the enactment of Resolution RDC 31/2014, ANVISA established a simplified procedure for the approval, post-approval, and renewal of "clone" drugs comprising: (1) branded and non-branded generic drugs; (2) branded copies of "similar" drugs; (3) specific, dynamised (namely, homeopathic), and herbal drugs; and (4) biological products.

According to Resolution RDC 31/2014, ANVISA is responsible for simplifying and accelerating the granting of marketing approval of such products through the "clone procedure," in which a primary clone application for a clone drug is filed before ANVISA. The marketing approval of a clone drug is connected to the marketing approval of a "mother drug", a product that has been previously registered through the regular approval procedure. The primary clone application is a simplified application that is linked to the technical and clinical reports of a "mother application", and may only differ from the mother drug in brand name, packaging layout, and the wording of the package insert and labelling.

Under Article 15 of RDC 31/2014, the grant of marketing approval of the primary clone application is subjected to the analysis of the following documents by ANVISA: (1) receipt of payment of the necessary administrative fees; (2) forms FP1 and PF2 (available on ANVISA's website); and (3) declaration of the connection to the mother application pursuant to Annex I.[14] Where applicable to the category of drug, the package wording and layout, as well as the drug name and differential supplement, are also examined.

Regulatory pathway for conducting clinical trials in Brazil

The legal framework concerning clinical trials in Brazil relates mainly, but not restrictively, to Resolution No. 466/2012 of the National Council of Health (CNS). This resolution establishes the guidelines for conducting clinical trials. This legal framework emphasises the main ethical aspects, the institutional ethics committee (CEP) attributes, and the National Commission for Ethics in Research (CONEP) attributes. It also lists the contents of Informed Consent Forms (ICF), protocols, and brochures.

ANVISA's Resolution RDC 09/2015 establishes the list of documents and procedures required for the approval of clinical research concerning drugs.

Brazilian regulatory approval follows a sequential process in which the first step is the translation of the study and/or its submission into Portuguese.[15] In this regard, even though Resolution 09/2015 revoked Resolution 39/2008, which explicitly established the submission of the research protocol in Portuguese, it is highly recommended by ANVISA that all documents are filed in Portuguese, otherwise the technical area might delay the process by ordering the translation.

The first ethical approval must be released by the CEP of the coordinating site. This release is required because it is one of the requirements for submission to CONEP. All trials supported by foreign sponsors require an additional ethical approval from CONEP, whose responsibilities include developing regulations for the protection of subjects in clinical trials.

In terms of coordinating the institutional CEP network, CONEP evaluates protocols relating to human genetics and reproduction, new drugs, procedures, devices, vaccines, and research that involves international cooperation. CONEP reviews the documentation from the coordinating site only. Once the approval is issued, it is extended to the other sites participating in the study.

In respect of the ethical aspects of clinical trials, Resolution 466/2012 established in its item III.3.d that post-trial access must be provided by the study's investigator whenever the drug's effectiveness is demonstrably favourable to the patient. The particularity of Brazilian post-trial access regulation consists in the fact that the supply shall remain for an indefinite period, as long as prescribed by the doctor who is responsible for the study. Last, all clinical protocols carried out in Brazil must be approved by ANVISA. ANVISA is responsible for issuing the Special Communicate (CE).[16] ANVISA also evaluates protocol methodological issues and the relevance of data for future submissions.

For studies sponsored by international companies, ANVISA analyses the clinical trial information. ANVISA will only issue its approval following issuance of approvals from the CEPs. Once satisfied that the approval should be issued, ANVISA issues the Special Communiqué.

All therapeutic activities requested for the pharmaceutical product to be registered must be supported by clinical trial reports. Such clinical trials must be approved by the health authority of the country where the clinical trial was conducted. The clinical trials must also have been conducted with the finished pharmaceutical product presented for registration.

Fast-track pathway for drugs for rare diseases

In December 28, 2017, ANVISA issued Resolution RDC 205/2017, establishing fast-track pathways for rare diseases drugs, which are defined as those destined to treat diseases with prevalence of 65/1000 patients, in relation to clinical studies, Good Manufacture Practice Certificates and marketing approval.

According to Resolution RDC 205/2017, ANVISA may consent to clinical studies without

the opinion of the Research Ethics Committee (CEP); has 30 days to approve the drug clinical development dossier (DDCM); and must issue Good Manufacture Practice Certificates within 120 days of the filing of the request.

Furthermore, ANVISA has up to 60 days as of submission of the marketing approval application to grant approval or to issue an official action.

In order to submit marketing approval application through the fast-track pathway established by Resolution RDC 205/2017, the applicant must at the same time submit the requirement for pricing approval to CMED, and afterwards must commercialise the approved drug within one year of the date of approval.

Pricing

According to Law No. 10,742/2003 and Article 1 of the Drug Market Regulation Chamber (CMED) Resolution No. 02, of March 5, 2004, drug manufacturers shall inform CMED whenever they intend to market new products and new pharmaceutical presentations.

For the purpose of price establishment, drugs with a new molecule, not yet registered in the country, are considered new products, whereas all drugs that contain molecules already registered with ANVISA are considered new pharmaceutical presentations.

New drugs

New products are classified into Categories I and II, according to the following criteria:

Category I comprises new product with a molecule patented in the country that brings gain to the treatment in relation to the drugs already used for the same therapeutic indication, with confirmation of one of the following requirements:

(i) greater efficacy in relation to existing drugs for the same therapeutic indication;

(ii) same efficacy with a significant decrease in the adverse effects; or

(iii) same efficacy with a significant reduction in the global cost of treatment.

The Technical-Executive Committee of CMED may consider other added therapeutic advantages, as long as they are scientifically confirmed, in order to classify a new drug into Category I.

Category II comprises new products that do not fit the definition provided for in Category I.

New presentations

New presentations of products classified into Categories I, II, and V, which may be subsequently launched in the market, shall follow the same category classification originally determined, for a period of five years.

The new pharmaceutical presentations shall be classified into the following categories:

Category III comprises new pharmaceutical presentation of a drug already marketed by the company itself in the same pharmaceutical form.

Category IV comprises a new drug presentation that fits one of the following situations:

(i) drug considered new on the list of the ones marketed by the company, except if it meets the requirements to be classified into Category V;

(ii) drug already marketed by the company, in a new pharmaceutical form.

Category V comprises drugs fitting one of the following situations:

(i) new pharmaceutical form in the country;

(ii) new association of active ingredients already existing in the country;

Finally, Category VI comprises drugs classified as generics, in accordance with Law no. 9,787, 1999, related to item XXI of article 3 of Law No. 6,360 dated 23 September 1976. Sole paragraph.

Requirements for price approval

Drug manufacturers that intend to market new products or new presentations submit an Informative Document to CMED, applying for one of the categories mentioned above and providing CMED with the following information.

Category I

For the classification of a drug into Category I, the Informative Document shall include the following information:

(i) brand name of drug in Brazil and the other brand names for the same drug, used in the countries mentioned in item VII of this paragraph and in the manufacturer's origin country;

(ii) drug approval number and EAN code, both comprised of 13 digits;

(iii) substances from which the drug is formulated;

(iv) copy of package leaflet;

(v) presentation form in which the drug will be marketed;

(vi) the price at which the company intends to market each presentation, with the discrimination of taxes and marketing margins;

(vii) manufacturer's price, accompanied by the due source proof, traded in Australia, Canada, Spain, United States of America, France, Greece, Italy, New Zealand, Portugal, and the manufacturer's price in the product's country of origin, excluding taxes;

(viii) manufacturer's name and the manufacturing site of the active ingredient and the finished drug;

(ix) potential number of patients to be treated with the drug, with the indication of the corresponding period;

(x) cost-efficacy comparative analysis between the drug and the existing therapeutic alternatives;

(xi) presentation of the following information on the product's patent: a) number of the first international patent application, date of application, and the country where it was filed; b) number of patent application at INPI; c) innovation presented by the product which the patent application was based on;

(xii) where available, presentation of economic assessment studies published;

(xiii) phase III clinical trials conducted, which are relevant for the comparison of the new drug with those existing in the country for the same therapeutic indication, if any; and

(xiv) new therapeutic indications for the same drug – in trial, in phase of approval, or approved in other countries, if any.

The Factory Price – FP proposed by the company shall not be higher than the lowest FP applied for the same product in the countries listed in item (vii), taxes being added, as appropriate. In order to check the FP authorised, the product must have been previously marketed in at least three of those countries. If such condition is not met, the Technical-Executive Committee of CMED, considering the public interest, may establish a provisional price, signing a term of commitment by which the company shall commit itself to: (a) submit

the approved provisional price for review every six months, until the product is marketed in at least three of the mentioned countries; (b) publicise the launch of the product and its respective price in the countries mentioned above.

For the conversion of the price expressed in foreign currency into the Brazilian currency Real, the average exchange rate divulged by the Brazilian Central Bank (BACEN, in Portuguese) will be applied, calculated for the period of 60 business days previous to the date of approval of the Report by the Executive Secretariat of CMED. The company may request, until the report's approval, the update of the price proposed in case of significant exchange appreciation or depreciation. In case of appeal against CMED's decision, the average exchange rate published by the Brazilian Central Bank (BACEN) will be applied, calculated for the period of 60 business days previous to the date of the decision, with the purpose of conversion of the expressed price from foreign currency to Real.

Categories II and V

For the classification of the product into Category II or Category V, the Informative Document to be submitted to CMED shall contain the following information:

(i) brand name of drug in Brazil and the other brand names for the same drug, used in the countries mentioned in item VII of this paragraph and in the manufacturer's origin country;

(ii) drug approval number and EAN code, both comprised of 13 digits;

(iii) substances from which the drug is formulated;

(iv) copy of package leaflet;

(v) presentation form in which the drug will be marketed;

(vi) the price at which the company intends to market each presentation, with a breakdown of taxes and marketing margins;

(vii) manufacturer's price, accompanied by the due source proof, traded in Australia, Canada, Spain, United States of America, France, Greece, Italy, New Zealand, Portugal, and the manufacturer's price in the product's country of origin, excluding taxes;

(viii) manufacturer's name and the manufacturing site of the active ingredient and the finished drug;

(ix) phase III clinical trials conducted, which are relevant for comparison between the new drug and those existing in the country for the same therapeutic indication, if any; and

(x) new therapeutic indications for the same drug – in trial, in phase of approval, or approved in other countries, if any.

The FP authorised for the product classified into Category II will be defined based on the cost of treatment with the drugs used for the same therapeutic indication, and it must not be, in any case, higher than the lowest price traded among the countries listed in item (vii) above.

The drug to be used as a comparator will be defined based on an analysis by CMED, which should consider drugs used for the treatment at issue in the country, as well as the existing scientific evidence. The price of the new product must not incur a higher cost of treatment for consumers than the drug chosen as a comparator.

If the company does not market the product in other countries, the price of products with the same active ingredient in the countries listed in item (vii) will be used as reference.

For the drugs classified into Category V, the criteria for establishing the authorised FP shall be the following:

(i) In case of new associations in the country: (a) if the drugs that compose the association are commercialised separately, the association's price must not be higher than the sum of the monodrugs' prices, observing the strength proportion of active ingredients and the number of units, as long as the price does not incur a higher cost of treatment than other treatment(s) already existing; and (b) if the new association replaces, with confirmed advantages, the treatment with the monodrugs already commercialised taken separately, the company may present a justification for the proposed price, the relevance of which shall be assessed by the Technical-Executive Committee of CMED.

(ii) In case of new pharmaceutical forms, the price will be defined based on the cost of treatment with the drugs existing in Brazil for the same therapeutic indication, and it must not be, in any case, higher than the lowest price applied among the countries listed in item (vii) above.

For a drug with an active ingredient in a new pharmaceutical form in the country, that has confirmed gains for the treatment in relation to drugs available in the Brazilian market, the average relative difference of prices applied in the countries listed in item (vii) above shall be used as reference for the price definition. If the gains result from technology developed exclusively in the country, the company may present a justification for the price proposed, which will be assessed by the Technical-Executive Committee.

Categories III, IV and VI

For the classification of the product into Category II or Category V, the Informative Document to be submitted to CMED shall contain the following information:

(i) brand name of drug in Brazil and the other brand names for the same drug, used in the countries mentioned in item VII of this paragraph and in the manufacturer's origin country;

(ii) drug approval number and EAN code, both comprised of 13 digits;

(iii) substances from which the drug is formulated;

(iv) copy of package leaflet;

(v) presentation form in which the drug will be marketed; and

(vi) the price at which the company intends to market each presentation, with a breakdown of taxes and marketing margins.

The Informative Document of the product classified into Category III shall also include the list of all presentations of the drug on the market.

The FP authorised for the product classified into Category III must not be higher than the arithmetic average of the drug presentation prices, with the same strength and pharmaceutical form, already commercialised by the company itself. If there are not presentations with the same strength, the average shall be calculated based on all presentations of the drug, in the same pharmaceutical form, following the criterion of direct proportion of the active ingredient strength. When the modification of the active ingredient strength results in gain to the treatment, the criterion of treatment cost with the drug defined as comparative shall be considered.

The FP authorised for the product classified into Category IV must not be higher than the average price of the drug presentations with the same active ingredient and the same strength available in the market, in the same pharmaceutical form, considered according to the profits from each presentation, based on the following criteria: (i) the average shall be calculated based on presentations of equal strength existing in the market; and (ii) if there are no presentations with equal strength, the average shall be calculated based on all presentations

of the same formula and pharmaceutical form existing in the market, following the criterion of direct proportion of the active ingredient strength.

The FP of products classified into Categories III or IV cannot be higher than the FP of the corresponding reference drug.

The FP authorised for the product classified into Category VI must not be higher than 65% of the price of the corresponding reference drug.

When there is a new presentation of a generic drug already commercialised by the company, the FP authorised for the product classified into Category VI must not be higher than the arithmetic average of the prices of the other generic drug presentations commercialised by the company itself, with the same strength and pharmaceutical form, and it must not be higher than 65% of the price of the corresponding reference drug.

Price Adequacy Coefficient – PAC

According to CMED Resolution No. 02/2004, a compulsory discount for sales directed towards Governmental Entities, called Price Adequacy Coefficient – PAC, must be applied to the FP of products listed in further regulations issued by CMED. The value of PAC shall be updated every year by CMED.

The value of PAC currently in force in Brazil is 19.27% off the FP, as per CMED Ordinance No. 06, of March 30, 2017, and it must be applied to products listed on Annex I of CMED Ordinance No. 15, of August 31, 2017.

Access to drugs

As the healthcare system is primarily public in Brazil, in many cases, patients do not have out-of-pocket expenses, inasmuch as drugs considered to be essential to public health are provided by the Government.

According to Article 196 of Federal Constitution, health is a right of all and a duty of the State. Therefore, in order to organise treatments and the supply of drugs through the Universal Healthcare System (SUS), it was published Law No. 12,401/2011, that created the National Committee for Health Technology Incorporation – CONITEC, which has the purpose of analysing the incorporation of health technologies (treatments, drugs, medical devices, etc.) into SUS.

CONITEC's recommendations are issued based on: (i) scientific evidence regarding efficacy, and safety of drugs; and (ii) economic evaluation of the drugs to be incorporated from the perspective of the public healthcare system. Accordingly, it is highly recommended to provide CONITEC with real-world evidence, in addition to clinical data, in order to evidence the cost-effectiveness of new products and treatments.

According to legal provisions, CONITEC has 180 days to analyse requests to incorporate drugs into SUS. All the reports are submitted to public consultations and after CONITEC´s recommendation, the final decision regarding the incorporation of the drug into SUS, through a Clinical Protocol and Therapeutic Guidelines (CPRG), is made by the Secretary of Science, Technology and Strategic Inputs of the Ministry of Health.

At the private healthcare system, health insurance companies must supply patients at least with drugs included in the List of Procedures issued by the National Agency of Supplementary Health – ANS.

Only drugs with marketing approval granted by ANVISA may be included in both CONITEC's CPRG and ANS' List of Procedures.

For drugs not included in CONITEC's CPRG or ANS' List of Procedures, patients must file lawsuits asking the Courts to order the Government to supply them with the products, based on the mentioned article 196 of Federal Constitution.

The vast majority of judicial precedents regarding this matter are favourable to patients. There are judicial decisions ordering the Government or health insurance companies to provide patients with drugs even if they have no marketing approval granted by ANVISA.

On May 22, 2019, the Supreme Court issued a final decision on the Special Appeal No. 657718, establishing the following requirements for the supply of drugs that are not part of the lists of the SUS.

1. The Government may not be required to supply experimental drugs.
2. The lack of registration with ANVISA prevents, as a rule, the supply of drugs by judicial decision.
3. It is possible, exceptionally, to grant judicial authorisation for a drug not approved in Brazil, in the event of ANVISA's unreasonable delay in reviewing the marketing approval application (longer than that provided for in Law No. 13.411/2016), when three requirements are met:
    i. the existence of a marketing approval application for the drug in Brazil, except in the case of orphan drugs for rare and ultra-rare diseases;
    ii. the drug must be already approved by renowned regulatory agencies abroad; and
    iii. the inexistence of a therapeutic substitute approved in Brazil.
4. Lawsuits requiring the supply of drugs without registration with ANVISA have to be filed against the Federal Government.

The Special Appeal No. 566471, which will discuss the obligation of the Government to supply high-cost drugs to patients, is still pending before the Supreme Court and is expected to be decided in late 2019.

Finally, the Ministry of Health published on June 12, 2019, Ordinance No. 1,297/2019, establishing a pilot project for risk-sharing agreements involving particular therapeutic indications of rare-disease drugs that are not incorporated into the SUS yet. Ordinance No. 1,297/2019 is expected to be the basis for a general regulation on risk-sharing agreements in Brazil.

The main purpose of Ordinance No. 1,297/2019 is to assess the cost-effectiveness of the treatments based on real-world data and estimating the number of patients in the country, seeking to support the evaluation of incorporation of such therapeutic indications in the SUS.

In summary, the risk-sharing agreements to be executed with the owner of the drug shall include the following:

1. reduction of the drug price;
2. description of the disease and eligibility criteria of subgroups of patients benefiting from the risk-sharing agreement;
3. definition of expected health outcome criteria and clinical effectiveness parameters;
4. the maximum number of patients per year who will receive the drug from the Ministry of Health, based on epidemiological criteria and/or estimate of demand, it being established that, beyond such maximum number, the owner of the drug will bear the cost of the drug for the other patients;

5. definition of the criteria for interrupting the supply of the drug to patients who do not present the expected health outcomes, within a defined timeframe, according to the best scientific evidence available, and
6. definition of the periodicity of evaluation of the parameters of clinical effectiveness, according to the best scientific evidence available.

The additional evidence produced through the pilot project of risk-sharing agreements established by Ordinance No. 1,297/2019 shall be submitted to CONITEC within three years.

* * *

Endnotes

1. This requirement is pursuant to ANVISA Bylaw No. 9,782/99.
2. Act No. 6,360/76.
3. Act No. 9,787/99.
4. *Id*.
5. *Id*.
6. ANVISA Resolution RDC 200/2017.
7. *Id*.
8. According to Law No. 9,787 – XXV – bioavailability indicates the velocity and extension of an active ingredient absorption in a dosage form, from its concentration/time curve in the systemic circulation or its excretion in the urine.
9. ANVISA Resolution RDC 55/2010.
10. *Id*.
11. See Law No. 9,787/99 (generic drugs).
12. ANVISA Resolution RDC 55/2010.
13. *Id*.
14. Annex I is a form submitted for both the mother drug and the clone drug requesting marketing authorisation for the clone under the clone procedure.
15. The documentation refers to the translated dossier, including the protocol, investigator brochure, informed consent form, and sponsor and institutional declarations, which are sent to each site's institutional ethics committee (CEP) for review.
16. The Special Communiqué is the official approval document.

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A partner since 2016, Rodrigo Augusto Oliveira Rocci graduated from Mackenzie Presbyterian University School of Law and has been involved and contributed to the department since he joined the firm in 2008, coming from an in-house experience in Sanofi.

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Canada

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Abstract

In Canada, drugs are reimbursed by a combination of public and private payers. Public reimbursement prices are set following a clinical and pharmacoeconomic review and negotiations between the payers and manufacturers. The price charged at the pharmacy is generally the same for both public and private payers and corresponds to the publicly available formulary list price.

Market introduction/overview

Canada has a population of approximately 37 million and it was forecast by the Canadian Institute for Health Information that prescription drug spending in 2018 would be approximately $33.7 billion. Approximately 41.8% of prescription drug spending is funded by public plans. Generic drugs account for approximately 80% of claims.

Healthcare in Canada is primarily, but not exclusively, publicly funded. Prescription drugs, in particular, are reimbursed both publicly and privately. As discussed further below, whether or not a drug is publicly reimbursed depends on: (i) the patient; (ii) the drug; and (iii) the setting. Public plans are administered by the federal government, as well as the provincial and territorial governments, leading to variations in eligibility for public reimbursement depending on a person's public coverage.

In June 2019, a federal Advisory Council on National Pharmacare recommended that the federal government work with provincial and territorial governments to establish a universal, single-payer, public system of prescription drug coverage in Canada. Whether and to what extent the Council's recommendation is implemented is likely to depend on the outcome of an October 2019 federal election.

Pharmaceutical pricing and reimbursement

Regulatory classification

Market authorisation

Drugs are approved by Health Canada. Approval for new drugs is sought by way of a New Drug Submission (NDS). Once Health Canada completes its review and determines that a new drug is safe and effective, the drug receives a market authorisation, known as a Notice of Compliance (NOC), as well as a Drug Identification Number (DIN).

Generic drugs are often approved by way of an Abbreviated New Drug Submission (ANDS), in which safety and efficacy of the generic drug is established by reference to an already-approved innovative product. Generic drugs also receive a NOC and a DIN. When approved

by way of an ANDS, the NOC also includes a declaration of equivalence to the reference product.

Biosimilars are not eligible to be approved by way of ANDS in Canada and must be approved by NDS. Accordingly, biosimilars do not receive a declaration of equivalence.

Prescription vs. non-prescription

Requirements for sale (e.g., a prescription) are set both federally and provincially. Generally, drugs fall into one of four categories:

- Schedule I drugs require a prescription for sale.
- Schedule II drugs do not require a prescription. However, a healthcare professional must be involved in the sale and they cannot be kept in a self-selection area. These products are generally kept behind the counter at pharmacies.
- Schedule III drugs can be sold from a self-selection area but require that a healthcare professional be available for consultation. These are generally sold in pharmacies.
- Unscheduled drugs can be sold in any retail outlet.

Some provinces have additional schedules. For example, in British Columbia, Schedule IV drugs are drugs that can be prescribed by a pharmacist in accordance with certain guidelines.

The federal Prescription Drug List established by Health Canada enumerates drugs that must be sold by prescription in all provinces. Further scheduling of drugs is the responsibility of the provinces. However, all provinces base scheduling decisions on the National Association of Pharmacy Regulatory Authorities (NAPRA) drug schedule. Some provinces implement the schedule without changes, while others will modify it.

Biologic and biosimilar drugs are scheduled in the same way as small-molecule drugs and generally fall into Schedule I. Generic drugs receive the same scheduling as the reference innovator product.

Interchangeability

Interchangeability of drugs is regulated provincially. In some provinces, generics must apply for a designation of interchangeability and, if granted, will be listed as interchangeable. Other provinces leave interchangeability to the discretion of the dispensing pharmacist.

Generally, a designation of equivalence from Health Canada will satisfy the requirements for interchangeability in provinces where it is left to the discretion of pharmacists. In other provinces, such a declaration may simplify the application process. Because biosimilars do not receive declarations of equivalence, interchangeability is less straightforward and may vary from province to province.

Eligibility for reimbursement

In theory, and subject to further discussion below, all drug products are eligible for reimbursement. However, each plan may place restrictions on the types of drugs eligible for reimbursement. For example, some plans may not pay for non-prescription drugs.

Public payers (and some private payers) will generally only reimburse the cost of the lowest-cost alternative which, if a generic is available, is the generic cost. A more expensive alternative can be dispensed but unless certain criteria are met (e.g., a "no-sub" order from a physician), the payer will only reimburse the lower cost and the patient will have to pay the difference out of pocket.

Who are the payers?

In Canada, drugs can be reimbursed publicly or privately. Public payers include health plans

operated by the 13 provincial/territorial governments, as well as various federal programmes (e.g., covering Canada's Indigenous population, military, and prison populations).

The largest public health plans are the provincial health plans. These plans are created by provincial statutes and each establishes a formulary of drugs that are reimbursed for eligible residents. Generally, the provincial/territorial plans provide coverage to older individuals and those with limited incomes, although some provinces provide broader coverage.

Private payers include private insurance plans and cash-paying patients. Private insurance can be purchased by an individual's employer or by the individual. Private plans may also cover individuals eligible for public coverage in respect of co-pays or deductibles as well as drugs not reimbursed by the applicable public plan. In some provinces, however, the private plans will align with the provincial formulary to a certain extent.

For individuals admitted to hospital, drugs are generally paid for by the hospital. Hospitals are publicly funded, and each hospital establishes its own formulary of drugs that it provides.

What is the process for securing reimbursement for a new pharmaceutical product?

Innovative products

For public payers outside of Quebec, once a drug is approved (or prior to receipt of market approval), the first step in obtaining drug coverage is an application for a Common Drug Review (CDR) or pan-Canadian Oncology Drug Review (pCODR). Both of these reviews are administered by the Canadian Agency for Drugs and Technologies in Health (CADTH).

For each submission, CADTH constitutes a review team based on qualifications, expertise, and compliance with conflict-of-interest guidelines. The review involves an examination of the clinical, economic, and patient evidence. The outcome of the CADTH review is a listing recommendation to public drug plans: 'reimburse'; 'reimburse with clinical criteria and/or conditions'; or 'do not reimburse'.

Drugs are recommended for reimbursement if they demonstrate comparable or added clinical benefit and acceptable cost/cost-effectiveness when compared with other drugs. Drugs are recommended for reimbursement with conditions if they demonstrate: (i) comparable or added clinical benefit and acceptable cost/cost-effectiveness only in a subgroup or only when compared with a drug that is also reimbursed with conditions; (ii) comparable or added clinical benefit but unacceptable cost/cost-effectiveness; or (iii) clinical benefit with uncertainty in a therapeutic area with unmet clinical need. Drugs receive a recommendation of 'do not reimburse' when they do not demonstrate comparable clinical benefit or demonstrate inferior clinical outcomes or significant clinical harm.

CADTH has a target review period of 180 days. Embargoed decisions are then issued to manufacturers and the drug plans. During the 10-day embargo period, the drug plans may submit a request for clarification and/or the manufacturer may make a request for reconsideration or file a resubmission based on a reduced price. Once the embargo period ends (pending any reconsideration), the decision is made public. Appeals are not permitted. However, the jurisprudence indicates that judicial review by the courts of such a decision may be possible.

In Quebec, a similar review is undertaken by the *Institut national d'excellence en santé et en services sociaux* (INESSS).

Unless the drug is considered unsuitable for national negotiations, the next step is for the manufacturer to negotiate with the pan-Canadian Pharmaceutical Alliance (pCPA) to agree on conditions for listing on public formularies. The pCPA was formed by provincial drug plans with various goals, including improving the consistency of drug-listing decisions and

capitalising on combined buying power. Under the pCPA, a lead jurisdiction will undertake negotiations with manufacturers on behalf of most or all of the Canadian public payers, resulting in a Letter of Intent (LOI). Generally, the LOI will include the list price and any clinical criteria for reimbursement, and may also include a confidential payment to public payers.

Finally, after entering into an LOI, each individual public payer will enter into a listing agreement with the manufacturer. The listing agreement will largely reflect the contents of the LOI and result in the inclusion of the product on the payer's formulary. The formulary will include the agreed formulary list price and clinical conditions for reimbursement, if any.

The process for inclusion on the formularies of private payers is less structured. However, we have begun to see an increase in listing agreements with private plans.

Generic products and biosimilars

Once approved for market, generic drugs undergo a simplified process to become listed on provincial formularies, generally requiring only an application to the payer.

Biosimilars undergo a hybrid process. CADTH undertakes a more limited review and provides a summary of the evidence but no listing recommendation. Manufacturers then negotiate with the pCPA as above, and, if successful, enter into listing agreements.

How is the reimbursement amount set? What methodology is used?

Following the negotiations outlined above, drugs are listed on provincial formularies at a price that is agreed upon by the manufacturer and the public payer. Generally, the formulary list prices are similar across all jurisdictions.

As discussed above, manufacturers of innovative products will often enter into listing agreements that include a highly confidential "rebate". This is paid directly by the manufacturer to the payer and will reduce the effective cost of the drug to the public payer.

Listed generic products are also subject to price controls. To be eligible for listing on public formularies, generics must follow the pricing regime set out by the pCPA. Generally, if there is only one generic on the market, the allowed price is 75–85% of the innovative product. If there are two products, the allowed price is capped at 50% of the innovative price. Once there are three or more generics, oral solids are capped at 25%, while other dosage forms are capped at 35% of the innovative price. Certain enumerated oral solids are subject to further pricing restrictions at either 10% or 18% of the innovative price depending on the molecule.

Generic manufacturers generally set their prices at the maximum allowed price.

Once generic products are available on public formularies, the public payer will only reimburse the lowest-cost alternative, which is generally the generic, except in limited situations.

How are drug prices set? What is the relationship between pricing and reimbursement?

Manufacturers are permitted to set their own prices, subject to the considerations discussed elsewhere in this chapter.

For drugs that are listed on public formularies, the drug is generally sold by pharmacies at the same price as the reimbursement price as set out above. For individuals covered by public payers, pharmacists are only permitted to charge the agreed list price plus a legislated mark-up and dispensing fee. While in theory a pharmacy could sell at a different price for other patients, this is difficult in practice; the result being that the same price is generally used for both public and private payers.

Private payers may, however, allow a higher mark-up or dispensing fee.

Issues that affect pricing

In addition to the other agencies discussed above, drug prices for patented medicines in Canada may also be affected by the Patented Medicine Prices Review Board (PMPRB). The PMPRB is constituted under Canada's federal *Patent Act*, RSC 1985, c P-4, and describes itself as an independent, quasi-judicial body with a statutory mandate to ensure that the prices of patented medicines in Canada are not excessive. The PMPRB performs this mandate by comparing actual prices to maximum non-excessive ceiling prices that the Board sets at introduction, and annually thereafter, using information obtained from patentees and public sources. The PMPRB also reports on pharmaceutical sales, price, and R&D trends in Canada.

The PMPRB's jurisdiction under the *Patent Act* is limited to patentees of inventions pertaining to medicines sold in Canada. The scope of that jurisdiction has been explored on an ongoing basis through litigation in a number of judicial review cases before the Canadian courts. Courts have held that the term "medicine" must be interpreted broadly, and that there must be a rational connection or nexus between the invention described in the patent and the medicine. In order to determine whether such a nexus exists, courts have held that one does not have to, and ought not to, go beyond the face of a patent, although the patent should be considered as a whole. Rather, courts have held that the nexus can be one of the "merest slender thread". Courts also have held that the invention must be intended or capable of being used for medicine, or for the preparation or production of medicine.

In order to furnish the PMPRB with information to perform its mandate, patentees within its jurisdiction are required to comply with mandatory reporting obligations set out in the Patent Act, as well as the *Patented Medicines Regulations*, SOR/94-688. Although they do not have the force of law, the PMPRB also publishes Guidelines intended to assist patentees in complying with their obligations. Price information is treated as privileged by the PMPRB and includes the quantity of medicine sold in final dosage form – either the average price per package or the net revenue from sales – and the publicly available, ex-factory price in Canada and each of seven defined comparator countries. In support of the PMPRB's reporting mandate, patentees are also required to report total gross revenues for all sales in Canada and a summary of all expenditures made by the patentee towards the cost of research and development carried out in Canada by or on behalf of the patentee.

The PMPRB conducts investigations, issues orders requiring patentees to comply with their obligations under the *Patent Act*, and conducts hearings regarding excessive prices. In the event that a patented medicine has been sold in Canada at a price the PMPRB deems excessive, the PMPRB may order the patentee to offset the resulting excess revenues through price reductions for the medicine in question or another patented medicine, and/or by making payment to Her Majesty in right of Canada. Where a patentee is found to have engaged in a policy of excessive pricing, the PMPRB may require the patentee to offset up to twice the excess revenues. The PMPRB's hearings are typically conducted in public and the key documents in the proceeding, including reasons for any order, are published on the PMPRB's website.

The PMPRB's orders can be enforced in the same manner as orders of Canada's Federal Court or superior courts. In addition, failure to comply with the PMPRB's reporting requirements or orders are summary conviction offences punishable by daily fines or imprisonment. Orders of the PMPRB are not directly appealable, but may be challenged and quashed on an application for judicial review before the Federal Court.

In practice, the PMPRB often negotiates with patentees to achieve voluntary compliance with the requirements of the *Patent Act*. In particular, many patentees choose to enter into

voluntary compliance undertakings (VCUs) to deal with excess revenues, rather than taking the matter to a hearing before the PMPRB. These VCUs may include similar terms to an Order of the PMPRB regarding offsetting price reductions or payments to the Crown, and are made public on the PMPRB's website.

The PMPRB publishes many of the details of its activities in its Annual Report, including information regarding failures to file, failures to report, VCUs, and proceedings regarding excessive pricing. The PMPRB also issues a variety of other communications directed to stakeholders and the general public through its website.

Policy issues that affect pricing and reimbursement

Policy issues affecting pricing have been discussed in the pricing and reimbursement section above.

Emerging trends

There have been continued discussions surrounding the development of a national pharmacare plan. In the 2019 Budget, the federal government announced funding to create a Canadian Drug Agency to provide a coordinated approach on prescription drugs, to develop a national formulary, and to develop a national strategy for high-cost drugs for rare diseases. In June 2019, a federal Advisory Council on National Pharmacare recommended that the federal government work with provincial and territorial governments to establish a universal, single-payer, public system of prescription drug coverage in Canada. Whether and to what extent the Council's recommendation is implemented is likely to depend on the outcome of an October 2019 federal election.

A number of recent initiatives have also explored changes to the PMPRB regime. These include proposed amendments to the *Patented Medicines Regulations* introduced by the federal government in late 2017, as well as efforts by the PMPRB to modernise its Guidelines. Although position papers and drafts have been made available for public comment, no changes have been adopted at the time of writing.

Successful market access

In negotiating with the pCPA and public payers, it is important to understand their objectives and challenges and to be realistic about the product and its potential impact on the public purse. Expectations of the business should be evaluated in light of these considerations.

It is also important to ensure all submissions are robust and information is presented in a clear and concise way that tells the story of how the product fits into the Canadian landscape. International learning can be leveraged to assist in preparing the submission.

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China

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Abstract

PRC Law – in terms of pharmaceutical law – has developed very quickly over the past few years, especially in an effort to encourage new drugs and technology transfer, as well as to adapt to the increasing development of the Chinese health situation.

Through different kinds of regimes, and in an effort to facilitate the medical service system and encourage the development of new drugs in this sector for the boom in this market in China, the PRC government has been seeking to update its medical healthcare system. Its initiatives have included:

- modification of the foreign investment catalogue in terms of pharmaceuticals;
- reform on the simplification of pharmaceutical registration, the market authorisation holder regime, two-invoice regime and pricing regime;
- reform of public hospitals in connection with the pricing of medical services;
- telemedicine;
- reform of the online sale of pharmaceuticals;
- reform of public health with elder caring systems;
- 4+7 target-quantity procurement; and
- reform of the medical system in encouraging private medical institutions.

Amongst all these factors, pricing and reimbursement policies are the two most important and sensitive for the fast development of this industry in China.

Market introduction/overview

The healthcare system in China consists of both public and private medical institutions and insurance programmes. As announced by the Ministry of Human Resources and Social Security ("MOHRSS") (now named National Healthcare Safety Administration, "NHSA") in 2012, public medical insurance, which is also called the basic healthcare safety system of the PRC, already covers over 1.3 billion people, over 95% of the population at the end of 2011.

According to statistics published in May 2019 by the National Health Commission of the PRC (which replaced the Health and Family Planning Commission of the PRC), the PRC had 33,000 hospitals at the end of February 2019 including 12,000 public hospitals and 21,000 private hospitals. All the medical institutions throughout the country received 1.314 billion visits in January and February 2019. The average outpatient expenses per visit are RMB 330.00 for first-class public hospitals, and RMB 206.50 for second-class public

hospitals, and the average inpatient expenses per visit are RMB 13,563.70 for first-class public hospitals and RMB 6,256.50 for second-class public hospitals, according to the statistics for January and February 2019.

According to the statistics, the market size of chemical pharmaceuticals in China is expected to reach around RMB 878 billion in 2020; the market size of bio pharmaceuticals in China is expected to reach around RMB 334 billion; and the market size of traditional Chinese medicine is expected to reach around RMB 580 billion.

According to the *Planning Report of the Chronic Diseases* (2017–2025) issued by the State Council in January 2017, chronic diseases have become the most important in China, especially cardiovascular diseases, cancers, chronic respiratory system disease, diabetes, oral diseases, and diseases in connection with the endocrine system, kidneys, bones, or the nervous system. This is closely related to the rapid development of industrialisation and the rapid growth of the ageing population in China. Further, the lifestyle, the environment and food safety also have more impact on the health of Chinese people.

According to the *negative list for foreign investment ("Negative List")*, a medical institution can only be established by foreign investors and its Chinese partners in the forms of Sino-foreign equity joint venture or Sino-foreign cooperative joint venture.

Although the *Negative List* does not prohibit the establishment of pharmaceutical trading companies in China, in practice, the establishment of pharmaceutical trading companies may encounter some difficulties depending on the local regulations and practice of the National Medical Products Administration (the "NMPA").

PRC Law implements the market authorisation regime for imported drugs and domestic manufactured drugs. All pharmaceuticals which can be sold on the Chinese market must be subject to registration with NMPA.

In 2016, PRC implemented the market authorisation holder regime for the majority of drugs except narcotic drugs, psychotropic drugs, medical toxic drugs, radioactive drugs, vaccines and blood products, in order to encourage medical research institutions and research staff in China to register and hold the drug market authorisation. Such pilot regime will last for two years until 4 November 2018. The pilot period has been extended for another year, until 4 November 2019.

The *Drug Administration Law of PRC* is in the process of amendment and, according to the draft version published for public comments, the market authorisation holder regime will likely become the official regime after the amended *Drug Administration Law* is enacted. This new regime gives more flexibility with regard to the application and transfer of drug market authorisation in China, in an effort to encourage the development of new drugs. This new regime will also trigger high-level initiatives for pharmaceutical manufacturing companies in the structuring of their business in China, in an effort to seek funding investment for the purpose of development of new drugs.

Pharmaceutical pricing and reimbursement

Regulatory classification

How are pharmaceutical products regulated?

The PRC adopts a classification system for prescription drugs and non-prescription drugs and subdivides non-prescription drugs into Class A drugs and Class B drugs, according to their level of safety.

Prescription drugs refer to the drugs that may only be purchased, dispensed or used with prescriptions by licensed doctors or licensed assistant doctors.

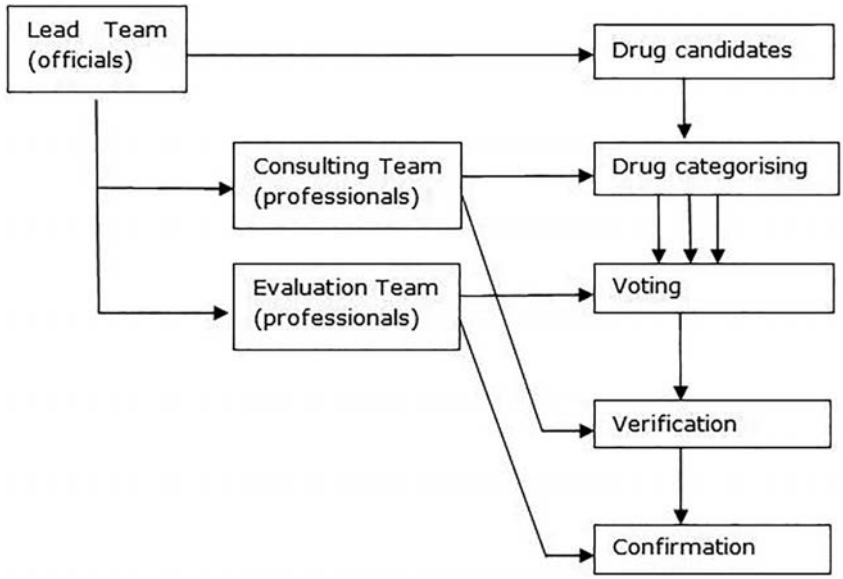
Non-prescription drugs refer to the drugs announced by the NMPA which can be purchased or used by consumers upon their own judgment without prescriptions by licensed doctors or licensed assistant doctors.

What pharmaceutical products are eligible/ineligible for reimbursement?

The pharmaceutical products eligible for reimbursement are listed in the following catalogues:

- the National Catalogue of Drugs issued by the NHSA; and
- the Provincial Catalogue of Drugs issued by the provincial bureau of healthcare safety administration.

The NHSA selects the drugs to be added to the National Catalogue with the assistance of its provincial counterparts. The NHSA must also consult with the NDRC, Ministry of Finance, National Health Commission, NMPA and the State Traditional Chinese Medicines Administration and their respective provincial counterparts. The procedure for the selection of drugs to be included in the National Catalogue is as follows:



The selection procedure of the drugs to be included in the provincial catalogue by each provincial level authority is generally similar to the diagram above.

The NHSA has forbidden reimbursement for the following drugs:

1. drugs whose dominant function concerns nutrition;
2. medicinal animal organs and nuts;
3. medicinal liquor made by steeping TCM materials;
4. oral effervescence preparations and preparations with fruit flavour; and
5. blood and protein products (excluding those for emergency medical treatment).

The NHSA may add additional drugs to this list at its discretion.

Who is/Who are the payer(s)?

The basic medical care insurance fund is the basic payer of the medical costs based on its rules. In addition, private insurance will also reimburse fully or partially medical costs based on its commercial terms.

What is the process for securing reimbursement for a new pharmaceutical product?

A new pharmaceutical product can only be reimbursed if it is selected by NHSA to be included in the National Catalogue or by the provincial level healthcare safety administration to be included in the Provincial Catalogue. The drug manufacturer is not entitled to apply for the selection of the drug to be included in the Catalogues.

How is the reimbursement amount set? What methodology is used?

The National and Provincial Catalogues are divided into two price-dependent categories: Category I and Category II. The reimbursement of drugs is subject to the local rules formulated by the local governments, and such rules vary from one province to another. Generally, the drugs in Category I are directly reimbursed according to the proportions provided in the local rules, while Category II drugs can be reimbursed according to the proportions provided in the local rules only after the insured pays a certain amount at his/her own expense.

How are drug prices set? What is the relationship between pricing and reimbursement?

The NDRC, National Health Commission and MOHRSS initiated a pharmaceutical pricing reform on 1 June 2015 and cancelled the government pricing regulations for the majority of drugs as of 1 June 2015, except for narcotic drugs and first class psychotropic drugs, which are still subject to the price caps for ex-factory price and retail price, aiming to cause the actual transaction prices of drugs to be priced mainly through market competition.

Narcotic drugs and first-class psychotropic drugs are still subject to the following price caps: (i) ex-factory or ex-port pricing; and (ii) retail pricing.

The sales prices upon exit from the factory or port are as follows:

- Ex-factory price = manufacturing cost and expenses X (1 - profit margin) X (1 + VAT rate).
- Export price = CIF price X (1 + tariff rate) X (1 + VAT rate) + clearance charges.

The retail pricing approach involves the competent authorities setting a price cap for drug retailers. The retail price cap is calculated based on the sum of the cost of ex-factory or ex-port drugs, tax, reasonable sales expenses and reasonable profit margin.

The NDRC sets different standards for maximum rates of sales expenses and profit margins for different drugs as per the following table:

Drug category	Rate of sales expenses	Profit margin
Class I new drug: New drug never marketed in domestic or overseas market	30%	45%
Class II new drug: New drug never marketed in domestic market but marketed overseas, which includes a new administration path (oral, injection, etc.) never marketed in either domestic or overseas markets	20%	25%
Class III new drug: New combination of chemical substances	18%	18%
Class IV new drug: Domestically marketed drug with a new administration path or a new dosage form	15%	15%
Class V new drug: Drug marketed in domestic market with new applications	12%	12%
Generics	10%	10%

Relationship between pricing and reimbursement

With regard to the drugs covered by the medical insurance funds, the government authorities announced in the pharmaceutical pricing reform in 2015 that the reimbursement standards will be introduced as a mechanism for guiding the setting of drug prices in a reasonable manner. Such standards at the national level are not available for the time being. Some local authorities have published the local catalogue of reimbursement standards.

Issues that affect pricing

Except for narcotic drugs and Class I psychotropic drugs, drugs prices are set mainly through market competition after the cancellation of government pricing on drugs. According to the pharmaceutical pricing reform in 2015, the pricing of different categories of drugs is affected by different issues:

(1) for the drugs covered by the medical insurance funds, the reimbursement standards formulated by the government authorities will act as a mechanism for guiding the setting of drug prices in a reasonable manner;

(2) with regard to patent drugs and exclusively produced drugs, the prices thereof are set through establishing a public and transparent negotiation mechanism for setting prices in which multiple parties participate;

(3) with regard to blood products not listed in the catalogues of reimbursable drugs, immunity and prevention drugs that are purchased by the State in a centralised manner, and AIDS antiviral drugs and contraceptives provided by the State for free, the prices thereof are set through bidding purchase or negotiation;

(4) narcotic drugs and Class I psychotropic drugs are still subject to the maximum factory prices and the maximum retail prices for the time being; and

(5) with regard to other drugs, the prices thereof are set by the producers and retailers thereof on their own, according to their production and operation costs and the market supply and demand.

In addition to the above factors, other factors may also affect the pricing, especially the two-invoice system which may change the commercialisation model of pharmaceutical manufacturers with their distributors; tax regulations in connection with the deductibility of related sales commission and sales expenses; and cooperation models with their Chinese distributors.

Policy issues that affect pricing and reimbursement

The recent series of reform policies adopted by the PRC significantly affect the pharmaceutical pricing, especially the following:

- Two-Invoice System for Drug Procurement among Public Medical Institutions taking effect as of 26 December 2016 on a trial basis. The two-invoice system is a system under which invoices are issued by drug manufacturers to drug distributors on a once-off basis, while invoices are issued by drug distributors to medical institutions on a once-off basis. This policy is aiming to improve transparency in drug prices and eliminate excessive profit margins associated with multi-tier distribution models.
- Healthy China 2030 and 13th Five Year Plan for Deepening the Reform of the Pharmaceutical and Healthcare System. According to the aforesaid policies, the Circular on Fully Carrying out the Work of Promoting the Comprehensive Reform of Public Hospitals taking effect as of 19 April 2017 was promulgated. According to this new

law, the decades-long policy of drug mark-ups (amounting to 15% in public hospitals) must be completely cancelled in order to fully promote the comprehensive reform of the public hospitals.

- Circular of the General Office of the State Council on Issuing the Pilot Program for Conducting Centralised Drug Procurement and Use by the State, taking effect as of 1 January 2019. Eleven cities – Beijing, Tianjin, Shanghai, Chongqing, Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu and Xi'an – have been selected to choose pilot varieties from generic drugs which have passed the evaluation of consistency in quality and efficacy (including approval for marketing, based on the new classification of registration of chemical drugs, hereinafter referred to as "consistency evaluation"), and carry out pilot work for centralised drug procurement and use conducted by the state ("4+7 target-quantity procurement'). The purpose of the pilot is to: (i) achieve a significant reduction of drug prices, to lower drug cost burden on patients; (ii) lower corporate transaction costs, purify the drug trading environment and improve the industry's ecology; iii) guide medical institutions to regulate the use of drugs, and support the reform of public hospitals, and; iv) explore and improve the centralised drug procurement mechanism and market-oriented drug pricing mechanism.
- Opinions of the General Office of the State Council on Reforming and Improving Policies on the Guaranteed Supply and Use of Generic Drug effective as of 21 March 2018. According to the aforesaid opinions, the research and development of generic drugs, including those generic drugs whose registration applications have not been filed within one year prior to the expiration of patents rights of the corresponding innovator drugs, shall be encouraged for manufacturing, the quality and efficacy of the generic drug shall be improved, and the capability of securing supply of the drug shall be enhanced to satisfy demands for drugs in clinical treatment and public health safety. To implement the aforesaid opinion, the National Health Commission and other 11 commissions and ministries jointly promulgated the Notice of Working Plan to Accelerate the Implementation of the Policies on the Guaranteed Supply and Use of Generic Drugs effective as of 18 December 2018, according to which, the first list of the recommended and supported generic drug catalogue should be promulgated before the end of June 2019. On 20 June 2019, the First List of the Recommended and Encouraged Generic Drug Catalogue was published by the National Health Commission of the PRC for public consultation for a period of five working days as of the date of publication.

Emerging trends

In October 2016, the Chinese government approved a blueprint called "Healthy China 2030", pledging to build a healthy China in the next 15 years with public health services covering all people. According to "Healthy China 2030", China will: comprehensively advance the reform of medical insurance reimbursement methods; actively promote payment methods according to disease types and capitation; take the initiative to explore payment by Diagnosis Related Group System (DRGs) and service performance to form a composite payment method under the total budget management; and improve the negotiation and risk-sharing mechanisms for health insurance agencies and medical institutions. Under "Healthy China 2030", the government will accelerate the settlement of cross-provincial medical expenses under the basic medical insurance and improve the mechanism of cooperation between medical and health institutions and elderly care institutions, to support the latter to engage in medical services.

On 10 June 2019, the National Health Commission, NDRC, Ministry of Science, Ministry of Finance, NHSA, Ministry of Natural Resources, Ministry of Housing and Urban-rural Development, State Administration for Market Regulation and China Insurance Regulatory Commission jointly published the Circular on Issuing the Opinions on Promoting the Sustainable, Healthy and Regulated Development of Privately-run Medical Institutions. According to this Circular, the Chinese government will encourage the establishment of private medical institutions. For such purpose, this Circular provides a series of measures to enlarge the provision of land for medical and health purposes, and the Circular also provides for a five-year transition period to allow the use of existing industrial or commercial-use premises to establish medical institutions. It is hoped the Circular will solve the problem of access to land by private medical institutions due to regulatory constraints.

Successful market access

Successful access to the Chinese pharmaceutical market relies on an in-depth knowledge of the relevant PRC laws and regulations, not only in terms of regulatory regulations, but also pricing, anti-corruption, compliance and tax regulations, as well as the preferential policies on the market, confirmation of whether the product is included in the catalogues of the reimbursable drugs, and compliance with the applicable laws and regulations.

Further, the frequent change of the legislative environment due to the above reform in China will also make players adapt and restructure themselves in order to be in line with PRC Laws, and gain market advantages in the course of such reform.

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France

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Abstract

The French health system is often considered one of the best and is envied by the whole world. It is characterised by a financing model based mainly on activity-based pricing that favours the amount of care produced, which varies greatly according to the care sectors.

Deloitte's health barometer shows a very strong attachment of the French to their health system. Indeed, 81% of French people say they are satisfied with the quality of care; 80% with the safety of care; and 75% with the competence of healthcare staff. However, most rural residents remain dissatisfied with the issue of geographical proximity (54% dissatisfied compared to only 28% in the Paris area). The study shows that the French are worried about the so-called "medical desert".

The French healthcare system is known worldwide as a solidarity-based system that is very comprehensive and protective for its users. One result, however, is relatively high expenditure that is becoming harder for the government to sustain.

French policy is to ensure the highest reimbursements for drugs and treatments that are determined to be the most necessary. Developments in medical research as well as policy changes can influence prices too, but reimbursements cover only those products that have received regulatory approval.

Market introduction/overview

The French population has a high life expectancy of 82.4 years. It is therefore above average for all OECD countries, which is 82.4 years of life expectancy. France has the 6th-highest life expectancy, with Japan (83.9 years) remaining in the lead.

The French healthcare system, called Social Security, is internationally known as an efficient and generous system. While it was ranked as best among its 191 members by the WHO, according to a study published by the British medical journal *The Lancet* in April 2017, France's system was ranked 15th among 195 countries and territories in terms of quality and accessibility.

The healthcare system incorporates a variety of organisations, institutions and resources in order to fulfil four main functions: providing services; supplying resources; ensuring funding; and administrative management.

In France, there are five types of healthcare workers:

- Professional service providers, which include:
    - Health establishments: public hospitals and private clinics.
    - Mobile professionals and auxiliaries: doctors, pharmacists, midwives, nurses and

physiotherapists.
    - Emergency medicine.
    - Social welfare services and associations.
    - Ambulatory surgery.
    - Telemedicine.
    - Home hospitalisation and treatments.
    - Nursing home services.
    - Specialised establishments for accommodating patients with specific needs, such as neurovascular units or centres for obese patients.
- Producers of goods and services (pharmaceutical industry).
- Public health institutions: the French healthcare system is overseen by the Minister of Health and the Minister of Social Affairs.
    - At the *national* level, the central government is in charge of implementing public health and safety policies. It oversees all health institutions, setting prices for products and treatments while maintaining funding for health institutions. For example, the National Institute of Health Monitoring and Public Health Council belongs to the public health institutions.
    - At the *regional* level, regional health agencies adapt national policies to a community's needs and constraints. They ensure the coordination between prevention, care and support as well as consistent resource management in order to ensure equal access to healthcare.
    - At the *local* level are the institutions and professionals who are in closest contact with patients and other people in the system. They are supervised by the regional health agencies.
- Providers of compulsory or supplementary health insurance plans.
- Recipients of healthcare (patients).

Access to care

In France, there are different types of health insurance depending on the professional situation:

- The general system covers more than four people out of five in France. It funds 78% of health expenses and includes employees in the private sector and, since January 1, 2018, the self-employed workers (Article L. 311-2 of the Social Security Code). It is managed by the Sickness Insurance Primary Fund (SIPF).
- The agricultural system concerns farm and ranching workers.
- A series of smaller public systems set up to address the needs of specific professions, such as railway workers, notary clerks and employees, and public servants.

The social security is available to employees, students, professional interns, beneficiaries of a minimum revenue allowance, pensioners or the unemployed receiving jobless benefits.

Some family members of insured people may also benefit from the same rights including a spouse or any children under 16 years old (or until 20 years old if they are students). They must register separately for Social Security and obtain their National Health Service card which proves their affiliation.

The SIPF general fund partially refunds most healthcare costs, but in order to receive full compensation for outlays, users often must adhere to supplementary healthcare coverage, known in France as "*mutuelles*".

Since January 2016, the French Universal Disease Protection programme allows any person resident in France on a continuous and legal basis to be able to benefit from medical fees reimbursement. The procedures are accordingly simplified.

Moreover, this protection ensures that unemployed people, or individuals whose personal situation has changed, can keep their same health insurance coverage.

Incidence and prevalence of disease

The National Institute of Statistics and Economic Studies (INSEE) published in 2018 the following data about prevalence of diseases as follows:

Disease	Prevalence rate per 100,000 persons as of 31 December 2015
Type 1 and 2 diabetes	4063
Malignant tumour	3330
Long term psychiatric conditions	2111
Coronary artery disease	1851
Heart disease	1645
Severe arterial hypertension	1176
Chronic arteriopathy with ischemic events	866
Disabling stroke	662
Chronic and serious respiratory failure	641
Alzheimer's disease and other dementia	542

Important issues discussed in national press

Social security gap

The national press often reports the problem of financing social security, known as the "social security gap". A report submitted to the Minister of Solidarity and Health, Agnès Buzyn, specifies reform of the financing of the health system. Indeed, the continuous increase in the number of patients with chronic diseases requires an evolution of management methods to better meet the need for long-term follow-up and coordination of their management. The report states that combined payment methods, on the other hand, can provide a more appropriate response to the diversity of patients' needs and promote the necessary transformations of the health system.

The social security deficit, which fell to €1.2 billion last year, is expected to "widen" again to at least €1.7 billion in 2019, according to a summary by the Audit Committee.

This could even increase to €4.4 billion if the State does not compensate the Social Security for the emergency measures adopted at the end of 2018. Anticipating the return of Social Security to balance, the State exceptionally required Social Security to bear €2.4 billion of uncompensated expenses by: desocialisation of overtime (at a cost of €1.2 billion); social lump sum for companies (€600 million); smoothing of thresholds for the Generalised Social Contribution (CSG) for pensioners (€300 million); and reduction of VAT from the State to the Social Security system (€300 million).

Medical desert

Regarding access to care, the national press often speaks of "medical deserts", which are territories where the medical supply is insufficient to meet the needs of the population. A report issued in October 2018 by the national delegates on access to care recommends to:

- encourage outpatient internships and support installation projects;
- develop the coordinated exercise;
- deploy telemedicine;
- support new modes of practice;
- promote inter-professional delegations and cooperation; and
- simplify liberal practice and free up medical time.

Euthanasia

France retains the ban on euthanasia, but the issue continues to generate debate, including within the medical profession.

Pharmaceutical pricing and reimbursement

Regulatory classification

Pharmaceutical products – more commonly known as medicines or drugs – are a fundamental component of both modern and traditional medicine. According to article L.5111-1 of the Public Health Code, "*a drug is any substance or composition presented as having curative or preventive properties against human or animal diseases, as well as any substance or composition that may be used or administered to humans or animals, with a view to establishing a medical diagnosis or restoring, correcting or modifying their physiological functions by exercising a pharmacological, immunological or metabolic action.*

"In particular, dietetic products are considered to be medicinal products if their composition contains chemical or biological substances that are not themselves food, but whose presence confers on these products either special properties sought in dietetic therapy or test meal properties.

"Products used for disinfecting premises and for dental prostheses are not considered to be medicinal products.

"Where, having regard to all its characteristics, a product is likely to satisfy both the definition of a medicinal product provided for in the first subparagraph and that of other categories of products governed by Community or national law, it shall, in case of doubt, be considered a medicinal product".

Different types of pharmaceutical products

In France, some pharmaceutical products require a medical prescription while others can be bought without medical prescription depending on the composition of the medicine or its use.

There are three types of pharmaceutical products:

- those requiring a medical prescription;
- those which do not require medical prescription; and
- more specialised treatments, including those reserved for hospital use or that can only be prescribed by a hospital, or that need a specific doctor's prescription or require more detailed monitoring during their use.

Article L. 5121-1 of the Public Health Code distinguishes drugs according to their preparation such as, for instance:

- *Bulk compounding:* drugs prepared for a particular patient due to the lack of available pharmaceutical products.
- *Hospital preparation:* drugs prepared according to pharmacopoeia instructions and in compliance with proper practices mentioned in the Article L. 5121-5 of the Public Health Code due to the lack of available or adapted pharmaceutical products.
- *Compounded medication:* drugs prepared in a pharmacy that are registered to the pharmacopoeia or on a national form and aimed to be directly dispensed to patients by the pharmacy.
- *Generic drug:* prepared with the same molecule of the reference medicinal products and with the same composition of active substances, the same pharmaceutical form and efficacy as the model of reference.
- *Biologic drugs:* the active substance of which is produced from a biological source and the quality of which requires a combination of physical, biological and chemical tests.
- *Biosimilar drugs:* biological drugs that have the same composition of active substances and pharmaceutical form as a reference biological medicine, which cannot be considered as generic drugs due to differences linked to the raw material or production process.

Refundable pharmaceutical products

In order to be eligible for reimbursement by Social Security, drugs must be covered by Chapter 3 of the Security Code.

Moreover, drugs have to be prescribed by a healthcare professional within the limits of prescription rights and must have a therapeutic use.

Currently, it is likely that homeopathic drugs may become non-refundable.

Process for getting a new drug approved

Before any drug is marketed in France, it is necessary to go through the marketing authorisation procedure as defined by article L.5121-8 of the Public Health Code and the following.

The marketing authorisation is subject to three main criteria: quality, safety, and efficacy according to article L. 5121-9 of the Public Health Code. It must be verified that: the actual qualitative and quantitative composition corresponds to that declared by the manufacturer; the medicinal product is not harmful under normal conditions of use; and the therapeutic effect announced is not lacking or is sufficiently justified by the applicant.

Marketing authorisations are issued by the Director of the ANSM (*Agence Nationale de Sécurité du Médicament et des Produits de Santé*) or his European equivalent, the Director of the European Medicines Agency (EMEA). They are then published in the Official Journal.

For new medicinal products intended to be marketed in more than one country, market access has been Community-based in the European Union since 1st January 1998, either through the centralised procedure defined in Regulation No 2309/93/EEC as amended by Regulation No 726/2004/EEC, or through the mutual recognition procedure provided for in Directive 2001/83/EC as amended by Directive 2004/27/EC and, since October 2005, through the decentralised procedure provided for in Directive 2004/27/EC.

The national procedure is increasingly being used less and less: it only applies to requests for the marketing of medicinal products limited to the national territory, which represents a limited number of medicinal products. It also continues to apply for the maintenance of marketing authorisations historically issued at national level.

In Europe, in the centralised procedure, the time limit for obtaining a marketing authorisation is 210 days, and may be shorter in the case of accelerated approval. In France, in the case of national procedures or national phases of decentralised or mutual recognition procedures, the time limits are also defined by the regulations. However, there are regular delays in these procedures. At the end of the mutual recognition procedure, the marketing authorisation shall be issued at national level within 30 days.

Who is/are the payers?

In France, the financing of the medical expense reimbursement system is organised into two main levels: compulsory and supplementary schemes.

Basic compulsory health insurance schemes are characterised by compulsory membership and contributions and are therefore based on broad solidarity, based on income-based contributions, and access to care defined according to need.

Supplementary schemes (mutual insurance companies, insurance companies, provident institutions) are based on a solidarity restricted to the members' field and offer variable coverage, defined by the type of contract subscribed. They cover the part of health care expenditure that is not covered by the compulsory basic scheme.

Some expenses are covered by the State. These include expenditure on prevention, medical and pharmaceutical research, and training of health professionals, universal complementary health insurance (CMU-C), and grants for military hospitals, emergency care, as well as benefits paid to beneficiaries of State Medical Assistance (AME).

Finally, a portion of the expenses may remain the responsibility of the care recipients.

Prescribed drugs are covered entirely or partially by the health insurance system. In general, a patient purchases the drugs and is later refunded though the spread of healthcare cards equipped with electronic chips, and internet-connected card readers, meaning the refunds can often be applied automatically at the time of purchase.

People who have signed up for supplementary health insurance policies often have the full cost of their treatments reimbursed, based on the terms of their contract.

Health insurance

At a departmental level, a health insurance policy is applied by 101 Primary Health Insurance Funds, one common Social Security Fund and five Social Security Funds. These Funds are private law bodies with a public service mission, and manage interactions and contacts with patients.

How is social security funded?

Resources which fund the social protection are:

- Social contributions: Charges collected directly based on salary and which must be paid by both employees and employers.
- The Generalised Social Contribution (CSG): a tax collected on all incomes.
- A series of other taxes dedicated to funding Social Security, including a flat-fee social tax, the social solidarity contribution required by companies, and a value-added tax on tobacco products.
- Other sources of funding from the State, different social security systems or other social security bodies.

Complementary health coverage

Any person can subscribe to complementary coverage plans in addition to Social Security,

which may also benefit family members. Many people do so because in general, the system does not fully refund doctor visits, drug prices or other treatments.

Such complementary plans, or *Mutuelles*, are financed by member contributions and organised as a non-profit-providing solidarity and assistance for its clients (article L. 111-1 of the Mutual Societies Code).

Individual contributions to a *Mutuelle* depend on a variety of personal circumstances (age, status of employee or unemployed person, place of residence, income, and the desired level of protection).

Pharmaceutical products eligible / ineligible for reimbursement

To be covered by the Health Insurance, a drug must be included in the list of pharmaceutical specialities reimbursable to social security contributors (positive list), published in the Official Journal, which specifies the only reimbursable therapeutic indications. The mission of examining drugs is the responsibility of the Transparency Commission integrated into the HAS (*Haute Autorité de Santé*). Its missions are to evaluate medicinal products that have obtained their marketing authorisation, when the laboratory that operates them wishes to obtain their inclusion on the list of reimbursable medicinal products and to give an opinion on the coverage of medicinal products by the Social Security and/or for their use in hospital, by assessing their "medical service rendered". Drugs with medical service rendered insufficient compared to other available drugs or therapies are not included in the list of reimbursable specialties.

The drug is scheduled for reimbursement for five years, but the Transparency Commission may, at any time, reassess the medical service provided if changes occur in therapeutic strategies. The scope of reimbursable therapeutic indications is based on the therapeutic strategy recommended by the Transparency Commission that, in certain cases, may lead to a restriction with regard to the marketing authorisation.

What is the process for securing reimbursement for a new pharmaceutical product?

To enable the reimbursement of a pharmaceutical product, companies have to obtain a product marketing authorisation.

Marketing authorisation

The marketing authorisation is issued by either:

- The European Commission, after receiving an opinion from the European Medicines Agency (EMA). The pharmaceutical laboratory chooses the rapporteur State or the referent State within the EU for submitting its product to the EMA, which has authority across the European Union. These procedures are used when the product is intended for several Member States of the European Union.
- The Director General of National Agency for Security of Medicinal product who scrutinises the product according to scientific criteria of quality, safety and efficiency. The new product must have a risk-benefit balance at least equal to products already on the market. It can submit a favourable or unfavourable opinion or a request for some additional information.

The product marketing authorisation must be accompanied by a summary of the product characteristics, as well as its labelling and packaging, and the accompanying information notice.

This authorisation can be changed or removed. Another option is to file for a temporary authorisation of use.

Primarily, the authorisation is requested by laboratories and granted to drugs whose security and efficiency are strongly presumed by the results of therapeutic tests. The authorisation request has to be filed or to be subject to a commitment to be filed within a specific period.

Secondly, the nominative authorisation is requested by the doctor to the benefit of a specific patient, who may not participate in biomedical research. The expected efficiency and safety should be based on current scientific knowledge.

These authorisations are granted for a limited period not exceeding one year, although they can be renewed.

Inscription on the List of Reimbursable Drugs (article L. 162-17 of the Social Security Code)

A pharmaceutical laboratory is free to set prices for the treatments it offers. However, for a drug to be eligible for Social Security reimbursement, a request must be submitted to the High Health Authority (HHA). The request is reviewed by the HHA's Commission on Transparency, which assesses the medical service provided (e.g. a drug must be sufficiently beneficial) and the improvement of the medical benefit – that is, the drug must make a major contribution compared with similar products (article R. 163-5 I 2° of the Social Security Code).

The Commission on Transparency's opinion is transmitted to the economic committee of a health product and the national union of medical insurance funds.

Article R. 163-5 of the Social Security Code provides that some drugs cannot be entered on list of reimbursable drugs:

- drugs that have forms, dosing and presentation not justified by a therapeutic use;
- drugs that do not improve medical service according to the Commission on Transparency or do not generate savings in the drugs' treatment;
- drugs that might generate an increase in consumption or unjustified expenditures;
- drugs whose price is not justified; and/or
- drugs that do not mention on their packaging, labelling, leaflet or advertisement a therapeutic use.

Both France's health minister and the Social Security minister adopt the final decision on reimbursement of the drugs.

Decisions regarding the inscription of the drugs on the list of reimbursable treatments are notified to a company within 180 days from the receipt of the request, as required by article R. 163-9 of the Social Security Code. The decisions are also published in France's official government bulletin (*Journal Officiel*).

The inscription is valid for five years and may be renewed (articles R. 163-2 and R. 163-10 of the Social Security Code).

Article R. 163-14 of the Social Security Code provides that refusal decisions are notified to the company with the grounds of refusal, legal remedies and periods.

Drugs that are no longer reimbursable

This decision belongs to the Health minister on the recommendation of the High Health Authority. The arrival of new drugs on the market which are less expensive and more efficient, for example, could justify a decision to withdraw some drugs from the list.

Who influences decisions?

According to article R. 163-16 of the Social Security Code, the opinions of the Transparency Commission are subject to a dual requirement of motivation and publicity. Where the notice relates to the listing, amendment of listing conditions or renewal of the listing of a drug on

the list of reimbursable specialties or on the list of drugs approved for community use, the notice is immediately communicated to the company producing the drug.

The company may, within 10 days of receipt of this opinion, request to be heard by the commission or send its written comments to it. The committee may modify its opinion in the light of the comments submitted.

In the event of a request for a hearing, the committee shall hold the date of the hearing, which shall be fixed by the committee, within a maximum period of 45 days following receipt of the company's request. Upon a reasoned request from the Minister of Health or Social Security to the Commission, this period may be reduced to one month.

Process to appeal a decision

The Court of Justice of the European Union has ruled that any decision not to include a medicinal product on the list of reimbursable specialities shall include a statement of reasons based on objective and verifiable criteria, including, if necessary, the opinions or recommendations of the experts on which the decisions are based. In addition, the applicant shall be informed of the means of appeal available to him under the legislation in force, and of the time limits within which such appeals may be lodged. When setting up their procedures for admission to reimbursement of medicinal products, Member States are required to comply with the requirements of Directive 89/105 of December 21, 1988, in particular to provide for the possibility of bringing legal and not only administrative proceedings against decisions refusing to include them on the positive list of reimbursable medicinal products (ECJ, November 27, 2001, Case C-424/99, *Commission v Austria*, ECR I, p. 9285).

In the event of refusal to include a drug on the list of reimbursable drugs, it is possible to bring an appeal for exceeding powers before the administrative judge. In one such case, a laboratory exercised this remedy following the refusal to include *Palexia LP* on the list of reimbursable specialties (French Council of State, 1st Chamber, December 26, 2018).

How is the reimbursement amount set? What methodology is used?

Article L. 162-16-4 of the Social Security Code provides that the Economic Committee for Medicinal Products sets the price based on the results of: economic and medical evaluations; the prices of other drugs with same therapeutic effect; expected volume sales; and foreseeable and actual conditions of use of the drugs, with the undertaking that operates the drug.

The French national union of medical insurance (*Union nationale des caisses d'assurance maladie*) is composed of representatives of the general system, the agricultural system and social security for self-employed persons. It sets the support rate of healthcare as well as the reimbursement rate of drugs. The medical service provided (MSP) takes into account the severity of the concerned disease, the efficiency of undesirable effects, the therapeutic strategy and the preventive, curative or symptomatic character of the drugs treatment.

There are several levels of medical service provided (major, moderate or low) that affect the reimbursement rate of the drugs. They are classified by the French Government as follows:

Drugs for which the MSP is insufficient do not get included on the list.

Categories of drugs	Reimbursement rate
Irreplaceable drugs for serious and debilitating diseases	100%
Drugs with a major or significant MSP and Bulk Compounding	65%
Drugs with moderate MSP	30%
Drugs with low MSP	15%

The reimbursement rate applies to the basis of the sale price or a "flat rate of responsibility" that is a reference rate for the reimbursement of some drugs. The "flat rate of responsibility" aims to cover equivalent products in terms of efficiency (generic drugs) on the basis of a single tariff. This tariff is calculated from the price of the cheapest generic drugs.

A franchise of €0.50 is levied on reimbursable drugs by the health insurance. The amount of the health franchise is capped to €50 per person each year.

The Health Insurance (Social Security) reimburses part or all of the medicines purchased in pharmacies. This depends on the drug concerned, as well as the conditions of prescription and delivery. The reimbursement rate depends on the medical service provided for the drug.

Since January 2019, 65% of nicotine substitutes have been reimbursed on medical prescription. To be reimbursed they must appear on the list of nicotine substitutes reimbursed.

How are drug prices set? What is the relationship between pricing and reimbursement?

Fixing the price

Two types of drugs may be distinguished:

- Drugs sold directly to the health establishment: the price is negotiated directly by health establishments.
- Drugs sold by pharmacies or by hospitals: the sale price to the public is set by convention between the pharmaceutical company and the Economic Committee for Medicinal Products. If no agreement can be reached, the committee sets the price itself. If the Health and Social Security ministers oppose it, they set the price, within 15 days after the committee's decision (article L. 162-16-4 of the Social Security Code).

Criteria for fixing the price

As previously mentioned, in setting the price the Committee takes into account: the improvement provided by the drug; the results of economic and medical evaluations; the price of drugs with the same therapeutic effect; sales volumes; and the foreseeable and actual conditions of use of the drugs.

The criteria of the improvement of the medical service provided correspond to: the added value of the new drug over and above existing drugs; and the efficiency and the tolerance levels for patients. There are five levels of the improvement of the medical service provided which are: major, important, moderate, low and insufficient.

The Economic Committee for Medicinal Products implements the directions received by the competent ministers. These directions are intended to ensure, in particular, respect of the government's goals for national health insurance expenditures (article L. 162-17-3 of the Social Security Code).

The detailed price of drugs

The public price of the drugs is composed of the pre-tax manufacturer's price, margins (wholesaler's margin, official margin and dispensation fees) and the value-added tax.

It comprises the payment of wholesalers, notably through margin and discounts. The ministerial order dated December 26, 2011 created a unique payment of the wholesalers equal to 6.68% of the pre-tax manufacturer's price. This coefficient only concerns the part of the price ranging from €0 to €450. Beyond this amount, the coefficient is equal to 0.

For the retail pharmacist's margin, several coefficients are applied according to the different tranches of the product's pre-tax manufacturing price (ministerial order dated December 12, 2017):

Part of the pre-tax manufacturer price between	Pre-tax coefficient from 2018
€0 and €1.91	10%
€1.92 and €22.90	21.4%
€22.91 and €150.00	8.5%
€150.01 and €1515.00	6%
Beyond €1515.00	0%

Evolution of the sales of reimbursable drugs in pharmacies[1]

	Sales, pre-tax manufacturer price (billion euros)	Sales, public price including tax (billion euros
2015	18.0	25.1
2016	18.0	24.9
Evolution	0.0%	-0.50%

The overall growth rate of drugs expenditure is based on three effects:

- The *price effect*, corresponding to changes in the unit prices of drugs on the market.
- The *box effect,* or the difference between the number of units sold in 2015 and those in 2016, for example.
- The *structure effect*, reflecting the evolution of market share. For example, if it is negative for a certain drug, that may indicate sales migrating towards more expensive alternatives.

The average price of drugs, in pharmacies:

	2012	2013	2014	2015	2016
Average pre-tax manufacturer price of one box (€)	7.46	7.25	7.15	7.15	7.15
Average public price, including tax of one box (€)	10.39	10.15	10.00	9.96	9.90
Average margin[2] (€)	2.72	2.70	2.64	2.60	2.55

The average pre-tax manufacturer price has decreased from 2008 to 2014, when it stabilised at €7.15. The average public price, including tax and the average margin, continues to decline.

Market	Average pre-tax manufacturer price (€)	Average public price, including tax (+ fees) (€)	Average margin (€)
Generic	3.86	6.27	2.29
Originals	6.34	8.89	2.36

Discounts

There are two types of discounts: conventional and the unconventional discounts.

- *Conventional discounts*

  Article L. 162-18 of the Social Security Code provides the companies (laboratories) that may offer a discount through a national convention with the National Health Insurance Fund.

  These discounts correspond to sums due in application to the clauses provided in the contract between the Economic Committee for Medicinal Products and the laboratories. In 2016, the gross amount of such discounts amounted to €1,005 million. Most of these discounts only concern certain laboratories and certain drugs (50% of the rebates consist of those from the five main laboratories operating in France, and 44% are made up of just 10 drugs). Price or volume clauses represent a combined 41% of the total discounts, an amount of €409 million.

- *Unconventional discounts*

  Article L. 162-16-5-1 of the Social Security Code contains provisions regarding discounts for drugs which benefit from a temporary authorisation of use.

  According to the activity report of the Economic Committee for Medicinal Products, in 2016, the amount of such rebates amounted to €136 million.

Since December 21, 1988, the European Directive 89/105/EEC, known as the Transparency Directive, has imposed a regulatory framework for European countries to set prices. These provisions essentially concern regulators, who must display the criteria used to determine the price of medicines, respect response times and justify their decision on price regulation. Marketing authorisation holders must provide information for the regulator's decision. The regulation therefore concerns the manufacturer's price excluding tax.

In France, drug prices are mostly administered, although free prices exist for some specialties. Non-refundable specialities have a completely free price and distribution margins. These are either drugs for which the manufacturer has not claimed reimbursement from health insurance (the most common case), or drugs that have not been included on the list of products that can be reimbursed in a particular town or hospital.

Ambulatory drugs are reimbursed at an administered price, and were regulated until 2003. The price was the result of negotiations between the laboratory and the CEPS (Economic Committee for Health Products).

Since 2003, the price of innovative specialities has been subject to a certain degree of freedom, since the laboratory proposes it and it is then approved by the CEPS.

Hospital drug prices were completely unregulated until 2003 and were the result of negotiations between laboratories and hospitals. The implementation of activity-based pricing in hospitals has set rules for retroceded drugs as well as for expensive drugs.

Issues that affect pricing

Several facts and issues can affect the price of drugs in France.

The presence of generic and biosimilar drugs on the market

The availability of generic drugs leads to a decrease in the price of drugs for two reasons:

- The partial substitution of the original drug for the generic, as the price of the original decreases automatically under French regulations. Minimal price decreases are

implemented at the time of the generic product launching (20%) and 18 months later (12.5%).

- The price of the original is often also cut by laboratories in order to keep their product competitive.

A decrease of generic drugs is also implemented 18 months after the marketing launch (7%).

The price decrease of both drugs is linked, since the price of generic drugs is calculated according to the price of the original drugs.

These decreases apply to the pre-tax manufacturer's price.

Furthermore, French policy encourages consumers to choose less expensive generic options, with measures including:

- The "flat rate of responsibility" known as "TFR" concerning drugs where the penetration of generic drugs is considered to have been too low. The rate of reimbursement is single and is calculated on the basis of the lowest price of generic drugs. The laboratories are nonetheless free to set the price, though in practice this tends to produce an alignment between original drugs and generic drugs.
- The so-called "third-party payment against generic": Automatic reimbursement at the time of purchase (for example, in pharmacies) is possible only if patients accept generic versions of drugs if they are available.
- Various policies aimed at encouraging both doctors and pharmacies to favour the use of generics.

The development of biosimilar drugs may contribute to a decline in the price of biologic drugs (those produced from a living cell).

The public authorities assign annual price decreases to the Economic Committee for Medicinal Products. In 2016, for example, these directives led to savings of €794 million.

Supply chain

The cost of distribution can influence drug prices. As seen above, the public price includes margins that are applied to wholesalers and pharmacists, which can fluctuate.

To decrease the cost of distribution, the French court of Audit recommends regular reviews of pharmacy remunerations. The goal is for remuneration of the wholesalers to be based on the volumes delivered and not on a drug's price.

Drug counterfeiting

Drug counterfeiting may refer to various concepts, depending on the instances.

On May 29, 2017, the 7th World Health Assembly of the World Health Organisation (WTO) agreed to adopt the new name "substandard and falsified" (SF) medical products for what were designated as "substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC)" medical products. The new reference focuses only on the public health implications and not on intellectual property rights.

The WHO uses the following definitions:

- *Substandard:* also called "out of specification", which are authorised medical products that fail to meet either their quality standards or specifications, or both.
- *Unregistered/unlicensed* medical products that have not undergone evaluation and/or approval by the National or Regional Regulatory Authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

- *Falsified* medical products that deliberately/fraudulently misrepresent their identity, composition or source.

The European Medicines Agency, EMEA, also distinguishes Falsified Medicines defined as "fake medicines that are designed to mimic real medicines" from Counterfeit Medicines, described as "medicines that do not comply with intellectual-property rights or that infringe trademark law".

Counterfeit medicines can take different forms relating to the exterior packaging, the primary packaging of the drug, or the drug itself.

Falsified Medicines are fought at both the national and the European Union level with a broad legislative framework, notably:

- Directive 2001/62 on the prevention of entry into the legal supply chain of falsified medicinal products;
- Commission Delegated Regulation 2016/161 on how medicine authenticity should be verified; and
- Regulation 699/2014 on the design of the common logo to identify persons offering medicinal products for sale at distance to the public.

Drug counterfeiting is also combated through the general rules that aim to protect intellectual property rights, which involve police and customs authorities as well as civil and criminal law courts.

The link between the price of drugs and research and development

According to the pharmaceutical industry,[3] the price of drugs is linked to the necessary investments in researching, developing and manufacturing processes which can require significant funding over several years. Indeed, if the costs of research are high, the price of drugs are also quite likely to be high.

Thus, considering the high price of some medicines, reports from Expert Panels from the European Union[4] and from the United Nations[5] have proposed exploring delinkage between the costs of research and development from sales.

Competition

Competition authorities look very carefully at the medicines market and pricing. For instance, on December 19, 2013, the Competition Authority (*Autorité de la concurrence*) issued opinion n°13-A-24 about competition in the sector of drugs distribution downstream. The Authority held that dysfunctions in full competition can influence the development of the market, and thereby impact drug prices. Thus, the Authority observed a lack of information about drug pricing and suggested more transparency so that consumers would be able to compare prices between different pharmacies, promoting competition. On April 26, 2016, the Competition Authority issued an opinion on electronic commerce of medicine. Furthermore, since November 21, 2017, the Competition Authority has been investigating competition in the medicine and biological markets. Also, the European Commission has initiated formal investigation regarding Aspen Pharma' s pricing practices, and the European Court of Justice ruled on drug pricing in Germany.[6]

Transparency

Due to the rise in drug prices due to an opaque system, a group of associations called on the French government to commit itself to the "transparency" resolution presented to the WHO General Assembly on Health from 20 to 28 May 2019 in Geneva.

In France, unprecedented rationing was introduced on Hepatitis C treatments between 2014

and 2017 because it was impossible to reimburse all those who needed it. Similarly, treatments for various cancers are subject to administrative barriers to prescription, due to their price.

These associations denounce the lack of transparency in the development, manufacturing and marketing of medicines.

Foreign direct import

According to the Leem organisation (drug companies), in 2017, France imported €18.3 billion worth of medicines. These imports came mainly from Germany (17.1%), the United States (16.1%), Switzerland (12%) and Ireland (9.6%). The trade in medicines represented a trade surplus of €6.8 billion for France in 2017, but this is down sharply from 2016 (-12%).

The parallel intra-Community import of medicinal products has its origins in the coexistence of free movement and the right of States to set an administrative price for reimbursable medicinal products.

Parallel trade is the result of government decisions in some southern European countries (Greece, the Iberian Peninsula, but also France), where prices are administered to the detriment of other countries that have price freedom.

In the States concerned, parallel trade benefits only intermediaries and, exceptionally, social protection bodies. As for patients, they are exposed to supply disruptions in the French market.

In 2015, European parallel trade was estimated at €5.4 billion, without the organisation of distribution by companies being able to provide satisfactory solutions. It remains a key concern for laboratories.

Policy issues that affect pricing and reimbursement

The French government can influence pricing and reimbursement in several ways. The French Court of Audit (*la Cour des comptes*) identifies several policies in its report "Social Security 2017" dated September 2017.

Legal criteria according to Article L. 162-16-4 of the Social Security Code

Please see section, "How is the reimbursement amount set? What methodology is used" in "Pharmaceutical pricing and reimbursement".

The framework agreement

This agreement, concluded on December 31, 2015 between the Economic Committee for Medicinal Products and the pharmaceutical industry, aims to allow pharmaceutical companies to maintain an attractive price on the market, and is influenced by the initial price of a drug along with the conventional discounts.

The guarantee of the European price of the 2003 agreement influences the price of drugs by introducing a minimum price for drugs. A company cannot introduce a drug with a price lower than the minimum price in the four following countries: Germany; Spain; Italy; and the United Kingdom.

This guarantee applies to all drugs with an improvement of medical service provided (classified I to IV), and to antibiotic drugs with a substance offering a determined level IV of improvement.

The European price is granted for five years and may be renewed by a maximum of one year. This guarantee slows down the price decline for a drug.

The ministerial guidelines

Ministerial guidelines set objectives for the chairman of the Economic Committee for Medicinal Products regarding price negotiations with pharmaceutical companies.

The objectives are the following: speed of access to drug treatments; upgrading of the therapeutic progress; transparency; the proper use of drugs; the efficiency of expenditure; and in order to comply with the national health insurance system's spending objectives.

The savings targets

As seen above, the public authorities determine the amount that should be saved on individual drugs. This can take different forms: medical control of prescriptions; development of the distribution of generic drugs; deeming some drugs to be no longer reimbursable; or tariff reductions.

Population growth

In just over a decade, the world will probably have about 8.5 billion people, and nearly 10 billion by 2050, compared to 7.7 billion today according to the United Nations Population Division (World Population Prospects, 2019 Revision).

In France, the ageing of the population has led to the multiplication of certain diseases. The main expenditure item remains one-off hospitalisation, at more than €31 billion per year. Growth has been very rapid in six years, with 566,000 more patients for a total of €4 million. Diabetes, with 3.2 million patients treated and a bill of €7 billion, is also associated with age.

According to the magazine *Le Quotidien du Pharmacien*, France has 20 million chronic patients. Indeed, the medicalised mapping of health expenditure for 2017, presented by the *Caisse nationale d'assurance-maladie* (CNAM), reveals that 20 million French people have used care related to the management of a chronic pathology, representing 35% of the 57.6 million beneficiaries of the general scheme.

Cost of healthcare as a percentage of GDP

According to the 2017 edition of the *Panorama of Health* published by the OECD, France spends US$4,600 *per capita* on health, a 15% increase over the OECD average of about US$ 4,000. With 11% of GDP devoted to health expenditure, France ranks 5th among OECD countries, after the United States, Switzerland, Germany and Sweden. The number of doctors and nurses *per capita* is close to the OECD average, but the number of hospital beds is much higher (6.1 beds per 1,000 inhabitants in France compared to 4.7 beds on average).

Cost of research and development

The costs associated with the development of new medicines are increasing (almost €1 billion) according to the Leem organisation, which justifies strong protection of innovation. This is why intellectual property is one of the fundamental elements in the development of innovation. Because research companies invest in long and costly scientific programmes, they must be able to rely on the protection afforded by these rights. In 2016, France carried out 10% of international industrial studies.

Cost of innovation

Therapeutic innovation is contributing to increased spending. In total, 2.6 million people are now treated for cancer, including 1.2 million in the active phase, for an annual cost of €15 billion. Lung cancer costs on average €20,000 per year per patient, with a total expenditure of €1.6 billion. In 2017, the "list in addition" item will increase from €1,600 to €4,000. This special reserve allows hospital patients to use the most innovative and expensive drugs without draining the institution's normal budget.

Affordable access to care

Access to care is one of the fundamental rights of the user. It can be defined as the right of everyone to receive preventive or curative care without reference to a social or health situation. This is why, on January 1, 2000, universal health coverage (CMU) was introduced for the poor in order to generalise access to health insurance and to ensure that everyone has effective access to health care through the introduction of social security coverage.

How do politics affect pricing and reimbursement policy?

Unlike in other European countries, it is not social security that negotiates drug prices and reimbursement rates, but an inter-ministerial committee, the Economic Committee on Health Products (CEPS), under the joint authority of the Ministry of Health and the Ministry of the Economy.

Even if the pharmaceutical industry is not a member of this committee, it is sometimes forced to accept relatively high prices, as the Court of Auditors' 2017 report on the financing of social security still notes. For example, Crestor, a very expensive statin for social security, achieved a price four times higher than other similar generic drugs, without improving the medical service provided.

The Court of Auditors' 2017 report notes several cases where a drug manufacturer, to maintain a relatively high price, has openly used the employment and investment argument.

Emerging trends

On February 8, 2018, the French government issued an information notice in which the pharmaceutical industry was reminded to implement European Regulation 2016/16, which aims to secure the legal supply of drugs and prevent counterfeit products from being introduced in the supply chain. The regulatory rules came into force on February 9, 2019.

Possibility for pharmacists to dispense certain medicines

The draft law on the organisation and transformation of the health system opens up the possibility for pharmacists to dispense certain medicines currently on prescription.

Social regime for students

On February 15, 2018, the government definitively put an end to the social regime for students by adopting the draft law on guidance for student success. The regime will disappear on August 31, 2019. From that date, students are linked to the general social security system and will no longer pay contributions.

Therapeutic cannabis

The National Drug Safety Agency (ANSM) has announced the conditions for the delivery of cannabis for therapeutic purposes, which will initially be carried out on an experimental basis, subject to validation by the Ministry of Health.

This will be reserved for some patients whose symptoms could not be relieved by other medications.

Five indications have been selected by the Temporary Scientific Specialty Committee (TSC): neuropathic pain; certain forms of severe epilepsy; supportive cancer care; palliative care; and painful spasticity (contraction) of multiple sclerosis or other diseases of the central nervous system.

Tens of thousands of patients could be affected. A two-year experiment is planned to verify the relevance of the proposed framework.

Cannabis will be prescribed on a secure prescription by volunteer and trained doctors, specialists in the diseases concerned and working in multidisciplinary referral centres. It will then be available, from next year, in pharmacies, in the form of capsules, oil or dried flowers.

Successful market access

Successful market access will necessarily involve a balance between research costs and the prevention of competition in the drugs market. Constant innovation through patents is the key to ensuring constant revenue streams amid the steady introduction of generic alternatives.

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Endnotes

1. Extract from the activity report 2016 of the Economic Committee for Medicinal Products.
2. The distribution margin corresponds to margin of the wholesaler, margin of the pharmacist and fees for the dispensation.
3. Extract from the article, "The patent and the brand, two invaluable sesames" on the official website of pharmaceutical industry (*Les entreprises du medicament)*.
4. European Commission, Expert Panel on Effective Ways of Investing in Health, Opinion on Innovative payment models for high-cost innovative medicines, January 17, 2018.
5. United Nations Secretary-General's High Level Panel Report of the United Nations Secretary-General's High Level Panel on Access to Medicines, September 14, 2016.
6. ECJ, case C-148/15, October 19, 2016.

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Abstract

Market access for pharmaceuticals in Germany differs from the systems implemented and followed in many other countries in that there is no pricing and reimbursement approval required when launching a new pharmaceutical.

This, however, does not mean that pharmaceutical companies are completely free to charge any price they deem appropriate for their products (either existing or new pharmaceuticals). Quite the contrary, there are a number of mechanisms which directly or indirectly regulate prices or contribute to cost savings in the healthcare system. These mechanisms range from price-freezing, to compulsory rebates, reference prices limiting the reimbursement amount, and negotiated reimbursement prices for new pharmaceuticals, which kick in one year after product launch under Germany's Pharmaceuticals Market Reorganisation Act (*Arzneimittelmarkt Neuordnungsgesetz* or '**AMNOG**'). The AMNOG process was implemented in 2011 and is the key price-regulation mechanism for innovative pharmaceuticals.

The AMNOG process comprises two phases, starting with a health technology assessment ('**HTA**') conducted by Germany's Federal Joint Committee (*Gemeinsamer Bundesausschuss* or **G-BA**), followed by the reimbursement price negotiations between the Association of Statutory Health Insurance Funds ('**GKV-SV**') and the respective pharmaceutical company. The negotiated reimbursement price applies as of the 13th month after the initial product launch of the new pharmaceutical in Germany. If no agreement can be reached, the reimbursement price will be determined by an arbitration committee and will be equally applicable as of the 13th month after product launch.

The AMNOG process has fundamentally changed the market access regime in Germany and is therefore seen as something of a learning curve. While statutory health insurance funds ('**SHIs**') and the German government regard the AMNOG system as successful overall, the pharmaceutical industry is still raising numerous concerns pertaining to: (i) a relatively high number of negative assessments; (ii) data requirements which cannot be fulfilled in the early stages of product launch; (iii) undue pressure on prices by choosing generic comparators as a reference point for 'bottom-up' price negotiations; and (iv) an unbalanced governance structure which gives the GKV-SV the combined power of first influencing the additional benefit assessment conducted by the G-BA, and then negotiating reimbursement price negotiations with the respective pharmaceutical company.

Against this background, successful market access in Germany requires careful preparation, which should be initiated as early as possible. The design of pivotal trials should be structured in close collaboration with market access experts, to anticipate requirements for

the additional benefit assessment. Moreover, close collaboration with medical experts is needed in order to determine and justify the appropriate comparator for the AMNOG process.

Finally, legal advice should also be sought at an early stage because a subsequent judicial review of the substance of the decisions under the AMNOG process is possible only within certain procedural limits.

Market introduction

Market overview

Statutory and private health insurance

Germany currently has 82.2 million residents, who have access to free healthcare services based on a statutorily funded system, currently operating around 110 SHIs, which cover approx. 90% of the German population. The premiums of the SHI, levied as a percentage of gross wages up to a maximum level, are shared between the employee and the employer. Non-earning dependants of SHI members, e.g. children, are covered free of charge. Premiums of unemployed people are borne by social security.

The SHI's premiums are centrally pooled and reallocated to individual SHIs using a risk-adjusted capitation formula, taking into account age, sex, and morbidity from 80 chronic and/or serious illnesses. The SHI system is based on the principle of solidarity, meaning that all members jointly carry the individual risk of the costs of treatments in case of illness. Every member of the SHI, regardless of their income level, has an equal right to medical treatment and continued payment of wages in case of illness.

The remaining 10% of the German population are covered by private insurance, access to which is limited by a minimum income level (except for civil servants and public-sector employees, who can top up their specific health insurance regime with private insurance regardless of their income level).

Health expenditure

Total health expenditure in Germany in 2017 reached €374 billion (approx. 11% of GDP), 33% of which was spent on in-patient treatment, 17% on out-patient treatment, 17% on pharmaceuticals, and the remaining 33% on additional services and/or administration. SHIs spent around €178.7 billion in the first three quarters of 2018, generating a surplus of €1.86 billion.

As to pharmaceuticals, approx. 10% of the total health expenditure is spent on generic products, and 7% relates to patent-protected products.

In 2018, 36 pharmaceuticals (excluding biosimilar) with new active substances were launched in Germany. Twelve of them are licensed for the treatment of cancer; ten for metabolic diseases; and 15 for orphan diseases. The launch of 36 pharmaceuticals with new active substances is remarkable high and exceeds the ten-year average of 32 launches. As to the incidence and prevalence of diseases, cardiovascular diseases are amongst the most frequent causes of death in Germany (approx. 40%), followed by cancer (25%).

Taking into account the demographic change, health expenditures will significantly increase due to the ageing population and population decline in Germany. Based on current calculations, by 2060, every third resident will be 65 years or older.

Key market players

There are various players in the market that participate in self-governing decision-making

processes, while the legislator sets out the overall conditions and criteria for healthcare services.

Federal Ministry of Health / Federal Institute for Pharmaceuticals and Medical Devices

The Federal Ministry of Health ('**BMG**') is the competent federal authority for all health-related policy issues. The Federal Institute for Pharmaceuticals and Medical Devices ('**BfArM**') is an independent federal department within the BMG. Its main responsibility is to conduct the marketing authorisation process for pharmaceuticals in national proceedings.

Federal Joint Committee (G-BA)

The most important self-governing body is the G-BA. The G-BA is a public legal entity comprising the leading umbrella organisations, namely the associations of physicians and dentists, the hospital federation, and the federal association of SHIs. In addition, patient representatives can participate in all sessions, albeit with no voting rights.

The legal basis of G-BA operations is the No. 5 Book of the German Social Code, which defines and specifies the competences of the G-BA. The G-BA is under the statutory supervision of the BMG. Resolutions and directives passed by the G-BA are reviewed by the Federal Ministry of Health, and published if no objections are made. The directives enacted by the G-BA are legally binding on third parties as subordinate regulations. Thereby, they apply to the GKV-SV, individual patients, responsible physicians and dentists and any other service provider within the SHI system.

Institute for Quality and Efficiency in Healthcare

The Institute for Quality and Efficiency in Healthcare ('**IQWiG**') is an independent HTA institution. Amongst other responsibilities, it evaluates the effectiveness and/or cost-effectiveness of pharmaceuticals, either at the request of the G-BA or, in exceptional cases, on its own initiative. Its assessments are non-binding on the G-BA, but are presumed to be scientifically correct by the German social courts.

Federal Association of SHIs

The Federal Association of SHIs ('**GKV-SV**') is the federal level association of all SHIs. Members of the GKV-SV are represented in the G-BA and can thereby influence its decision-making process. As regards pharmaceuticals with new active pharmaceutical ingredients ('**APIs**'), the GKV-SV is also the contractual party negotiating and concluding agreements on reimbursement prices with the respective pharmaceutical companies.

Associations of pharmaceutical companies

The pharmaceutical industry is primarily represented and organised by four associations, namely: the association of research-based pharmaceutical companies ('**VFA**'); the federal association of the pharmaceutical industry ('**BPI**'), which also represents medium-sized pharmaceutical companies; the federal association of pharmaceutical manufacturers ('**BAH**'), which represents prescription ('**RX**') and over-the-counter ('**OTC**') companies; and Pro Generika, which represents generic companies only.

Pharmaceutical pricing and reimbursement

Access to treatment with pharmaceuticals: no fourth hurdle

As a general rule, all patients covered by the SHI are entitled to adequate treatment of diseases, including the administration of pharmaceuticals. The SHI system is based on the principle of providing benefits in kind. This means that patients do not have to pay for

medical treatment themselves in the first place and then seek reimbursement from their individual SHI. Instead, patients receive the medical treatment in kind, including pharmaceuticals, without making any of their own payments (except for statutorily regulated co-payments), and the SHI then reimburses the pharmacists.

The right to treatments with pharmaceuticals generally covers all pharmaceuticals available on the market, i.e. all products with a valid marketing authorisation in place. Unlike systems in many other countries, the patient's access to the treatment with a pharmaceutical is not dependent on any further approval of pricing and reimbursement (i.e. there is no so-called 'fourth hurdle'). Nevertheless, this right is subject to certain restrictions.

Restrictions on patient's right to treatment with pharmaceuticals

Exclusion of OTC products from reimbursement

First, non-prescription pharmaceuticals are generally excluded from reimbursement. Thus, this limits patients' right to treatment with pharmaceuticals. Patients requiring these non-prescription pharmaceuticals must purchase them at their own expense.

There are only two exceptions to this general rule, pertaining to: children under 12 years old or adolescents under 18 years old with developmental disorders; and specific OTC pharmaceuticals which are recognised as standard treatment for severe diseases. In these scenarios, patients will receive the products from pharmacies without making any payment of their own (except for statutorily regulated co-payments).

Second, pharmaceuticals licensed for the treatment of minor diseases (so-called 'trifle pharmaceuticals') are likewise excluded from reimbursement. The same applies to 'lifestyle pharmaceuticals' which are not designed to treat diseases but simply to improve the quality of life (e.g. pharmaceuticals licensed for the treatment of erectile dysfunction, smoking cessation or body-weight control).

Restrictions by G-BA Guidelines

In addition, the G-BA has the right to exclude or restrict the reimbursement of pharmaceuticals by way of guidelines or therapeutic recommendations. In this case, the respective pharmaceuticals may only be prescribed at the expense of the patient's SHI on the basis of explicit justification of specific medical reasons by the physician. Conversely, in the absence of a justification for medical reasons, the patient must purchase the product at their own expense.

The G-BA may restrict or limit reimbursement of pharmaceuticals on the grounds that the therapeutic benefit, medical necessity or cost-effectiveness of the product cannot be established, or that a more cost-effective treatment with equivalent therapeutic benefit is available. In this respect, it should be noted that the burden of proof for the lack of therapeutic benefit or the lack of cost-effectiveness is with the G-BA. Moreover, when assessing the therapeutic benefit and medical necessity of a pharmaceutical, the G-BA must not contradict the findings and assessments made by the competent regulatory authority, which has granted the marketing authorisation (i.e. BfArM). Finally, restrictions or exclusions of reimbursement are considered as an '*ultima ratio*' tool, and can only be determined if cost-effectiveness cannot be established by other price regulation mechanisms.

Price regulation mechanisms for pharmaceuticals

In the absence of a fourth hurdle, pharmaceutical companies may, in general, freely determine market prices when launching their products. However, there are various mechanisms which directly or indirectly regulate prices or contribute to cost-savings in the

healthcare system. These price regulation mechanisms range from price-freezing to compulsory rebates, reference prices limiting the reimbursement amount (incurring co-payment obligations by patients), and negotiated reimbursement prices for new pharmaceuticals.

Mandatory rebates/price freezing

The following rebates must be granted by the pharmaceutical companies:

- general rebate of 7% of the manufacturer's price to be paid by the pharmaceutical companies to the SHIs for all pharmaceuticals which are not subject to a more specific price regulation;
- special rebate of 10% of the manufacturer's price to be paid by the pharmaceutical companies to the SHIs for generics;
- special rebates for vaccines to be paid by the pharmaceutical companies to the SHIs which are calculated on the basis of actual average prices in the four Member States of the EU with gross national incomes coming closest to the German one; and
- price-freezing until end of 2022 for all pharmaceuticals launched before 1st August 2009.

Reference price system

Another important price regulation mechanism covering the vast majority of pharmaceuticals is the reference price system which was introduced in 1989. In 2017, 81% of all prescriptions issued for treatments with pharmaceuticals referred to products regulated by the reference price system, thereby covering 37% of the overall expenditures by the SHIs for pharmaceuticals.

Under the reference price regulation, pharmaceuticals are allocated to specific 'reference price groups'. These groups can be established on the basis of: (i) products having the same API; (ii) products having pharmacological or therapeutically comparable APIs; or (iii) products having comparable therapeutic effects, including combination products consisting of more than one API. These reference groups are established by the G-BA and can also combine generic and patent-protected products. Patent-protected products can only be exempted from the reference price system if a pharmaceutical company can prove that such product has an additional therapeutic benefit compared to other pharmaceuticals of the same group. This additional therapeutic benefit must generally be established on the basis of RCT, including head-to-head studies with relevant patient end-points, including mortality, morbidity and quality of life.

Once the G-BA has established the reference price groups and defined the comparative figures to calculate the prices, the GKV-SV determines the reference prices for all products belonging to the same reference group. As a general principle, the reference prices must be set at a level ensuring a sufficient, cost-effective, quality-assured and appropriate treatment of patients.

The reference price allocated to a product constitutes the maximum amount of reimbursement to be paid to the pharmacist by the SHI. Therefore, if the market price of the pharmaceutical exceeds the applicable reference price, the patient will need to make a corresponding co-payment to the pharmacist. To avoid these co-payments, a patient will usually ask the physician to prescribe a product of the same reference group with a market price available below or equal to the reference price. Therefore, in most cases, pharmaceutical companies lower their market prices to the respective reference price to avoid this substitution by prescription of competing products.

AMNOG process for innovative pharmaceuticals

Background

While the reference price system has proven to be quite effective in regulating pricing and reimbursement for established products, the situation is different for new and innovative products. As a matter of fact, reference groups can only be built if a minimum number of comparable pharmaceuticals are already available on the market. If, however, a new product with a new pharmacological mode of action enters the market, it is often difficult to include such product in an existing reference price group or to build a new reference price group.

Against this background, in 2011, the German legislator decided to introduce a new price regulation scheme, the so-called 'AMNOG process' (see above). The AMNOG process generally applies to all pharmaceuticals with new APIs, and consists of a two-step process, namely: first, an HTA assessment conducted by the G-BA; which is followed, secondly, by price negotiations between GKV-SV and the respective pharmaceutical company.

Beyond that, since 2017 a marketing authorisation has also been granted for those pharmaceuticals subject to the AMNOG process which consist of established APIs enjoying the protection of clinical data. The underlying rationale was to cover situations such as with the established API *Alemtuzumab*, for which a new indication covering multiple sclerosis was granted. However, The AMNOG process does not apply to pharmaceuticals that are likely to cause only minor expenses to be borne by SHIs. Manufacturers of such pharmaceuticals may request release from the process, which is granted by the G-BA.

The G-BA has assessed the threshold in this context to €1 million. In the recent past, there had been discussions on the question of whether expenses incurred in the in-patient sector were included in the €1 million threshold. Against this background, the legislator clarified that not only expenses generated by panel doctors must be included in the calculation process, but also those in the inpatient sector, as these expenses must be borne by SHIs as well.

HTA process

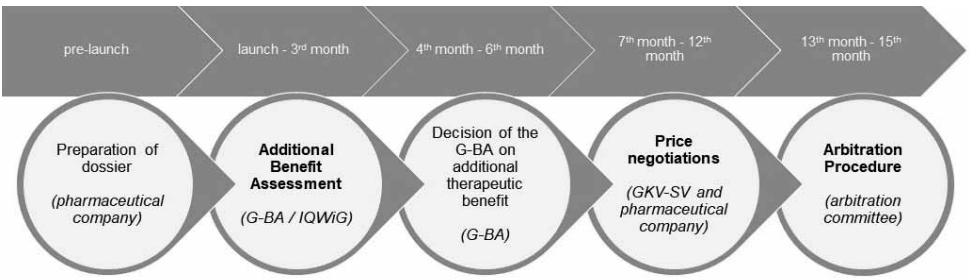
The AMNOG process does not change the general principle that pharmaceutical companies remain free to determine the launch price for innovative pharmaceuticals. Upon launch, however, they are obliged to submit a dossier to the G-BA in order to establish the cost-effectiveness of the new pharmaceutical. The G-BA then conducts a comprehensive HTA as to the so-called product's 'additional therapeutic benefit' in comparison to recognised standard therapies ('**additional benefit assessment**'). To this end, the G-BA usually engages the IQWiG, which is charged with the scientific assessment of the dossier.

Once the IQWiG has completed its scientific assessment, the G-BA takes a final decision within six months. This decision contains the final rating of the additional therapeutic benefit of the relevant pharmaceutical with respect to the selected comparator. The additional therapeutic benefit must be specified across a range of different levels. While level 1 reflects an extensive additional benefit over the defined comparator, level 6 is equal to a 'negative additional benefit'. Moreover, the G-BA also states the level of evidence by which such benefit is established. Again, these levels of evidence cover a broad range, including a proof of an additional therapeutic benefit as well as a mere indicator.

If no additional therapeutic benefit can be established, the respective pharmaceutical shall be allocated to an existing reference price group, if possible. If a suitable reference group neither exists nor can be established, the reimbursement price will be negotiated between the GKV-SV and the pharmaceutical company. However, the negotiated reimbursement

price must generally not exceed the annual costs of treatment of the comparator, unless specific circumstances justify a higher reimbursement price.

Reimbursement price negotiations



Following the additional benefit assessment by the G-BA, pharmaceutical companies enter into price negotiations with the GKV-SV. These negotiations shall conclude with a reimbursement price agreement agreed between the parties, the most important provision of this agreement being the reimbursement price. Other provisions of this agreement usually refer to volume discounts, replacement of mandatory rebates, termination rights, etc. The conclusion of this agreement shall occur within a period of six months after the publication of the G-BA's resolution. If the parties cannot reach an agreement, an arbitration process is triggered.

For pharmaceuticals for which an additional therapeutic benefit has been acknowledged, the price negotiations must take into account various criteria, the most important being the G-BA's assessment on the level and evidence of the additional therapeutic benefit. In addition, the actual costs for the pharmaceutical in other EU Member States shall be considered as well as the annual therapeutic costs of comparable pharmaceuticals. Generally, there is no strict algorithm to be followed when determining the reimbursement price. In practice, however, the SHI pursues a 'bottom-up' approach based on the costs of the defined comparator and a 'premium' for the innovative product reflecting its additional therapeutic benefit. In contrast, pharmaceutical companies try to pursue a 'top-down' approach, using the launch price as a starting point, and offering a respective rebate, taking into account the G-BA assessment as well as all other, legally applicable criteria.

The negotiated reimbursement price applies to all pharmaceuticals containing the same new API. Thus, if a different pharmaceutical company launches another product with the same new API after the first launch, the reimbursement price agreed with the pharmaceutical company having launched the first product containing this API applies to this other product (and all subsequent products) too.

Reimbursement price agreements can be terminated, at the earliest, one year after signing. However, in case of a new additional benefit assessment by the G-BA, a prior termination is possible. In case of a termination, the formerly agreed reimbursement price remains temporarily in place until an agreement on the new reimbursement price is reached, which will be applied retroactively as of the effective termination date of the old agreement. The statutory time period for the conclusion of a new agreement is six months, otherwise the arbitration process will be triggered.

Arbitration procedure

If no reimbursement price agreement can be reached within the statutory period of six months, an arbitration committee shall determine over a period of three months those elements of the reimbursement price agreement on which the original parties had been unable

to reach a consensus. The arbitration committee is composed of representatives of the GKV-SV and the respective associations of the pharmaceutical companies. It is further composed of three impartial permanent members, as well as two further members of each party. This arbitration procedure is technically an administrative procedure. The arbitration committee is bound by the legal criteria set out under the German social law system but enjoys broad discretion when it comes to the actual determination of the reimbursement price.

The reimbursement price which has been either agreed by the parties or set by the arbitration committee will be applicable with retroactive effect as of the 13th month after the initial product launch. Consequently, the pharmaceutical company has a right of free-pricing its product during the first 12 months after its launch. This has been criticised by representatives of the SHI; nevertheless, this petition has not resulted in any change in the current AMNOG system so far.

Special problems: Blended pricing in case of a mixed HTA

When determining the reimbursement price, special attention must be paid to a situation in which an additional therapeutic benefit was accepted by the G-BA assessment for one specific indication of a new product but denied for another indication of the same product.

Theoretically, there could be two different options to determine the reimbursement price in such scenario: First, it could be considered to determine a blended price, which would reflect the fact of superiority in one indication and non-inferiority in the other indication. Alternatively, the price could be set reflecting the additional therapeutical benefit in one indication only. In such scenario, the new product then would have to be excluded from prescription for the other indication for which no superiority has been shown. This is because the prescription of the product with a higher price without showing any additional therapeutical benefit would have to be considered as inefficient and uneconomic for such indication.

To ensure broad access to innovative products in all indications, it had been a standard and well-established practice to agree on blended prices in such scenario. However, very much to the surprise of the industry and the SHI, the Higher Social Court of Berlin-Brandenburg decided in March 2017 against the model of blended pricing. The court held that no blended prices could be determined, if such blended price would exceed the costs of the respective comparator applicable for patients in the indication without additional therapeutic benefit.

However, this decision was revoked by the decision of the Federal Social Court in summer 2018. The Federal Social Court held that blended pricing was a legitimate method to reflect a mixed HTA assessment by the G-BA across indications. Also, the court reinforced the general principle of flexibility and discretion when fixing such blended price either by the parties or the arbitration body, and strongly rejected the concept of a strict algorithm with respect to the costs of a comparable generic treatment.

Judicial review

The decisions by the arbitration committee are subject to judicial review by the higher social court of Berlin-Brandenburg. The courts' review will be limited to the assessment of whether the arbitration committee has established and considered all relevant facts, followed applicable procedural rules and duly taken into consideration substantive legal criteria. The latter include – in case of a determined additional therapeutic benefit of the product – the additional therapeutic benefit as defined by the G-BA, actual market prices in the EU, as well as annual costs of comparable pharmaceuticals.

The actual derivation and determination of the reimbursement price, as such, however, is only subject to limited judicial review, given that such decision is discretionary in nature and must be based on a subjective assessment of all relevant facts and circumstances of the individual

case. Finally, legal proceedings have no automatic suspensive effect so that the reimbursement price set by the arbitration committee will apply with effect from the 13th month after initial product launch unless suspensive effect is exceptionally granted at the request of either party.

Policy issues

Background of AMNOG process

The AMNOG process applies to all pharmaceuticals with new APIs, and does not distinguish between different areas of indications or treatments. As such, it is designed to be neutral, being strictly based on the assessment of clinical data. In practice, however, policy issues can indirectly influence the decision-making process, both with a view to cost-containment and control on the one hand, and access to innovative pharmaceuticals on the other.

Main challenges of AMNOG process

Since its implementation, the AMNOG process has been labelled as a learning system by political representatives and other stakeholders. By this notion, it is acknowledged that there is no expectation that the system will work perfectly and smoothly from day one, but that it may need to be adjusted and modified as it evolves in its daily practice. When assessing the experience gained through the AMNOG process since its entry into force in 2011, a number of observations can be made:

High number of negative assessments

The percentage of assessments in which no additional therapeutic benefit could be proven is considerably high (43% of overall 228 assessments by G-BA made between 2011 and 2016). With regard to sub-groups to stratified substances, this percentage increases to 61% and even to 76% with respect to specific patient populations. These figures have been consistently increasing over the past years.

While new pharmaceuticals in the field of oncology have been assigned more positive additional benefit assessments, the results for pharmaceuticals in the fields of diabetes and neurology, which account for almost one-third of all assessments, have been far less positive. In most cases, the absence of an additional therapeutic benefit was not due to a negative assessment of clinical data, but was based on the grounds of a lack of specific data for respective sub-groups. This lack of evidence has triggered criticism from the pharmaceutical industry with regard to the G-BA's practice of possibly 'slicing' patient populations into sub-groups and demanding data which cannot be available at the early stages of market entry of an innovative product.

Determination of low-cost comparators

Further critical comments refer to the insufficient distinction between the G-BA assessment process on the one hand and the reimbursement price negotiation process on the other. As the price negotiations are based, in practice, on the price of the respective comparator (bottom-up approach), the determination of the suitable comparator in the G-BA assessment process is of utmost importance. It is argued by the pharmaceutical industry that the selection of suitable comparators by the G-BA has been biased in a number of cases because of the selection of a generic 'low-cost comparator', even though alternative, more innovative and thus more expensive, comparators would have been more appropriate.

It should be noted that the price pressure of low-cost comparators is so strong that almost 90% of the reimbursement prices negotiated or determined by arbitration are below the average price of the same drugs in comparable European countries, and around 60% are even below their lowest prices.

Unbalanced governance

Associated hereto is the question of governance within the G-BA. As a matter of fact, the GKV-SV is able to significantly influence decisions of the G-BA by its own representatives. Thus, under the current system, the GKV-SV is able to influence the substantive basis for the price negotiations, which it then conducts itself.

Transparency of reimbursement prices

Technically, the reimbursement price is determined as a rebate to be granted by the pharmaceutical company to the SHI on the manufacturer's market price. Contrary to the mandatory rebates, this rebate is not granted directly from the pharmaceutical company to the SHIs but via the distribution channels to wholesalers and pharmacists. Thus, in practice, the reimbursement price lowers the actual market price of the respective pharmaceutical and, as such, is completely transparent and publicly known. Because of this, reimbursement prices under the AMNOG process can have an indirect pricing effect on other markets, which reference their reimbursement prices to the German system. This has triggered a debate by the pharmaceutical industry on amending the AMNOG mechanism in a way that the agreed rebates, similar to the mandatory rebates outlined above, are granted directly to the SHIs, so that the actual, publicly known market price remains unaffected.

Opt-out

Generally, within a period of 14 days after the first round of negotiations with the GKV-SV, a pharmaceutical company may opt-out of the AMNOG procedure by withdrawing its product from the German market (opt-out right). This leads to a complete cancellation of the AMNOG process, and no reimbursement price will either be agreed or determined by the arbitration committee. In practice, a number of withdrawals of products for which an additional therapeutic benefit could not be established, has occurred. The reason for this is that in these cases, the reimbursement price must generally not exceed the annual costs of the cheapest comparator. If generic products are selected as comparators, the maximum reimbursement price for these innovative products is limited by this generic price level.

In this context, data published in 2017 show that the availability rate of innovative products has dropped from 98.5% to 80.24% due to pharmaceutical companies not entering the German market. Already at this point in time, a total of 28 products were no longer available on the German market.

Free pricing in first year after product launch

Then again, the pharmaceutical industry has been criticised by the SHI for setting 'astronomically high' prices for certain products and thereby allegedly abusing the possibility of free pricing during the first 12 months of a product's launch (a prominent example is the launch price for the Hepatitis C drug *Sofosbuvir* being, when it was launched in Germany at a market price of over €700 per tablet). Against this background, the SHI is still lobbying for a restriction of the right for free pricing in year one.

Limited impact on prescriptions by physicians

Finally, it should be noted that the G-BA assessment seems to have limited influence on the prescription decisions made by physicians. Even new pharmaceuticals which have received a positive additional benefit assessment by the G-BA seem to penetrate the German market rather slowly. In fact, local and regional SHIs often put pressure on physicians not to prescribe innovative products on the grounds that sufficient medical treatment could also be achieved by prescribing less expensive generic alternatives.

Emerging trends

Pharma Dialogue

Under the leadership of the German Ministry of Health, a campaign called 'Pharma Dialogue' designed to include all stakeholders (e.g. the pharmaceutical industry and the SHI), was initiated in 2014, aiming to address problems and issues which need to be resolved in order to ensure better conditions for access to innovative pharmaceuticals. In 2018, for the first time, representatives of the governing parties of the German Parliament as well as of state parliaments participated in the Pharma Dialogue. It was discussed how to safeguard the supply of pharmaceuticals and how to strengthen the pharmaceutical industry in Germany with a focus was on digitalisation, innovative approaches and the know-how-transfer between universities and the private sector.

AMNOG reform act: New information system for physicians

With the AMNOG-reform act ('**AMVSG**'), which came into effect in May 2017, *inter alia* a new information system is to be established aiming to provide physicians with quick and direct access to all assessments made by the G-BA. Regarding the implementation of the system, a first draft of the Directive concerning the Electronic Medicinal Product Information ('**EAIMV**') was published in October 2018. According to this draft, the software already used for prescribing pharmaceuticals, which provides information on APIs and the scope of the marketing authorisation, shall include information regarding the patient groups for which an additional therapeutic benefit may be established. The additional therapeutic benefit must be shown in connection with the appropriate comparative therapy, separated und summarised for the different patient groups.

The system will provide a concise and comprehensive summary with a maximum of 3,000 characters regarding the main grounds of the GBA's decision on the additional therapeutic benefit. Additionally, it will show the benefits of the evaluated medicinal product for the different patient groups. However, the pharmaceutical industry is criticising the draft on the grounds that it does not take the guidelines by the medical societies into account, stressing that the decision to choose a treatment depends on more than just an additional benefit. The information system should be considered as an instrument for price control rather than prescription control.

EU harmonisation on HTA

The recent proposal for a European regulation on harmonised rules regarding HTAs by the European Commission has been intensely debated in Germany. While the national associations of the pharmaceutical industry have taken the positive view that such harmonisation could facilitate and streamline the hitherto very fragmented market access process in the EU, the G-BA has been rather critical of this for a number of reasons, including the perspective of losing its influence if the HTA process is shifted from national authorities to European institutions.

Eventually, since *inter alia* the German Parliament considered the approach as non-compliant with subsidiarity, it sent a reasoned opinion to the European Commission, which was found justified. The EU lacks competence for harmonising clinical assessment; it is especially not permitted to bypass Member States' responsibility for health services by way of the internal market competence. The obligations connected to a joint assessment entail intervention in the health policies of the Member States, because the HTAs that are the subject of the legislation constitute an essential element of the 'management of medical care'. Hence, the EU Parliament mitigated the draft in several points; it shall, for example, be possible for Member States to conduct additional HTAs, and the HTA shall not be exclusive.

The impact of the ECJ judgment regarding fixed prices for prescription-only pharmaceuticals

The judgment of the ECJ issued in October 2016, ruling that foreign mail order pharmacies are not bound by the German pricing regime, has triggered a debate as to whether the hitherto liberal German pharmacy mail order regulation can still be upheld. National pharmacists are lobbying for a ban of distribution of prescription pharmaceuticals ('**RX products**') by mail order pharmacies.

The German Federal Minister of Health published key points regarding future developments for the pharmacy market. In terms of RX products, he suggested a limited bonus of €2.50 for foreign pharmacies per pack of prescription-only pharmaceuticals, and a stronger evaluation of developments in the field of RX products, meaning that a stronger regulation could apply for foreign mail order pharmacies if their market share of RX products reached a threshold of 5%. National pharmacists especially criticised and rejected the suggested bonus system, arguing this would abolish the principle of equal prices in the German pharmaceutical market, which would jeopardise the availability of medicinal products in Germany.

Finally, against the background of the ECJ judgment, a verdict of the Federal Administrative Court is expected in terms of the question of whether the German pricing regime for prescription-only medicinal products discriminates against national, i.e. German pharmacists concerning their right to freely pursue a professional activity pursuant to Art. 12 para. 1 and Art. 3 para. 1 of the German Basic Law.

Security in supply with medicinal products

The Act for More Security in Supply with Medicinal Products ('**GSAV**'), which is still at the beginning of the legislative process, has been proposed as a reaction to the recall of contaminated *Valsartan* products. While it focuses on supply security aspects, it also entails relevant changes regarding the additional benefit assessment and the competences of the G-BA.

First, the GSAV *inter alia* aims at fostering the use of biosimilars. To this end, prescribing biosimilars shall be generally considered to be cost-efficient within the SHI. Additionally, the G-BA shall be assigned new competences to publish guidelines stipulating which originators may be substituted by biosimilars. Connected to that, automatic substitution will gradually be introduced for defined biosimilars. Eventually, target agreements concerning minimum quotas for prescribing biosimilars, and for efficient prescribing on regional levels, shall be promoted.

Furthermore, the Act provides changes regarding orphan drugs. Currently, orphan drugs not exceeding a turnover of €50 million, are privileged in terms of the additional benefit assessment in that an additional therapeutic benefit will be assumed, with no need to provide further evidence in the respective dossier. With the GSAV, the G-BA can restrict the possibility to prescribe orphan drugs to certain panel doctors or other institutions which participate in data-collection programmes regarding the use of orphan drugs. This has triggered a debate whether limited access to orphan drugs may be expected with this change. Furthermore, when determining the turnover of an orphan drug, sales generated in the inpatient sector shall also be included, although reimbursement for inpatient treatment will not be subject to AMNOG prices but to the DRG system. Against this background, it is assumed that orphan drugs will exceed the turnover threshold of €50 million faster, and thereby become subject to the standard AMNOG process.

The GSAV bill also targets special pricing and reimbursement rules for medicinal products for the therapy of coagulation disorder in case of haemophilia. According to the bill, the

manufacturer's price for such medicinal products shall be oriented towards the volume-weighted arithmetic average purchase prices which hospitals and physicians have paid for these products in 2017 and 2018. The pharmaceutical companies will then have to report this price to the GKV-SV where it will be checked for plausibility. If either the pharmaceutical companies do not announce the respective average price, or the GKV-SV does not consider the reported price plausible, it may determine the future manufacturer's price itself pursuant to the SHI-notifications.

Another aspect addressed by the GSAV is an improvement in the supply of cannabis-based medicinal products. *De lege lata*, such cannabis-based medicinal products are already covered by the SHI under specific conditions, although additional SHI approval is required for reimbursement. In accordance with the GSAV reform, the requirement for SHI approval will be simplified, and the process will be shortened. The overall aim is to safeguard a frictionless and continuous supply of cannabis-based medicinal products.

Finally, the bill includes an attempt to align the pricing for cytostatic treatments. Cytostatic treatments enjoy an exceptional position in the German statutory framework in that prices have, up to now, been subject to individual rebate contracts between single SHIs and pharmaceutical companies. This situation has caused significant price differences for the same cytostatic treatment, depending on the negotiating power of individual SHIs. To address this problem, the bill provides that such rebate contracts shall no longer be concluded by individual SHIs, but only SHI-overarching. It is expected that the GSAV will enter into force by July 2019.

Access to doctors' appointments and better medical care

Especially due to shortages of vaccines in 2018, the German government is planning to reopen the market to all vaccine manufacturers and to move away from selective contracting schemes. To this end, the government issued a draft bill for the Act for Earlier Doctor's Appointments and Better Medical Care ('**TSVG**'), which is still subject to further steps in the legislative process. Under this, the government proposes to limit the SHI reimbursements for pharmacists to the pharmacists' actual purchase price paid to the respective manufacturer. By this means, incentives to pharmacists regarding lower individual price negotiations with vaccine manufacturers will be eliminated.

Additionally, the draft bill of the TSVG includes provisions to increase the mandatory rebates for vaccines that manufacturers must grant:

- First, in future, the calculation of these rebates shall be oriented towards the actual average prices in the four states of the EEA – not only the EU – the gross national incomes of which come closest to Germany's.
- As a second action, the draft bill proposes an additional rebate-surcharge for vaccines for the benefit of SHIs. For that purpose, the mandatory rebate based on the EEA reference prices shall be increased by 5% of the manufacturer's price for vaccines in general, and even by 10% for vaccines addressing seasonal influenza. This suggestion is yet subject to criticism, as another markdown might make the German vaccine market even more unattractive for manufacturers. Thus, this measure would risk rather adverse effects instead of improving the medical supply of vaccines.

Successful market access

Even in the absence of a fourth hurdle, successful market access by pharmaceutical companies in Germany requires careful preparation and a well-structured approach. It is

crucial that this process is only initiated after marketing authorisation has been granted. Market access and regulatory experts should therefore work closely together in integrated teams throughout the whole marketing authorisation application process.

To this end, the design of the pivotal trials should be discussed and structured not only with respect to regulatory and clinical aspects but also anticipating requirements for a successful additional benefit assessment under the AMNOG process. As outlined above, a high number of negative additional benefit assessments is based on the mere absence of clinical data requested by the G-BA. Such a situation can only be avoided if the market access perspective is integrated in the marketing authorisation process as early as possible.

Furthermore, close collaboration between market access and medical experts is needed in order to map out a strategy concerning the G-BA's determination of the appropriate comparator for the AMNOG process. Given the 'bottom-up' nature of the price negotiation process, the determination of the appropriate comparator can substantially influence the potential for agreeing the ultimate reimbursement price.

Finally, it is important to involve internal or external legal experts at the earliest stage of the AMNOG process, given that courts are reluctant to challenge the scientific assessment made by the IQWiG or G-BA in substance. Thus, as judicial review will be limited to potential violations of procedural rules, as well as misinterpretation of substantive legal requirements, it is even more important to identify such potential legal trigger-points at the very beginning, and to integrate them in the overall process.

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India

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Abstract

Healthcare is the largest industry in India, in terms of revenue and employment. Being the fastest-growing sector, the Indian healthcare market is expected to be worth US$ 372 billion by the year 2022. By 2020, India is set to be among the top three healthcare markets in the world.

Healthcare and pharmaceuticals are at an all-time high and India is increasingly becoming a destination for medical tourism. In such circumstances, more and more opportunities are being created for expansion of the industry.

With the world's largest healthcare scheme in place and the rate at which the industry is growing, there are several challenges as well as prospects in store for both pre-existing and new pharmaceutical entities.

In the following chapter, we endeavour to throw some light on the major policies effected by the Government of India over the past year, against the backdrop of the country's laws and regulations and the varied healthcare and pharmaceutical landscape.

Market introduction/overview

India is expected to become the world's largest high quality drugs supplier and the pharmaceutical sector aims to grow in value to US$ 120–130 billion by 2030, from the current US$ 38 billion. The turnover of the domestic pharmaceutical market reached US$ 18.12 billion in 2018, growing 9.4% year-on-year from US$ 17.87 billion in 2017. In February 2019, the Indian pharmaceutical market grew by 10% year-on-year.

With more than 3,000 pharmaceutical companies and over 10,500 manufacturing facilities, India continues to remain the pharmacy of the world by being the largest provider of generic medicines globally. India's pharmaceutical exports amounted to US$ 17.27 billion in 2018 and have already exceeded US$ 15.52 billion in January 2019. Exports from India satisfy 40% of the generic demand in the US; 25% of all medicines in the UK; and 50% of the world's vaccine requirements. India is additionally the fourth-largest medical devices market in the world.

Despite the exponential growth, India is increasingly addressing the need for skilled workers in the medical sector, home-based care services, access to medicines in rural areas, and affordability. One of the initiatives by the Indian Government is 'Pharma Vision 2020', which is aimed at making India a global leader in end-to-end drug manufacture, resulting in reduced costs of production and increased investment.

Pharmaceutical pricing and reimbursement

The Indian pharmaceutical market, albeit a highly regulated market, is a scattered one. A brief insight follows into the key Ministries discharging various roles pertaining to health, pharmaceutical products, etc. in India:

1. Ministry of Health & Family Welfare ('MoHFW'): The Ministry is primarily responsible for ensuring the availability of quality healthcare on an equitable, accessible and affordable basis, by establishing a comprehensive primary healthcare delivery system and well-functioning linkages with a secondary and tertiary healthcare delivery system. As per the Union Budget 2019–20, the allocation to the Ministry of Health and Family Welfare has increased by 13.1% to Rs 61,398 crore (US$ 8.98 billion).

   The MoHFW has two departments *viz*., the Department of Health & Family Welfare and the Department of Health Research ('DHR'). The Directorate General of Health Services ('DGHS') is the attached office of the Department of Health & Family Welfare and has subordinate offices spread all over the country. The DGHS renders technical advice on all medical and public health matters and is involved in the implementation of various health services.

   The Central Drugs Standard Control Organisation ('CDSCO') under the DGHS, is the National Regulatory Authority ('NRA') of India. The CDSCO is responsible for the approval of drugs; conduct of clinical trials; laying down standards for drugs; control over the quality of imported drugs in the country; and coordinating the activities of State Drug Control Organisations by providing expert advice, with a view to bringing about uniformity in the enforcement of the Drugs and Cosmetics Act, 1940 ('D&C Act') and the Drugs & Cosmetics Rules, 1945 ('D&C Rules').

   On the other hand, the aim of the DHR is to bring modern health technologies to the people through research and innovations related to diagnosis, treatment methods and vaccines for prevention; to translate them into products and processes and, in synergy with concerned organisations, introduce innovations into the public health system.

2. Ministry of Chemicals & Fertilizers: The Ministry of Chemicals and Fertilizers in India is the administrative unit of the following three departments:

   a) Department of Chemicals and Petrochemicals.

   b) Department of Fertilisers.

   c) Department of Pharmaceuticals ('DoP').

   The DoP was created with the objective of giving greater focus and thrust to the development of the pharmaceutical sector in the country, and regulating issues related to the pricing and availability of medicines at affordable prices, research & development, protection of intellectual property rights, and international commitments related to the pharmaceutical sector which required integration with other Ministries.

   The National Pharmaceutical Pricing Authority ('NPPA') was constituted on August 29, 1997 as an attached office of the DoP, as an independent Regulator for the pricing of drugs and to ensure the availability and accessibility of medicines at affordable prices in the country.

   While the governing statutes in the country are the D&C Act, along with the D&C Rules framed thereunder, and the Essential Commodities Act, 1955, the following is a list of some of the notable rules/policies framed under the said Acts in order to further the aforesaid objectives of the Government:

1. Drugs (Price Control) Order, 2013 – Issued in exercise of Section 3 of the Essential Commodities Act, this Order envisages regulation of prices of essential drugs, including notified medical devices, in the country and monitoring of prices of non-essential drugs.
2. The Uniform Code of Pharmaceutical Marketing Practices (UCPMP) – The UCPMP was implemented with effect from January 1, 2015 as a voluntary code for marketing practices for the Indian Pharmaceutical Industry. The Department is now proposing to make UCPMP mandatory, along with introducing penal provisions if companies are found to be in violation of the Code.
3. Medical Devices Rules, 2017 – The Medical Device Rules, 2017 were notified by the MoHFW, in exercise of its powers under Sections 12 & 33 of the D&C Act, on January 31, 2017, and came into effect from January 1, 2018. The Rules attempt to establish a uniform regime for Indian medical device manufacturing and marketing.
4. National Health Policy, 2017 – This policy, which is a guidance document for the health sector in five-year plans, envisages the attainment of the highest possible level of health and wellbeing for all ages, through preventive and pre-emptive healthcare orientation in all developmental policies, and universal access to good quality healthcare services. It aims to achieve this through increasing access, improving quality and lowering the cost of healthcare delivery.
5. New Drugs and Clinical Trials Rules, 2019 – The Rules were notified by the MoHFW, in exercise of its powers under Sections 12 & 33 of the D&C Act, on March 19, 2019, primarily with an intention to regulate clinical trials in the county. One significant change is the automatic approval granted to new drugs in the country if the said drugs have been previously approved in select developed markets, and if global trials have included Indian patients.
6. SUGAM – An online licensing system introduced by CDSCO, enabling online submission of applications requesting permissions related to drugs, clinical trials, ethics committees, medical devices, vaccines and cosmetics. The system builds up the database of approved drugs, manufacturers & formulations, retailers & wholesalers in India. The portal also consolidates and publishes data about permissions and licences being issued by various states' Food & Drug Administration offices in the country. This includes details of manufacturers, manufacturing sites and drug formulations. Manufacturers can view their consolidated data about permissions issued to them from State FDAs.

Drug pricing

In India, while all drugs are considered essential under the Essential Commodities Act, the Government does not control the prices of all drugs. Only those medicines which satisfy the priority healthcare needs of the majority of the population are brought within price control regulations, by including them in the National List of Essential Medicines ('NLEM'), which is a dynamic list, and is revised from time to time by the MoHFW. The list then forms part of the Drugs (Price Control) Order, 2013 ('DPCO 2013'), which is an order issued by the Government of India under Section 3 of Essential Commodities Act, 1955 to regulate the prices of drugs.

The NPPA, the Drugs Controllers of the State, and Drugs Inspectors of the District are the enforcing authorities at National / State / District Levels.

Prices of all such drugs, which are included in the DPCO 2013, are controlled by the NPPA. The prices (or the ceiling prices) are calculated following a market-based methodology.

Prices of drugs which do not form part of the DPCO 2013 are merely monitored by the NPPA. That apart, the NPPA can, under extraordinary circumstances, for a certain period of time, control the price of any drug under the provisions of DPCO 2013. All the manufacturers in the country are mandated by law to follow the ceiling prices fixed and notified by the NPPA from time to time, else they risk facing recovery of the overcharged amount along with interest, and in some cases, penalty.

As of March 29, 2019, prices of a total of 847 drugs are controlled by the NPPA.

Price control now extends to medical devices as well. Currently, 23 medical devices have been notified as drugs and are regulated under the D&C Act. Of these, only four – cardiac stents, drug-eluting stents, condoms and intra-uterine devices – are included in the NLEM and are, therefore, subject to notified price caps.

Of late, the NPPA has taken steps to cap the trade margins in respect of 42 anti-cancer drugs, and it is proposed that capping of trade margins of other drugs/medical devices will follow suit.

In January 2019, by an amendment to the DPCO 2013, the Central Government exempted new drugs patented under the Indian Patent Act, 1970, from price control, for five years from the date of their marketing. Further, drugs used for treating orphan diseases (those affecting not more than 500,000 persons in India) will also be exempted from the provisions of DPCO 2013.

Policies affecting pharmaceuticals

The Ayushman Bharat Pradhan Mantri Jan Arogya Yojna ('PM-Jay') Scheme:

In September 2018, the Government of India launched one of its most ambitious healthcare plans in the country. Dubbed 'Modicare' by the media, the plan has been launched with the intention of providing universal access to healthcare to both the rural and urban population, without having to face financial hardship as a consequence. It is a completely government-funded health protection scheme.

The National Health Agency ('NHA'), an attached office of the MoHFW, has been constituted for a focused approach and effective implementation of PM-Jay, with full functional autonomy. Similarly, the state governments are expected to set up State Health Agencies ('SHA') to implement PM-Jay.

The NHA will provide overall vision and stewardship for design, roll-out, implementation and management of PM-Jay, in alliance with state governments. The NHA will play a critical role in fostering linkages as well as convergence of PM-Jay with health and related programmes of the Central and State Governments, including but not limited to Ayushman Bharat – Comprehensive Primary Health Care, the National Health Mission, the Rashtriya Swasthya Bima Yojana ('RSBY'), to name a few.

The PM-Jay scheme is touted to provide financial protection to 10.74 crore poor, deprived rural families and identified occupational categories of urban workers' families, as per the latest Socio-Economic Caste Census ('SECC') data, by offering a benefit cover of INR 5,00,000/- (Rupees Five Lakhs) per family per year. A list of eligible families has been drawn up and shared with the respective state governments as well as ANMs/BMO/BDOs of relevant areas. Only families whose names are included in the list, as well as families having an active RSBY card as of February 28, 2018, are entitled to avail the benefits of PM-Jay Scheme. There is no separate enrolment required for these families, and the benefits can be availed of without there being any other formalities.

The salient features of the scheme are summarised as follows:

1. there is no cap on the size of the family or age of the members;
2. cashless and paperless treatment are available to beneficiaries of all public and empanelled private hospitals;
3. the plan covers secondary and tertiary care hospitalisation;
4. 1,350 medical packages, across 23 medical specialities, including but not limited to surgery, medical and day care treatments, cost of medicines and diagnostics, have been notified. All pre-existing diseases are covered; and
5. eligible beneficiaries can avail services across India, offering the benefit of national portability.

Thus far, 22 states and union territories have joined the PM-Jay Scheme.

The government expects the Scheme to cost around INR 10,000 Crore to INR 12,000 Crore a year as of now. This will be paid for by the Central and the State Governments / Union Territories in a 60:40 ratio, and the participating States may choose from the following options in order to implement the scheme:

1. Trust Model – This includes each state setting up a trust to manage the funds collected for the schemes. Claims pay-outs are done via this trust.
2. Insurance Model – This includes implementing the Scheme through an insurance company.
3. Hybrid Model – The States may choose to adopt an integrated model of the aforesaid two models.

All Empanelled Health Care Providers (EHCP) have been directed to make use of the IT system of the Scheme to manage claims-related transactions. For districts with limited internet connectivity, an 'offline' model has also been included. The Scheme strives to make the process of claim management entirely paperless. The following are the timelines fixed under the Scheme:

1. Once a claim is raised by the EHCP, the process of either payment or investigation/rejection by the Trust/Insurer will take not more than 15 calendar days. For claims outside the State, a time of 30 calendar days has been provided.
2. in case a claim is pending beyond the stipulated 15/30 days timeline, the Trust/Insurer is required to update reasons for the delay on the online portal.
3. In case the Trust/Insurer is not able to adhere to the timelines, penalty of 1% of the claimed amount per week for a delay beyond 15/30 days is to be paid directly to the hospital.
4. A right of appeal and re-opening of claims must also be provided to the District-level Grievance Committee ('DGC'), within a period of 30 days. Appeal against the decision of the DGC can be made to the State-level Grievance Committee ('SGC') within 30 days.

That apart, a minimum set of criteria have been devised for hospitals keen to empanel with the Scheme. The following are the broad guidelines which have been recommended for empanelment:

1. Essential criteria: These are the requirements which have been laid down under the Clinical Establishments (Registration & Regulation) Act, 2010.
2. Advanced criteria: Hospitals would need to be empanelled separately for certain service packages (bundled) authorised for one or more specialties (e.g. cardiology, polytrauma,

oncology, neurosurgery, etc.) over and above the essential criteria to be able to provide services belonging to such specialty procedures.

In order to ensure that quality of services is maintained by the empanelled hospitals, they will be encouraged to attain quality milestones through incentivised payment structures. The indicative incentive mechanisms, a voluntary exercise at State discretion, with prior intimation to the NHA, are as follows:

Criteria	Incentive (over and above base package rate)
Entry level certification	10%
Full accreditation	15%
Aspirational/Backward districts	10%
Running PG/DNB course in the empanelled Specialty	10%

The Scheme recommends forming an Empanelment Advisory and Disciplinary Committee ('EADC') by the State Nodal Agency to empanel and regulate the functioning of the network hospitals for their respective States.

With respect to the rates of medical packages determined under the Scheme, these appear to be 15-20% lower than the Central Government Health Scheme ('CGHS'), which provides comprehensive medical care to government servants, pensioners and their dependants. Illustratively, while an angioplasty would cost about INR 1.5-2 lakh at a reputed private hospital, under the Scheme it could now cost between INR 50,000/- to INR 65,000/-. The rates of some medical procedures under the Scheme are as below:

Procedure name	Rates (Rupees)
Vertebral angioplasty, single stent (medicated)	50,000
Pulmonary artery stenting	40,000
Coronary artery bypass grafting	90,000
Pulmonary valve replacement	1,20,000
Lung cyst	45,000
Corneal grafting	8,500
Total hip replacement (cementless)	90,000
Total knee replacement	80,000
Radical hysterectomy or uterus removal	20,000
Incisional hernia repair	15,000
Caesarian delivery	9,000
Brain biopsy	15,000
Epilepsy surgery	50,000

Complaints against misuse/abuse of the Scheme by empanelled hospitals can be made to the respective SHAs by patients. In March 2019, upon a complaint made by a patient of a hospital having illegally charging her INR 70,000/- despite her being a beneficiary of the Scheme, the SHA directed the hospital to return three times the amount charged, *viz*. INR 2,10,000/-, to the patient. Additionally, the SHA has also issued show-cause notices to the hospital and is in the process of initiating legal action.

Other policies

The Government funds and operates several other healthcare schemes and policies, of which the following may be noteworthy:

- Ayushman Bharat National Health Protection Mission – the scheme aims to cover more than 50 million poor and vulnerable beneficiaries and offers to cover up to Rs. 500,000 to families against secondary and tertiary care hospitalisation.

- Central Government Health Scheme – the scheme operates pan-India to provide free or subsidised medical care to Government employees, pensioners and their dependants. The scheme covers diagnosis, treatment, medical procedures and even reimbursements for cost of medicines and hospitalisation. Before the launch of the Ayushman Bharat Mission, the CGHS was the most expansive healthcare plan in the country. It continues to be the only Government-backed policy providing for reimbursement of medicines and/or procedures in India. Under the scheme, a beneficiary may procure free/subsidised treatment from empanelled hospitals and obtain medicines from CGHS dispensaries only. Reimbursements are valid only in case of treatment from Government hospitals, or private medical centres in case of emergencies. The costs of selected medical devices is also reimbursed under the Scheme.
- Mission Indradhanush – launched by the MoHFW in 2014, this is aimed at expanding immunisation against seven vaccine-preventable diseases in children by 2020.
- Affordable Medicines and Reliable Implants for Treatment (AMRIT) Retail Pharmacy scheme – launched in 2015, these pharmacies sell both drugs and implants at significantly reduced prices, based on authentic prescriptions from doctors. By November 2017, more than 4.5 million patients had benefited from this Scheme.

Emerging trends

While the immediate focus is on successful implantation of the PM-Jay Scheme across the country, the Government of India is simultaneously deliberating over several other initiatives. Most notable of them is the Draft Pharmaceutical Policy 2017. The key objectives of the Policy are:

1. making essential drugs accessible at affordable prices to the masses;
2. providing a long-term, stable, policy environment for the pharmaceutical sector;
3. making India sufficiently self-reliant in end-to-end indigenous drug manufacturing;
4. ensuring world class quality of drugs for domestic consumption & exports; and
5. creating an environment for R&D to produce innovator drugs.

Other trends include:

- Enhanced demand for home-based care services due to increased life expectancy.
- The emergence of telemedicine has led to use of the internet of things and artificial intelligence for treatments and maintenance of records.
- Medical tourism has resulted in faster and better technologies for diagnostics and boosted new entities to enter into the market.
- Robotic surgeries are fast becoming the next explosion in the healthcare sector, especially due to the possibilities of minimally invasive surgeries and preventive diagnosis.
- Globally, India is now also emerging as one of the largest exporters of formulations and Active Pharmaceutical Ingredients (APIs). This has led to increased investment in R&D and infrastructure. Additionally, there is a steep rise in contract-based research and manufacturing services whereby companies prefer to outsource the same to India.
- Medical and wearable devices are on the rise, with heightened awareness and reduced cost of manufacturing.

Successful market access

Given the exponential rate of growth of the Indian healthcare sector, any new entrant is likely to succeed. However, with any super-competitive market, a few factors have to be considered before entering:

Price control: The price control regime is rigorous in the country. While the prices of drugs included in the NLEM are strictly controlled, the prices of other drugs are closely monitored. For drugs which do not form part of the NLEM, companies are permitted to take a 10% price increase over the Maximum Retail Price prevalent in the preceding 12 months. The NLEM is a dynamic document and new formulations, including but not limited to medical devices, are added and deleted from time to time.

Cost of production: While one of the lowest costs is that of manufacturing, the expense of setting up a new manufacturing unit, or outsourcing to a pre-existing unit, have to be borne.

Profit margins: Excessive competition and competitive pricing go hand-in-hand in the market, reducing profit margins. Additionally, with price fixation operating, it is impossible to offer medicines at a higher price. The selling price of a medicine can only increase if all manufacturers agree to increase their prices, thereby increasing the average price.

Distribution network: India already has an extensive manufacture and supply chain in this sector. While little or no investment would have to be made in this area, ensuring that your product is given preference over other generics with the same composition could prove to be the main task.

Innovation vs generic/biosimilar: A huge factor regarding market entry is whether the entity is an innovator or generic manufacturer. Innovator companies face the additional burden of competing with debatably non-infringing generic companies, offering their products at sometimes one-tenth of the innovator's selling price. As a consumer market, India does not differentiate between generics and innovators. However, as with every consumer group, accessibility and affordability play the key role. It is pertinent to note that the revenue share of generics in the market is 70%, while that of patented drugs is 21%.

Return on investment: This factor needs to be considered before entering a market where there may be several other companies offering the same medicine. In the case of an innovator company, the cost of conducting research in India may be significantly cheaper as compared to other countries. At the same time, the drug so innovated may be subject to fierce competition from generics and/or biosimilars even before its launch on the market. And the price of the innovated drug *vis-à-vis* the actual cost of production may provide an exorbitant price margin to the innovator.

Foreign Direct Investment: India allows 100% FDI by automatic route for greenfield pharmaceuticals; for brownfield pharmaceuticals, 74% by automatic route; and the rest (up to 100%) by Government approval.

Make in India Policy: The Government largely encourages manufacturing and use within India. Another facet of this policy is the necessity to work a patent in India. In case a drug is only imported under a granted patent, it must satisfy the reasonable requirements of the public and should be available at affordable prices, in order to avoid revocation of the patent or the grant of a compulsory licence. Several innovator companies now prefer to obtain a patent and thereafter provide voluntary licences to Indian pharmaceutical manufacturers to manufacture and/or market and distribute the concerned drug, in order to secure the patent, as also to ensure sufficient 'working' of the patent.

Patent system: The patent regime in India prescribes a stricter test for patentability in the

case of pharmaceuticals, in order to avoid 'evergreening' and to ensure that only actual innovation is rewarded with a monopoly. Section 3(d) of the Patents Act, 1970 provides that new forms of a known pharmaceutical are granted a patent only in the event it is found to show enhanced therapeutic efficacy over the known pharmaceutical through clinical data. Generic and biosimilar versions of patented drugs are also allowed to subsist if found to be non-infringing on the claims of the patent.

Drug licence: Any new drug will have to undergo the entire procedure of obtaining a licence from the Drugs Controller. Additionally, due to the absence of patent linkage, data used in the patent application will not be automatically considered for the grant of a drug licence.

Advertising & marketing: With the D&C Rules imposing a ban on the advertising of drugs, marketing of drugs is challenging, especially for new entrants who are also required to penetrate existing trade channels. The Essential Commodities (Control of Unethical Practices in Marketing of Drugs) Order, 2017 further restricts incentives to medical practitioners and bars the unethical marketing of drugs.

Research opportunities: As mentioned above, India offers an exceptional platform for contract-based research and development. With a massive pool of human resources and scientists, conducting research in India is a promising endeavour for new entrants.

With all its pros and cons, India remains one of the fastest-growing economies, with healthcare being one of the main sectors of both revenue and development. Aiming to be the largest healthcare market in the world, any new entrant would have to additionally bear in mind the ever-evolving features of the Indian market, given its diversity, economic disparities and plethora of opportunities.

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Ireland

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Abstract

In Ireland, State expenditure on medicines is approximately €2.5 billion *per annum*. For most medicines, other than medicines restricted to hospital or medical specialist use, the only route to State reimbursement is to appear on a positive reimbursement list. Other than for cancer drugs, there is a uniform application procedure to have a product added to the reimbursement list. There currently is no distinct approval pathway for rare disease medicines or hi-tech products.

Ireland has an ageing population and therefore demand for medicines, especially for chronic diseases, is increasing. In recent years, the State has reformed the Irish pricing and reimbursement system and introduced a number of measures to reduce healthcare expenditure. Suppliers are also entering into novel contractual arrangements to add value and demonstrate the cost-effectiveness of their products. Despite this, suppliers face significant challenges in securing reimbursement of new medicinal products in Ireland, especially hi-tech medicines and those for rare 'orphan' diseases.

Market introduction/Overview

The Irish healthcare system is a two-tier one, comprising the public healthcare system and the private healthcare system. The public healthcare system is funded by the State through taxation and social security contributions. Any person ordinarily resident in Ireland is entitled to receive healthcare through the public healthcare system. The private healthcare system is funded by private insurance and private funds. Private healthcare remains a popular option in Ireland, with around 40% of residents taking out private insurance.

In Ireland, healthcare policy and expenditure are determined by the Department of Health and Children, and administered through the Health Services Executive (HSE). The HSE operates a positive reimbursement list and HSE expenditure on medicines is approximately €2.5 billion *per annum*.

Over the past decade, the population of Ireland has increased by nearly 7% to approximately 4.8 million. The demographic ageing of the population means demand for medicines, especially for chronic diseases, is increasing. As a result, pharmaceutical expenditure is expected to grow, with key drivers for increased spending being hi-tech drugs and new hospital drugs.

The pricing and reimbursement landscape in Ireland has undergone significant change in recent years. New legislation introduced a number of measures to reduce healthcare expenditure, primarily a system of generic substitution and reference pricing. The State also entered into a four-year framework agreement with industry in 2016 for the supply

and pricing of medicines to help contain pharmaceutical costs.

Despite the savings provided by these measures, there has been little growth in the HSE budget for new medicines. Consequently, suppliers face significant challenges in securing reimbursement of new medicinal products, in particular hi-tech medicines and those for rare orphan diseases. This is compounded by the fact that there currently is no separate approval process for these products, which inevitably are deemed cost-ineffective when assessed on standard pharmacoeconomic criteria. However, even those products that are deemed to be cost-effective are facing reimbursement delays due to the lack of overall affordability for the Irish healthcare system.

The high cost of new innovative drugs and delays in reimbursement are among the key challenges for market access in Ireland.

Pharmaceutical pricing and reimbursement

Regulatory classification

There are two main supply categories of medicinal products in Ireland: (i) prescription-only; and (ii) non-prescription products.

Prescription-only medicines are those which require medical supervision and are available only with a doctor's or dentist's prescription, and dispensed through pharmacies. Prescription-only medicines tend to be dispensed to patients by community pharmacists and are reimbursed by the State.

Non-prescription medicines consist of two classes: (i) pharmacy-only products that are available under the supervision of a pharmacist; and (ii) general sale products that can, with reasonable safety, be sold without the supervision of a pharmacist. In general, non-prescription medicines are not reimbursed by the State, but certain non-prescription items are reimbursable where a doctor prescribes them.

The Medicinal Products (Control of Placing on the Market) Regulations 2007 (SI 540/2007), as amended, set out the criteria for determining the legal supply status of medicinal products. Generally, new medicines may only be supplied on prescription. After several years of use of the medicine, sufficient information may be available to justify a change in its legal supply status to non-prescription supply by a pharmacist. It may also be possible for medicines previously supplied only by a pharmacist to be supplied on general sale, if appropriate.

Who is/are the payors?

In Ireland, the State pays for nearly 80% of all medicines through reimbursement of community pharmacists. The cost to the State of medicines dispensed in the community depends on the different reimbursement schemes an eligible patient may use. The HSE Primary Care Reimbursement Service (PCRS) operates four principal reimbursement schemes:

- *General Medical Services Scheme (GMS)*: a patient receives their medicines after paying a €2.00 per item prescription charge (up to a maximum charge of €20.00 per person or family per month) or for a patient aged over 70, the prescription charge is €1.50 per item (up to a maximum charge of €15.00 per person or family per month). The pharmacist receives a dispensing fee, but no mark-up. The GMS scheme applies to those who do not have sufficient means to pay for their medicine, while prescription charges for people in emergency accommodation are to be phased out.

- *Drug Payment Scheme (DPS)*: a patient pays a maximum of €124 per month for medicines supplied to them and their family. If an interchangeable medicine is supplied, the reference price is used to calculate the monthly cost. The pharmacist receives both a mark-up and a dispensing fee.
- *Long Term Illness Scheme (LTI)*: provides medicines to patients with specific long-term medical conditions, such as diabetes, epilepsy, multiple sclerosis and cystic fibrosis, free of charge. The LTI scheme is not means-tested and therefore does not depend on a patient's income or other circumstances. Similar to the DPS, the pharmacist receives a mark-up and a dispensing fee.
- *Hi-Tech Scheme*: a patient receives expensive medicines required for long-term care and either pays the first €12 a month of the cost in accordance with the rules of the DPS, or receives the medicines free of charge, if they hold a medical card or the medicine is for a specific condition covered by the LTI. Under the hi-tech scheme, pharmacists receive a patient care fee of €62.03 per patient in the month when an item is dispensed, and €31.02 in the months where no item is dispensed. The non-dispensed patient care fee may only be paid for a maximum of three consecutive months in respect of a particular patient between each dispensing.

Payments to pharmacists are regulated by HSE Community Pharmacy Contractor Agreements and the Health Professionals (Reduction of Payments to Community Pharmacy Contractors) Regulations 2013 (SI 279/2013), as amended.

What is the process for securing reimbursement for a new pharmaceutical product?

The HSE is the relevant decision-making body for State reimbursement of medicines in Ireland. For this purpose, the Health (Pricing and Supply of medical Goods) Act 2013 (2013 Act) requires the HSE to maintain a positive list of reimbursable medicines (Reimbursement List).

For most medicines, other than medicines restricted to hospital or medical specialist use, the only route to state reimbursement is to appear on the Reimbursement List. Other than for cancer drugs, there is a uniform application procedure to have a product listed on the Reimbursement List. Unlike other EU Member States, there is no distinct approval pathway for rare disease medicines or hi-tech products.

For a medicinal product to appear on the Reimbursement List, the supplier must make a reimbursement application to the HSE. The HSE is required to make a decision on whether to add the item to the Reimbursement List within 180 days from the date on which it receives the application. In the event that additional information is required from the applicant, the HSE may extend this timeframe for as long as required to determine the application.

The 2013 Act provides that in reaching its decision, the HSE must take into account: (i) Health Technology Assessment guidelines published by the Health Information Quality Authority (HIQA), where the HSE considers these to be relevant; and (ii) the criteria under Schedule 3 of the 2013 Act.

In particular, Part 3 of Schedule 3 requires the HSE to have regard to:

- the health needs of the public;
- the cost-effectiveness of meeting health needs by supplying the item concerned rather than providing other health services;
- the availability and suitability of items for supply or reimbursement;
- the proposed costs, benefits and risks of the item or listed item relative to therapeutically

similar items or listed items provided in other health service settings, and the level of certainty in relation to the evidence of those costs, benefits and risks;

- the potential or actual budget impact of the item or listed item;
- the clinical need for the item or listed item;
- the appropriate level of clinical supervision required in relation to the item to ensure patient safety;
- the efficacy (performance in trial), effectiveness (performance in real situations) and added therapeutic benefit against existing standards of treatment (how much better it treats a condition than existing therapies); and
- the resources available to the HSE.

The 2013 Act also provides that the HSE may take into account any pricing and supply framework agreement with the Irish Pharmaceutical Healthcare Association (IPHA). The current framework agreement came into effect on 1 August 2016 and is operative for four years (2016 Agreement).

The 2013 Act, together with the 2016 Framework Agreement, set out the following procedure for assessing reimbursement applications for new medicinal products:

Upon receipt of a reimbursement application, the HSE commissions the National Centre for Pharmacoeconomics (NCPE) to conduct a cost-effectiveness or pharmacoeconomic analysis of the medicine. Initially, the NCPE (which is a team of clinicians, pharmacists, pharmacologists and statisticians) assesses all medicines in accordance with its "Rapid Review" procedure. The Rapid Review process takes approximately four weeks and is based on an abbreviated company submission intended to provide a summary of relevant information in relation to the cost-effectiveness of the product.

For high-cost products and those with significant budget impact, the HSE requests the NCPE to conduct a more in-depth pharmacoeconomic assessment, or Health Technology Assessment (HTA). Similarly, the HSE may request a pharmacoeconomic assessment for a product where concerns arise in relation to value for money. The aim of an HTA is to understand the cost-effectiveness of a product in more detail, particularly by comparison to alternative therapies available.

Generally, the NCPE has preliminary scoping discussions with the applicant before the company prepares a pharmacoeconomic dossier for submission. When assessing an applicant's submission, the NCPE considers the clinical effectiveness and health-related quality of life benefits and all relevant costs including potential savings from reduced healthcare resource use (e.g. hospitalisation), which the new product may provide. The main assessment criterion is the Incremental Cost Effectiveness Ratio (ICER) of the drug per Quality Adjusted Life Year (QALY).

Following assessment, the NCPE sends an appraisal report outlining its conclusions and recommendations to the HSE. In the case of cancer drugs, the report is also sent to the National Cancer Control Programme for consideration under the NCCP Therapeutic Review Process.

The HSE may, without further assessment, approve the product for reimbursement. Usually, this is the case for drugs that the NCPE considers to be cost-effective, i.e., those that in the NCPE's assessment have an ICER of €45,000 or lower per QALY.

For products falling outside this criterion, the HSE requests a recommendation from the HSE Drugs Group, which performs an in-depth assessment of the product. As part of the Drugs Group review, the HSE's Corporate Pharmacy Unit (CPU) may interact and lead any

commercial negotiations with the applicant. In the case of orphan products, the Drugs Group may refer the assessment to the Rare Diseases Medicinal Products/Technology Review Committee for recommendations.

The Drugs Group then provides its recommendation to the HSE senior leadership, which is the delegated decision-making body within the HSE that makes the final decision as to whether to add an item to the Reimbursement List. The HSE senior leadership may take one of three decisions:

- to add the product to the Reimbursement List;
- not to add the product to the Reimbursement List; or
- to meet with the applicant to address any issues arising or seek clarifications.

The 2013 Act requires the HSE to provide the applicant with a formal notice of its proposed decision on whether or not to reimburse. The notice must include a statement setting out the reasons on which the HSE's proposed decision is based and also inform the applicant of its right to make representations in writing to the HSE with respect to the proposal. The HSE must consider any representations made by the applicant, if applicable, prior to adopting a final decision on pricing and reimbursement, which it must notify to the applicant.

According to the 2016 Framework Agreement, where the HSE recommends a drug for reimbursement, but is unable to fund the product from within existing resources, it may inform the Department of Health. The Department of Health has discretion to submit a memorandum to the Government to request funding for such product.

Under the 2013 Act, an applicant may appeal the final decision of the HSE to the High Court within 30 days from the date of receiving notice of the relevant decision. The High Court will examine the decision and how it was reached by the HSE to determine if the decision was unconstitutional or illegal. If there are sufficient grounds, the Court may: (i) annul the decision and replace it with a decision that the HSE could have made and that the Court thinks appropriate; (ii) refer the matter back to the HSE for further consideration; or (iii) give the HSE such directions as the Court considers appropriate.

In practice, where a drug is not approved following assessment, an applicant will often first engage with the HSE in pricing negotiations to reach an acceptable price or enter into patient access schemes. As there is no explicit process for post-assessment negotiation, this stage lacks structure and set timelines, and often leads to delays in reimbursement.

How is the reimbursement amount set? What methodology is used?

In Ireland, the reimbursement price of drugs included on the Reimbursement List consists of two components: (i) the ex-factory price; and (ii) the wholesale mark-up.

The ex-factory price of a medicine is set under national pricing frameworks, currently the 2016 Agreement, and is underpinned by the 2013 Act. The 2016 Agreement should only strictly apply to IPHA members that are listed in Schedule 2 of the agreement. In practice, most suppliers follow the terms of the 2016 Agreement when seeking reimbursement.

The 2016 Agreement sets the ex-factory price at the currency-adjusted average ex-factory price (price to wholesaler) in 14 EU Member States, namely, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Luxembourg, Portugal, the Netherlands, Spain, Sweden and the UK. Medicinal products are subject to an annual price realignment to the average ex-factory price of the 14 Member States and only downwards price realignments are permitted. Suppliers must pay the HSE a rebate of 5.25% (1 June 2016–31 July 2018) and 5.5% (1 August 2018–31 July 2020) of the ex-factory price.

The 2016 Agreement also provides for a 50% price reduction in the original ex-factory price of a medicinal product (excluding biologics) that has lost patent protection once a competing generic is available on the Irish market. For patent-expired biologics, the 2016 Agreement requires a 30% reduction in its ex-factory price once a competing biosimilar enters the market. In addition, suppliers of the biologic must pay the HSE a rebate of 12.5% of the value of the reduced price.

The wholesale mark-up for community reimbursement schemes is set out in statutory instruments. The current statutory wholesale mark-up is 8% for room-temperature medicines and 12% for medicines which require refrigeration. A wholesale mark-up of approximately 8% is currently paid for all hi-tech medicines.

The 2013 Act also introduced a system of reference pricing for generic and brand-named medicines that are deemed interchangeable. The Act permits pharmacists to substitute lower-cost or generic medicines when a more expensive product is prescribed, provided all the medicinal products fall within the same group of interchangeable products. The Irish Health Products Regulatory Agency (HPRA) decides (on a case-by-case basis) which products are interchangeable and publishes the national list of interchangeable product groups. The 2013 Act specifically excludes biological medicines from being considered interchangeable.

The HSE then establishes a single reimbursement price for each interchangeable group, known as the reference price. A supplier can set the price of a product above the reference price, but the HSE will only reimburse at the reference price.

Under the 2013 Act, the HSE is required to take into account the following criteria when setting the reference price:

- ability of suppliers of the relevant items to meet patient demand;
- value for money provided by the relevant items;
- equivalent relevant prices (if practicably available) of the relevant items in all other EU Member States where one or more than one of the relevant items is marketed;
- relevant prices of therapeutically similar items;
- resources available to the HSE; and
- the terms of any agreement in place (whether entered into before, on or after the commencement of the 2013 Act) between the HSE and any representative body of the suppliers of drugs, medicines or medical or surgical appliances where the agreement relates, whether directly or indirectly, to the price of one or more of those items.

The final criterion above requires the HSE to take into account the terms of the 2016 Agreement and agreements between the HSE and the Irish Generic Medicines Association (IGMA). It is important to also note the penultimate criterion which specifically states that the "resources available to the HSE" must be taken into account. Lack of resources has been a factor which has been cited in decisions to not reimburse a number of drugs in recent times.

How are drug prices set? What is the relationship between pricing and reimbursement?

A supplier does not need to agree a price for a medicinal product before it is placed on the Irish market if reimbursement will not be sought. Where the product is to be included in the Reimbursement List, the price of the new medicine is subject to the criteria in the 2013 Act and the 2016 Agreement. That is, the product must be priced at the currency-adjusted average ex-factory price in the 14 reference EU Member States. If the product is not available in all 14 Member States on the date the supplier submits its initial reimbursement application to the HSE, the price of the product is calculated as the currency-adjusted average

ex-factory price in those reference Member States in which the medicine is available. Where the medicinal product is not available in any of the reference Member States, the supplier must propose a price. In addition, if the product is subject to a HTA and the supplier submits a lower price in the HTA application, the lower price will apply.

Where the proposed price of a medicine means that the product has an ICER exceeding €45,000 per QALY, and thereby is deemed not to be cost-effective, the HSE can meet with the supplier to negotiate and try to agree a price. Often pharmaceutical companies agree a straight rebate or discount, or offer a rebate or discount as part of a patient access scheme or another pricing mechanism, such as a risk-based sharing agreement, to add value and reduce the cost of the product. However, the details of these negotiations are highly confidential and where an agreement is reached between the HSE and the supplier, the outcome is rarely made public.

For medicinal products deemed interchangeable, suppliers are free to set the price of the product below or above the reference price. In the case of the latter, the HSE will only reimburse at the reference price. The patient must pay the additional cost above the reference price, unless a clinical exemption applies.

Issues that affect pricing

The price of medicinal products in Ireland is driven by a range of factors associated with demographic trends, competition, mandatory substitution, the resources available to the HSE and pharmaceutical policies. These factors are not mutually exclusive.

With an ageing population, the demand for medicines, especially for chronic diseases, is increasing. The 2013 Act introduced a number of measures to reduce the concomitant rise in healthcare expenditure, primarily generic substitution and reference pricing. In practice, this system results in suppliers of interchangeable medicines setting the price of their products at or below the relevant reference price.

Generic and biosimilar competition also affects the price of innovator products on the Irish market. Under the 2016 Agreement, the entry onto the market of a generic or biosimilar following the expiry of the innovator's patent, results in a significant mandatory cut in the price of the innovative product.

Policy issues that affect pricing and reimbursement

In Ireland, State expenditure on medicines is currently approximately €2.5 billion *per annum*. This is approximately 14% of the total health budget and represents over 7% of GDP. The long-term expenditure on medicinal products is expected to increase due to factors such as demographic trends and the development of hi-tech drug treatments.

Similar to other developed countries, Ireland is experiencing demographic change. By 2021 the Irish population aged 65 or over will increase by 40% from 2011 levels, representing an additional 200,000 people. Over the past decade, Ireland also has achieved significant improvement in life expectancy. As Irish patients live longer, they are likely to do so with an increasing burden of chronic disease.

In the context of such an ageing population, demand for medicines, especially for chronic diseases, will increase. As a result, there is likely to be additional pressure on future State funding and supply of medicinal products. This funding challenge is exacerbated by the fact that new innovative medicines are in the main hi-tech products that have a high cost attached to them. This is due to the significant research and development costs involved with bringing these innovative medicines to market.

Despite an ageing population, there has been little growth in the public expenditure budget for medicinal products in recent years due to the difficult economic climate. In 2019, the additional budget for innovative medicines was €10 million (0.4% of the annual medicines budget), which the HSE had nearly exhausted after eight weeks. For political and policy reasons, this position seems untenable, not least because lack of access to novel innovative medicines merely on budgetary grounds will meet considerable patient opposition. For example, in 2017 the Government made available additional funding for the cystic fibrosis drugs Orkambi® (INN: lumacaftor/ivacaftor) and Kalydeco® (INN: ivacaftor) following an intense public lobbying campaign.

More recently, the Government funded access to Keytruda® (INN: pembrolizumab) for those women affected by the national CervicalCheck controversy, but subsequently expanded access to all clinically suitable women with cervical cancer due to public pressure. Further, in June 2019 the HSE leadership team approved the orphan drug Spinraza® (INN: nusinersen) following a lengthy patient advocacy campaign, despite a negative recommendation by the HSE Drugs Group.

The State needs to adopt a pricing and reimbursement policy that strikes a balance between affordable access to medicines and fostering innovation. The introduction of additional severe price control measures in the reimbursement of innovative medicines to constrain public expenditure risks significantly impacting the future development and manufacture of innovative medicines, a key industry for the Irish economy.

Emerging trends

The pricing and reimbursement of medicinal products in Ireland has undergone significant changes in recent years. The 2013 Act and the 2016 Agreement introduced a number of measures to reduce healthcare expenditure; however, the pricing of drugs and market access remains controversial. Despite the mandatory price cuts in innovative biologics following the entry of a biosimilar onto the Irish market, the uptake of biosimilars in Ireland is very low. In June 2019, the HSE announced the implementation of a biosimilar incentivisation scheme where hospitals are offered €500 per patient switched from Humira® (NN: adalimumab) and Enbrel® (INN: etanercept) to biosimilar versions of the products. The HSE has indicated it intends to expand the scheme to other therapeutic areas.

The 2016 Agreement was intended to have a dual purpose: to provide significant cost savings to the State, whilst on the other hand, facilitating the reimbursement and market access of new medicines. Over recent years, there has been a growing trend in reimbursement delays. For example, for 10 new innovative medicines recently approved by the HSE, the average waiting time for a reimbursement decision was 890 days. Generally, delays occur when price negotiations are required between the HSE and pharmaceutical companies, but increasingly delays are also occurring after a new medicinal product has received a positive HSE decision that it will be added to the Reimbursement List. This is due to a lack of affordability of the HSE to fund these medicines within its current budget. Consequently, there are considerable delays in market access for innovative medicinal products in Ireland compared to the 14 reference Member States. This is leading to increasing frustration and lobbying from the Irish innovative industry and from patient groups.

Recently, the reimbursement process has come under scrutiny in relation to orphan products. In 2017, the marketing authorisation holder for the orphan product Translarna® (INN: atularen) launched the first legal proceedings in the Irish Courts appealing a HSE reimbursement decision. Ultimately, the proceedings were discontinued and the product

subsequently received reimbursement. Also, in February 2018, the Oireachtas Joint Committee on Health issued a report on the evaluation of orphan drugs that highlighted the inadequacy of the current reimbursement system and the use of the QALY assessment criterion for orphan products. The Committee recommended considerable change to the evaluation process of orphan drugs and for the Department of Health to commence a review of the 2013 Act to identify potential legislative barriers to the reimbursement of orphan drugs and corresponding legislative amendments. There were subsequent Committee debates in 2018 on the issue of evaluating orphan drugs and proposed legislation; the Health (Pricing and Supply of Medical Goods) (Amendment) Bill 2018, seeks to establish a unique process for assessing orphan drugs for reimbursement in Ireland.

With an ageing population in Ireland and the increase in new innovative hi-tech drugs, the cost pressures for reimbursement mean the HSE is increasingly focused on real world evidence and patient outcomes to demonstrate clinical and cost-effectiveness. Suppliers are also entering into novel contractual arrangements; in particular, nurse-led support services and medication adherence programmes for chronic diseases to add value, and risk-sharing or performance-based agreements to manage uncertainty as to clinical value and cost-effectiveness of products.

The Irish Government also is seeking greater co-ordination on access to medicines and has joined two cross-border initiatives, the BeNeLuxa Initiative and the Valleta Declaration, that seek to collaborate on HTAs and price negotiations of new medicines across various EU Member States.

Successful market access

Cost and efficacy are the main issues of concern for the HSE. In order to successfully gain market access in Ireland, adherence to the criteria set out in the 2013 Act and the 2016 Agreement is key. The 2016 Agreement provides a good foundation for pharmaceutical companies to follow to ensure that they meet the requirements, but evidence of good clinical efficacy remains one of the critical success factors.

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Italy

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Introduction

In Italy, the structure of the public healthcare system revolves around the "*Servizio Sanitario Nazionale*" (SSN, national health service), a complex articulated group of entities, bodies and functions established with Law no. 833 of 1978, which draws its inspiration from the principles of universality, equality and equal access to medical care laid out in art. 32 of the Italian Constitution. As with all universalised models, one of the most critical aspects of the SSN is its economic and financial sustainability.

Pharmaceutical assistance is one of the spheres of competence of the SSN, so in the constant search for an equilibrium between universalised provision and limited financial resources, market access for pharmaceuticals is fully involved. Regulation of the reimbursement prices of medicines plays a fundamental, although not exclusive role, in this: the sector regulations envisage additional and competing tools of governance, such as the imposition of expenditure limits (caps), patient co-payment, activation of alternative forms of distribution, centralised procurement, recommendations for prescribing physicians (e.g. to address the prescription of lower-cost products), etc., which make up the body of rules governing the pharmaceuticals market.

A singular element of Italian law is the plurality of pharmaceutical policy-making centres: the organisation of the SSN implements two levels of governance; the State and the Regions. The State is responsible for identifying the fundamental principles of the sector and for determining the Essential Levels of Assistance (LEA) that must be uniformly guaranteed throughout the country, and this cannot be otherwise limited or conditioned by the Regions. The Regions are responsible for defining healthcare policy, organisation and expenditure.

Recent studies show that action taken by the Regions with regard to pharmaceuticals, in order to reduce deficits or to prevent spending over the established limits, have created territorial differences with regard to access to pharmacological treatment and the penetration rate of drugs recently introduced on the market.

The correct form of interaction between the two levels of governance is still a topic for debate and also a matter of disputed jurisdiction, which has not yet reached a sufficiently acceptable conclusion, and this is one of the critical elements conditioning access to the market: when an agreement is reached at central level with the competent regulatory body, the subsequent regional processes may turn out to be complex and lengthy, with obvious consequences for access to the market for new drugs.

In this situation, successful market access in Italy depends on careful prior process planning, starting from the approach taken in the design of the clinical trials, to ensure that the endpoints are meaningful and measurable with respect to the assessment parameters adopted

by the regulatory authorities to establish reimbursement and pricing. In Italy, a detailed understanding of the legal and regulatory process on which the procedure is based is crucial to deliver an efficient result or, at the very least, to be sure of having the most appropriate safeguards.

Market introduction

Market overview: the economic context

The efforts to put its finances back on a sound footing, especially in the last 7–8 years, have enabled Italy's SSN to achieve a substantial situation of break-even, while keeping some indicators at high levels (such as life expectancy) which in the past have secured for Italy a strong position in the international ranking (WHO ranking for 2000).

Nevertheless, the value of rankings is often relative, since they vary depending on the valuation criteria used. More recent studies (Gimbe, 2018) indicate that the Italian SSN has gradually fallen behind the main European countries, also in terms of user "perception" of the quality of the services provided, especially among the weaker sections of the population or in regions with greater economic difficulties.

Specifically, constant cuts in public funding (a reduction of about €28 billion in 10 years) has generated a decrease in the ratio of healthcare spending to GDP from 7% in 2014 to 6.6% in 2018 (Italian Court of Auditors, Report on coordination of public finances, 2019).

In 2017, total pharmaceutical spending amounted to €28.1 billion (€464 *per capita*), of which €19.5 billion was funded by the SSN (€322 *per capita*) and €8.6 billion paid by patients (€142 *per capita*).

Not only is public funding of pharmaceutical spending high, its reduction over time (from 74% in 2001 to 69% in 2017) has not been particularly significant, despite measures to contain expenditure.

In Italy, however, the "composition" of private healthcare spending is denoted by a particular characteristic: unlike other European countries, only a minimal proportion is represented by "intermediate spending" by supplementary funds or insurers, whereas the largest share (88%) consists of out-of-pocket spending directly by patients.

Additionally, more than 7.2% of out-of-pocket spending is cost-sharing, in the form of both standard prescription charges and – to a larger extent – the price differential between branded pharmaceutical products and equivalent products. In other words, a high proportion of spending is induced by consumer behaviour among patients.

From the viewpoint of the pharmaceuticals industry, recent data from Farmindustria, the Italian association of pharmaceutical companies (Pharmaceutical Indicators, July 2018) show that Italy is now the leading EU producer in terms of value of production, ahead even of Germany, and this is due to the growth in exports.

The sector is therefore an important national economic growth driver, in terms of both employment and investment.

The National Health System

Italy currently has 60.59 million citizens who have access to the national healthcare service. Italy's SSN pays for a large (but not total) share of the Italian pharmaceutical market: it guarantees access to services that, in relation to specific clinical conditions or conditions of risk, are scientifically proven to provide a significant benefit (i.e. added value) in terms of individual or collective health, in relation to the resources employed in their provision.

Therefore the SSN does not include services that do not meet effectiveness and appropriateness requirements; those having such features are included in the mentioned Essential Levels of Assistance (LEA), identified solely and exclusively by the State and subdivided into three main areas: collective healthcare in work environments and daily life; district assistance; and hospital assistance.

With regard to medicines, the State, through the *Agenzia Italiana del Farmaco* (AIFA – www.agenziafarmaco.gov.it), is responsible not only for issuing national marketing authorisations, but also, through the specific Pricing and Reimbursement negotiation procedure, for the selection of drugs to be included in the LEAs, and dispensed with reimbursement by the SSN, therefore including products licensed by the EMA. The list of reimbursable drugs forms the National Pharmaceutical Handbook.

The distribution of drugs to patients is provided essentially through the network of licensed territorial pharmacies both public (n° 1.675) and private (n° 17.656) that are also now open to joint stock companies, who may acquire the ownership. Administration of drugs to patients is also envisaged as an integral part of hospitalisation services. This has significant consequences as regards regional measures of governance introduced to contain expenditure.

Key (public) players

The Legislator defines the legal framework and – at a State level – is responsible for identifying the fundamental principles of the pharmaceutical sector, for determining the LEA that must be uniformly guaranteed throughout the country, and for ruling on governance measures for pharmaceutical access and expenditure.

At a decision-making level there are various players:

- *Ministry of Health*: the central body of the SSN whose main planning functions are exercised by presenting the National Health Plan to the Italian Government, after consultations with the Regions. It is at this level that the LEA are established. The Ministry of Health operates side by side with the Ministry of the Economy, which is responsible for planning and coordinating all questions concerning State funding of the SSN. The Ministry of Health is assisted by the Higher Institute for Health (having technical-administrative responsibilities) and the Higher Health Council (an advisory body). With regard to pharmaceuticals, the Ministry of Health is responsible for licensing advertising for drugs (OTC-SOP) and medical devices.
- *Italian Agency for Medicines (AIFA)*: the national body responsible for pharmaceutical regulation in Italy. This public body operates on an autonomous, transparent and cost-effective basis, under the aegis of the Ministry of Health and the supervision of the Ministry of Health and the Ministry of the Economy. It collaborates with the Regions. For market access, the AIFA manages the pricing and reimbursement procedure with the assistance of the Technical Scientific Committee (TSC), which assesses the added value of drugs, and the Pricing and Reimbursement Committee (PRC), which negotiates the pricing and reimbursement conditions of drugs with the company. The AIFA is responsible for assessing the innovative status of drugs for access to specific benefits (see below) and also manages implementation of measures for the governance of spending (pay-back).
- *Regional drug commissions*: variously named and variously formed scientific commissions operating at regional level, tasked with identifying access for drugs and their availability for hospitals.

Pharmaceutical pricing and reimbursement

General regulatory considerations. Access of drugs on to the market

In Italy, regulation of the production, marketing authorisation and market access of drugs of industrial origin is consistent with the principles established by EU legislation. A drug may only be marketed after obtaining authorisation (AIC–MA), which, depending on the specific case, may be issued either by the EMA or by the relevant national regulatory body (AIFA).

In order to fast-track the market entry of drugs licensed directly by the EMA through the centralised procedure, the AIFA is required to enact the determinations relating to provision and to arrange for automatic inclusion in the C-nn class, within 60 days from publication of the European Commission's decision in the Official Journal of the European Union. At that point the MA holder, after communicating the ex-factory price and the retail price to the AIFA, may begin marketing the drug, without having to wait for the reimbursement price negotiation procedure to commence or to be concluded. In this case, the sale price is decided at the discretion of the MA holder, but the entire charge is borne by the patient.

This regulation supersedes the principle whereby access to the Italian market is subject to completion of the reimbursement assessment and price negotiation. In any case, the fact remains that although the company may begin selling the drug (it is not obliged to do so), reimbursement by the SSN is yet to be decided and this has an impact on the market access strategy.

Regulatory classification of drugs (general)

The classification of drugs is established at the moment of the marketing authorisation, or subsequently in case of switch, upon request of the MA holder. The AIFA is the competent authority. The drugs are divided into:

(i) prescription: this represents the "authorisation" of the doctor for a patient to have access to the drug; the prescription can be simple, special, to be renewed or limited, issued by hospitals or specialists; the greater the risk, the more rigorous the prescription and the greater the precautions governing dispensing; and

(ii) non-prescription: this class is divided into "over the counter" drugs (OTC) and "other self-medication" drugs (SOP); both are sold in pharmacies or para-pharmacies, the first "over the counter", the second "behind the counter"; both can be advertised to the public (upon prior authorisation of the Health Ministry) as recently ruled by a decision of the Italian Council of State. The pharmacist is free to decide the discount on the price shown on the packaging, provided that the discount is displayed clearly and legibly and is applied to all clients. Non-prescription drugs can be sold online through pharmacy websites registered on a list managed by the Ministry of Health. Non-prescription drugs are paid for entirely by the patient, so the price (which is the same throughout Italy) is established freely by the producer.

Regulatory classification of drugs eligible for reimbursement

For the purposes of reimbursement of drugs by the SSN, the law envisages listing to different "classes", on the basis of pharmacological-economic assessments that also consider medicines' necessity and effectiveness in the treatment of pathologies. The classification is performed by the AIFA during the process for pricing and reimbursement.

Currently, there are two "classes" in the list:

- Class A): essential drugs whose cost is borne in full by the SSN (subject to forms of cost-sharing envisaged by special laws). If these drugs are to be used only in hospitals,

they are identified with the letter H. All drugs listed in class A are prescription.

- Class C): other drugs whose cost is borne in full by the patient; this class includes OTCs (class c-*bis*) and SOPs and products that may already be sold on the market whose reimbursement by the SSN is yet to be negotiated (C-nn). In class C) are listed prescription drugs also (prescription is necessary to buy the drug, but the price is paid by the patient). OTC and SOP are not reimbursed.

Generic (or equivalent) medicines and biosimilars

A number of specific rules apply to generic drugs that are automatically assigned to the same reimbursement class as the related branded drug, without a price negotiation, if the owner company proposes a sale price "of evident interest to the SSN", according to criteria contained in Ministry Decree issued on 4 April 2013 (rebates from 30% to 75% are related to the level of public spending). Negotiation takes place when the proposed price for the generic drug is higher; in this case, the law provides that the rebate shall be at least 20%.

Generic drugs cannot be listed as reimbursed by the SSN before the expiry of the patent or the SPC of the originator even though the pricing and reimbursement have been negotiated (patent linkage).

For drugs listed in class A) not covered by a patent and with the same composition in terms of active ingredients, as well as the same pharmaceutical form, administration route, manner of release, number of unit doses, the SSN reimburses up to an amount equal to the lowest price of the corresponding generic drug available in the normal regional distribution cycle (so-called "reference price"). The purchase of a more expensive equivalent product is possible only at the specific request of the patient and subject to co-payment. The list of all the equivalent class A) drugs with their related reference prices (the "transparency list") is published by the AIFA and periodically reviewed.

Biosimilars are expressly excluded from the Transparency list so that there is no automatic replacement.

How patients get the drugs

Patients receive the reimbursed drugs through two channels: retail and direct distribution. The distinction between the two systems is significant, because it involves a change in price and reimbursement procedures, as well as application of a variety of tools for the governance of public spending.

The retail channel

As a rule, the supply of drugs reimbursed by the SSN is through authorised public or private pharmacies (retail channel), which guarantee full coverage of the entire country, including difficult-to-reach areas. Pharmacies are private entities operating through a concession by the SSN; some pharmacies are held by the municipality. In the retail channel, the drug is purchased by the SSN from a "price list", on the basis of the retail price indicated in the AIFA Act authorising reimbursement. This price includes the "allocated quotas"; namely the remuneration percentages for the players in the distribution chain, wholesalers and pharmacists. The quotas for wholesalers and pharmacists are determined directly by law, with binding minimums; an 8% quota of the producer's margin is expressly envisaged for generic drugs, and may be subject to negotiation (extra discounts) between wholesalers and pharmacists. Pharmacists are required by law to apply additional discounts for the SSN, according to the price category of the drug. These discounts mean that, in practice, the pharmacy margin is regressive; that is, it decreases in percentage terms as the price of the drug increases.

Direct distribution

Directly through their territorial and hospital services, the Regions can guarantee the supply of drugs required for patients being treated at home, residentially or semi-residentially, as well as drugs for the period immediately after hospitalisation or after an out-patient specialist appointment, for the first full cycle of treatment; this system is known as direct distribution. Drugs for direct distribution are acquired directly by the local health authorities through public tenders, starting from a base price no higher than the ex-factory price negotiated with the AIFA. In this way, thanks to carefully set starting prices and batch organisation, the competition among drug producers enables the SSN to obtain significant reductions on purchase prices. Subsequently, the local health authority dispenses the drug directly to patients through its healthcare facilities, without passing through wholesalers or approved pharmacies.

Distribution on behalf of the local health authority (DPC)

For cost-saving reasons, the Regions have the power to introduce a further form of distribution to patients, known as DPC, whereby the local health authority purchases drugs directly through tenders and subsequently supplies them to patients through the pharmacies (retail channel), which receive a consideration (which is not the same as the allocated quota but a further amount). This form of distribution may be activated only when the particular characteristics of the drugs in question mean that, given the clinical and/or management complexity of the pathology, the patient must make regular visits to the healthcare facility. The aim of this method of distribution is not therefore solely to achieve cost savings, but also to simultaneously guarantee continuity of assistance and monitoring of the suitability of use of specific drugs. When establishing price reimbursement, the AIFA indicates whether or not a drug may be dispensed through direct distribution, including it in a special list known as the Hospital/Territory Continuity Handbook: P-HT. This profile, too, needs to be carefully assessed for the purposes of access.

Early access to drugs

Reimbursed off-label use

The LEAs envisage additional "exceptional" cases of drug provision with costs borne by the SSN, one of which is medicines for "Listed" off-label use. Pursuant to law no. 648/1996, innovative drugs authorised for marketing in other countries but not in Italy, drugs without authorisation but undergoing clinical trials, and drugs to be used for a therapeutic purpose other than the authorised indication, included in a special list drawn up and regularly reviewed by the AIFA, may be distributed with costs borne in full by the SSN. This list ("list 648") also includes, for similar reimbursement purposes, and even if there is a therapeutic alternative among authorised medicines, drugs that may be used for a therapeutic indication other than the authorised indication, provided that said indication is known and complies with research conducted in the national and international medical-scientific community, in accordance with cost-effectiveness and suitability criteria. In this case, the AIFA activates appropriate monitoring tools to protect patient safety and promptly issues the necessary determinations. Requests for inclusion in list 648 may be made by physicians, patient associations, but not by the company that owns the drug.

Compassionate use

In Italy, drugs may be dispensed to patients free of charge on a "compassionate use" basis in these cases: i) as yet unauthorised, undergoing clinical trials and produced in pharmaceutical plants or imported in accordance with the authorisation procedures and current legal

requirements; ii) drugs with marketing authorisation for indications other than the authorised ones; and iii) authorised medicines not yet "available" in Italy (the Health Ministry has specified that "unavailable" refers also to cases where the patient is not eligible for reimbursement due to place in therapy restrictions). In exceptional cases, the AIFA allows compassionate use of medicines whose reimbursement and pricing have already been decided, which, for unforeseen reasons, are not available to patients for a defined period of time. This case applies irrespective of the type of MA (centralised, decentralised, mutual recognition).

Compassionate use may be requested (by physicians): for treatment of patients affected by serious pathologies, rare diseases, rare tumours or diseases placing them in life-threatening conditions; conditions for which no valid therapeutic alternatives are available, or that cannot be included in clinical trials or for therapeutic continuity purposes; and for patients who have already received clinically beneficial treatment under a completed clinical trial.

In the case of compassionate use, provision of the drug free of charge is guaranteed not by the SSN (which does not bear any cost) but directly by the pharmaceutical company (the company is not compelled to adhere to the request). Pharmaceutical companies are entitled to request activation of compassionate-use programs. This possibility needs to be carefully assessed due to the impact on market access of the products.

The fund instituted under law 326/2003

In Italy, a fund has been set up for the reimbursement by the SSN of "orphan drugs" for rare diseases, and of drugs offering hope of a treatment pending marketing for specific serious pathologies. The request for access to the fund is filed to the AIFA on a named-patient basis by the hospitals together with the diagnosis and the therapeutical plan.

AIFA

Criteria for definition of the price and reimbursement

According to the law, all the prices of medicines reimbursed by the SSN must be negotiated between the AIFA and the MA holder, in accordance with the procedures set out in deliberation no. 3/2001 of the inter-ministerial economic planning committee (CIPE) that sets criteria for the negotiation as follows:

- positive cost-effectiveness: the drug is considered useful in the treatment of pathologies for which there is no effective therapy, or delivers a more effective response than other drugs already available for the same *therapeutic indications*;
- a more favourable risk/benefit ratio compared to drugs already available for the same indications;
- assessment of the economic impact on the SSN, also in relation to the market shares achievable in the subsequent 24 months and the projected consumption data;
- per-day therapy cost, compared to other products of similar effectiveness;
- comparison with prices and consumption in other European countries; and
- health technology assessments (HTAs).

For cost-containment reasons, the AIFA may propose reductions in the prices of other drugs on the company price list admitted for reimbursement whose price has not been negotiated. The pharmaceutical company presents its proposals together with proper economic assessments of the product and the industrial context, with reference to investments in production, R&D, exports and a market forecast over a three-year period.

It is possible to arrange Managed Entry Agreements (MEAs); i.e. forms of reimbursement conditional upon the attainment of sales volumes (price-volume agreements, product ceiling,

cost-sharing), or reimbursement based on treatment results (risk-sharing, payment by results), or confidential reserved discounts may be applied to the supplies for public health authorities.

The AIFA often insists on setting a cap on expenditure for the drug in an amount negotiated with the company applicable for the validity period of the agreement. Should sales exceed the cap, the company is obliged to "pay back" the over-expenditure upon request of the AIFA. Usually the cap is fixed for the first access of the drug on to the market as a governance tool. To avoid an automatic renewal of the cap, it is advisable that the company timely address to the AIFA a request to re-negotiate, seeking either to increase the cap or to remove it.

The price negotiated with the AIFA:

- represents the maximum sale price for the SSN, which is then entitled to negotiate further commercial discounts;
- is subject to the addition of margins for wholesalers and pharmacists for sales in the retail channel;
- is valid for 24 months unless otherwise agreed by the parties;
- the agreement is automatically renewed for a further 24 months on the same conditions, should neither party send to the other party a proposed amendment to the conditions at least 90 days before the natural expiry of the contract; or
- should changes arise in the therapeutic indications and/or dosage, such that an increase in the level of usage of the medicine is foreseeable, either party may re-open the negotiation even before the end of the agreed period.

If an agreement is not reached, the drug is listed in class C (payment in full by patients). In this case, the maximum retail price, which is the same throughout Italy, is freely determined by the pharmaceutical company and may be increased only in the month of January of an odd-numbered year. Should the medicine listed in class C be sold to public authorities, however, the pharmaceutical companies are obliged to apply a 50% discount to the retail price.

The 2019 financial law establishes that the AIFA may, before the expiry of the negotiated agreement with the MA holder, re-open the negotiation procedures to re-negotiate the conditions of the existing agreement, "should market changes arise *medio tempore* such as to make an increase in the level of use of the medicine foreseeable or lead to an unfavourable cost-therapy ratio with respect to the alternatives in the national pharmaceutical handbook". This means that amendments may be made to the existing contract at the request of the AIFA (at any time) in the event of market changes. It is up to the AIFA to demonstrate and support the existence of changes constituting the conditions indicated by the law for re-negotiation to be requested. At the time of writing, there are no incidences of the application of this new rule.

In parallel with the negotiation of pricing and reimbursement, the status of innovative drugs may be requested (see below).

The above framework makes the prices of medicines in Italy lower than in other European countries (Farmindustria, *Pharmaceutical Indicators 2018*).

The negotiation procedure

The negotiation procedure is regulated by law. The standard procedure, for general application, has a duration of 180 days (non-mandatory) from filing of the application; the fast-track procedure is completed within 100 days from filing of the application, but applies only to orphan medicines, to other drugs of exceptional therapeutic and social importance listed in a specific AIFA deliberation, and to medicines that may only be used in hospitals

or facilities equivalent to hospitals. The fast-track procedure has priority and the reimbursement application may be filed before the issue of the MA, although commencement of the negotiation must be requested within 30 days of issue of the MA, otherwise the AIFA revokes the classification in the C-nn class.

The duration may be extended only once, in the event that additional elements are requested. The procedure may be suspended upon request of the company. During the negotiation, the medicine is automatically listed in the C-nn class and may be marketed without reimbursement by the SSN. The company is entitled to decide whether to sell the drug immediately or to wait until the reimbursement procedure has been completed. This decision has impact in the global market access strategy.

During the negotiation, the AIFA obtains opinions from:

- the Technical Scientific Committee (CTS), which provides an opinion on the therapeutic value of the medicine, its innovative content, etc.; and
- the Pricing and Reimbursement Committee (CPR), with regard to economic congruity and definition of the price.

The procedure is concluded with a ruling by the AIFA Director General, which takes effect upon publication in the Official Gazette. The same procedure applies to line extensions.

In Italy, the long term of the negotiation procedure represents a weak point for market access.

Remedies in case of delay or failure in the procedure

The deadline of 180 days for the conclusion of the procedure is not mandatory but in case of long-lasting negotiation due to silence/unjustified delay, the company is entitled to write warning letters to the AIFA, and eventually to apply to the Administrative Court to obtain a formal injunction to speed up and conclude the procedure. This remedy is not used in practice, and should be carefully evaluated due to the strong challenge it brings to the course of the negotiation and to the company's reputation.

In case there is failure to reach an agreement and the company is not satisfied with this outcome, it is possible to evaluate if there are arguments to support a judicial action before the Administrative Court. The judicial assessment may only concern the legal compliance of the process (i.e. logic and grounded decisions, transparency of the process) and not the merits of the reasons why the AIFA decided not to reimburse the drug. In practice, the most challenging issues are the price of the drug and its place in therapy.

Policy issues that affect pricing and reimbursement

Sustainable spending and tools of governance

A longer average lifespan, and access to innovative high-cost treatments, make sustainability a major issue. Over the years, additional measures have been introduced in Italy to reduce costs and ensure compliance with the public finance targets agreed with the EU. The question is at the top of the Government's political agenda and is a subject for debate and discussion among industry players with a view to finding solutions that embrace pharmaceutical innovation and financial sustainability.

Below is an overview of the main current tools of governance and the application difficulties encountered in practice.

Pharmaceutical spending limits (for reimbursed drugs only)

The Italian system is today based on a maximum annual spending limit for drugs and mandatory payback of any over-run (in whole or in part) by the pharma companies.

Public pharmaceutical spending may not exceed an overall limit of 14.85% of the national healthcare fund, which is set by law every year. It is subdivided into two main components: agreed spending (*spesa convenzionata*), for drugs distributed through the retail channel, accounting for 7.96% of the healthcare fund; and direct procurement spending for drugs purchased directly by the local health authorities, accounting for 6.89% of the fund.

The very recent reform introduced in December 2018 sets out different rules for the two types of spending as of 1st January 2019:

(i) Agreed spending: at the beginning of the year, the AIFA assigns a company budget to each MA holder, computed on the basis of the volumes recorded in the previous year, and subdivided into equivalent drugs and patented drugs. Should spending exceed the national limit, the entire over-run is paid back by the pharmaceutical companies, wholesalers and pharmacists proportionately to their allocated quotas. The companies pay back to the Regions the amounts determined by the AIFA in proportion to the overspend on their assigned company budgets; for wholesalers and pharmacists, the payback is based on a provisional re-determination (for six months and on a nationwide scale) of the respective allocated quotas on the drug sales prices. Should a company fail to make the full payback, the prices of drugs still covered by a patent are reduced by an amount equal to the outstanding sum plus a 20% penalty.

(ii) Spending for direct purchases (previously named hospital expenditure): a budget is no longer assigned; should spending exceed the national limit, the companies cover 50% of the deficit by making a payback to the Regions computed "*proportionately to the respective market share*", determined on the basis of their turnover. The system envisages: i) a separate limit for medicinal gases (0.20% of the healthcare fund); ii) special rules to safeguard small companies (who are not subject to payback obligations if their turnover is below €3 million); and iii) special measures for innovative and orphan drugs. The other 50% of the deficit is paid back by the Regions, proportionately to their respective overspends. Should the pharmaceutical companies not meet their payback obligations, the Regions may withhold the amount due from the considerations accrued in the supply contracts with the local health authorities.

At the moment, it is not possible to predict the real impact of the new rules on the pharmaceutical companies, but it is essential that every company conduct a full analysis of their position with respect to the portfolio of drugs already on the market or to be marketed in the future, in order to assess the effects and draw up reasonable projections, as far as possible. It should be considered that in the last few years, pharmaceutical spending has shown a constant upward trend in "direct purchases", with the cost of innovative medicines accounting for the largest share; moreover, given the confirmed under-funding of spending for direct purchases, the spending limit has been systematically over-run, with the consequence that the payback imposed on pharmaceutical companies has been particularly onerous, leading in some cases to significant erosion of earnings, especially among companies with a limited product portfolio.

Furthermore, objectively, the budget/payback system has had a greater impact on drugs (including generics) with more recent marketing authorisation, which need to build and consolidate market share. Territorial/approved spending, on the other hand, has almost always been below the assigned limit, but the current regulations do not provide for the surplus resources in one sector to be used to offset the deficit in the other.

Funds for innovative drugs

To facilitate sustainable spending and access to treatment, the legislator has set up two funds,

of €500 million each, for innovative drugs and innovative cancer drugs, and designated the AIFA to establish innovative-content criteria and determining conditions for access to the funds. Spending to purchase innovative drugs and innovative cancer drugs is included in spending covered by the limit on direct purchases only to the extent of the annual over-run on each fund.

The AIFA approved the criteria for assessing the innovative status of a drug, which refers to one or more indication, and not to the product as a whole. Innovative status may be "full", giving access to special funds (maximum duration 36 months), or "conditional", having as a sole consequence, mandatory inclusion in the Regional Therapeutic Handbooks. Conditional innovative status is reviewed mandatorily after 18 months.

The list of innovative drugs is updated on a monthly basis and published on the AIFA website.

Regional therapeutic handbooks (RTH)

The RTH are the lists of drugs to be used by public entities during patients' hospitalisation or on assistance continuity programs; they are one of the main pharmaceutical governance tools at local level.

Initially introduced in order to rationalise purchases (identification of drugs to be purchased by tender), the RTH has evolved to the point where it now has an active role in the selection of the drugs to be included, which considers a number of criteria (efficacy, safety, cost-benefit profile, etc.), with the addition of technical spec-sheets, recommendations for use, therapeutic guidelines, etc., drawn up by special committees to guide clinicians' prescription behaviour.

The administrative courts have ruled in favour of autonomous RTHs, as an expression of the Regions' discretionary organisational powers in the healthcare sector. The Regions are not required necessarily to purchase all the active ingredients on the market and eligible for reimbursement, but they may provide justification to identify those required to ensure the effectiveness of hospital treatments. Recently, however, the courts have ruled that the non-inclusion of a class H drug in the RTH (i.e., a drug reimbursed by the SSN but dispensed only in hospitals) was illegitimate, because in that case the AIFA classification is integral to the LEAs that must be uniformly guaranteed throughout the country to avoid discrimination among people in different regions.

The value of the RTHs is a moot point: the Regions defend their usefulness as their governance tool, highlighting the difference between the assessment criteria used by the regional commissions and those used by the AIFA commissions; many observers are concerned not only about the risk of divergence from the decisions of the national authority, but also about the effect of excessive fragmentation and diversification on patients' access to treatment, compounded by the prolongation of the time needed to bring newly authorised drugs on to the market. The time taken to include a new drug in the RTH varies from region to region, and may be more than a year, so companies planning market access need to acquire a thorough knowledge of the system to ensure an efficient procedure. In the case of drugs deemed "innovative" by the AIFA, the Regions must ensure immediate patient availability.

Therapeutic equivalence in purchase tenders

A key factor in regional drug purchasing policies is "therapeutic equivalence"; this involves a comparison of different active ingredients in order to identify, for the same indications, areas of therapeutic overlap where scientific knowledge has not found significant clinical differences in terms of effectiveness and safety.

The use of therapeutic equivalence in purchase procedures allows tenders to be organised in broader lots comprising multiple "*therapeutically equivalent*" active ingredients, thus

enlarging the scope of competition and leveraging the price differences between the products in order to obtain a lower final price. This generated significant territorial discrepancies; consequently, the legislator assigned responsibility for therapeutic equivalence determinations exclusively to the AIFA. According to the law, the therapeutic equivalence criterion may not be used in purchase tenders for biologics.

Prescription guidelines for biosimilars

Prescription guidelines adopted by the Regions to encourage prescription of lower-cost biosimilars affect market access policies. Automatic replacement with biosimilars (and among biosimilars) is not allowed; it is up to the physician to decide the interchangeability between biosimilars and the reference medicines. Under case law, regional guidance for prescribing physicians is legitimate, on condition that:

i) nationwide uniformity of the LEAs is conserved, for reasons of equality of treatment;

ii) the physician's decision-making independence is guaranteed with regard to therapeutic suitability.

Review of the National Pharmaceutical Handbook and delisting

The National Pharmaceutical Handbook is subject to regular reviews by the AIFA in order to identify drugs "overtaken" by subsequent technical-scientific progress whose cost-benefit ratio no longer justifies reimbursement by the SSN. In practice, the latest systematic review dates back to 2005.

In 2015, a law was passed requiring the AIFA to conduct an extraordinary review of the handbook and to renegotiate the reimbursement price of drugs in groups of therapeutically similar drugs, in order to align them with the lowest price for all the authorised packages that deliver the same treatment intensity given the same daily defined doses (DDD). If attempts to re-negotiate the price fail, the pharmaceutical companies may arrange with the AIFA for the expected saving – calculated as the price differential – to be returned on a payback basis, or for reclassification in class C (non-reimbursable drugs).

Other statutory tools

Other laws with a direct or indirect impact on the reimbursement price policy exist in Italy: after a legislative intervention to re-determine the allocated quotas, the producers are required to make a 1.83% payback to the Regions computed on the retail price net of VAT of drugs distributed through the retail channel.

Emerging trends

On 10 December 2018, the Ministry of Health adopted a policy document on pharmaceutical governance, which sets out the main planning guidelines for the healthcare sector. With regard to reimbursement prices, the main principle is that whereby therapeutically equivalent drugs must have the same SSN reimbursement price; higher prices may be recognised by the AIFA only if there is additional therapeutic value for patients, and must be commensurate with this added value.

Further recommendations are:

- periodic review of the National Pharmaceutical Handbook and the adoption of initiatives to attenuate or eliminate price differences between therapeutically equivalent drugs;
- review and update of price negotiation criteria with express incentivisation of the price/volume mechanism (also the State budget law for 2019 has directed to revise the criteria);

- update of the criteria for recognition of the innovative status of applicable drugs (also for price negotiation purposes);
- promotion of the use of equivalent drugs and biosimilars through awareness campaigns;
- the intensification of AIFA therapeutic-equivalence opinions for purchase tenders;
- simplification of the procedures for the issuance of opinions by AIFA committees (CTS-CPR);
- improved exchange of information on the expiry of drug patents, for timely commencement of price re-negotiations;
- the improvement of AIFA monitoring registers; and
- the review of pharmaceutical spending limits.

Other emerging trends:

- focus on customisation of drugs and on Advanced Therapeutic Medicinal Products (and specifically CAR-T) to be balanced with financial sustainability;
- lively public debate on whether to maintain the possibility of stipulating confidential discounts with the AIFA: the current government aims for absolute costs and price transparency; a possible criticism is the risk of a "reference price" at EU level; and
- raising interest in Patient Support Programs aimed at therapeutic compliance, both from pharma companies developing initiatives and public entities requiring in-tender quotation for specific services to patients.

Successful market access

Italian legislation is highly complex and is changing constantly: this represents a critical factor, to be taken into careful consideration. Successful market access requires exhaustive knowledge of laws, regulations and established practice, indicating that a thorough legal analysis of market access should be conducted, together with a strategic analysis.

There is also a tendency towards a strengthening of the regulatory role of the AIFA, in connection with the planned financial framework for pharmaceutical spending. However, this creates a potential conflict with the role of the Regions, which are calling for greater powers and responsibilities in healthcare. Since the co-existence of two pharmaceutical policy levels is not likely to be resolved in the current climate, special care and attention should be taken by companies planning access to the Italian market.

Finally, the decree updating the reimbursement price negotiation criteria, which can reasonably be expected to provide useful indications as regards valuation of market access, is still being drafted. Pharmaceutical policy guidelines focus not so much on overturning the existing criteria as on adapting them to guarantee a better cost/benefit ratio, and on enhancing the conditional reimbursement system. For a favourable assessment of market access, the strategic positioning of the product needs to be planned well in advance, and the price negotiations with the AIFA organised accordingly.

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Japan

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Abstract

Market introduction/overview

National Health Insurance System

Japan maintains a national health insurance system called the "Universal Health Insurance Coverage System". The characteristics of such system are: (i) covering all citizens through public medical insurance; (ii) freedom of choice of medical institution; (iii) high-quality medical services at a low cost; and (iv) being based on the social insurance system, which allows spending from the public subsidy to maintain universal health insurance coverage.

The Japanese health insurance market is the second-largest in Asia and the third-largest in the world. The most important issue currently facing the Japanese system is the fact that national medical expenditure has been expanding due to the increasing population of elderly people and expensive drugs.

Pharmaceutical pricing and reimbursement

Regulatory classification/outline of regulation

The manufacture and sale of drugs in Japan are regulated by the Minister of Health, Labour and Welfare (the "MHLW"). The MHLW issues Marketing Licences (defined below) and Licences for Manufacturing (defined below) through delegating to other government entities, as described below. Only someone who has obtained the proper Marketing Licence can market pharmaceuticals that are: (i) approved (as described below); or (ii) manufactured by someone who has obtained a Licence for Manufacturing (as defined below) or imported from an accredited Foreign Manufacturer (as described below).

Marketing Licence

A Marketing Licence is necessary to market drugs in Japan. A Marketing Licence may be obtained from the governor of the prefecture designated by the MHLW. Such licence allows the holder to engage in the business of marketing pharmaceuticals, quasi-pharmaceutical products or cosmetics (the "Pharmaceuticals, Etc.").[1]

Depending on the type of product, there are several kinds of Marketing Licence, such as the First-class Marketing Licence for Pharmaceuticals (for prescription pharmaceuticals), and the Second-class Marketing Licence for Pharmaceuticals (for non-prescription pharmaceuticals). In order to obtain the Marketing Licence: (i) the methods of quality control for the Pharmaceuticals, Etc., must comply with good quality practice (the "GQP") specified by the Ministerial Ordinance on Good Quality Practice for Pharmaceuticals, Quasi-pharmaceutical Products or Cosmetics;[2,3] and (ii) the methods of post-marketing safety

control for the Pharmaceuticals, Etc., must comply with the good vigilance practice (the "GVP") specified by the Ministerial Ordinance on Good Vigilance Practice After Marketing for Pharmaceuticals, Quasi-pharmaceutical Products, Cosmetics, Medical Devices or Regenerative Medicine Products.[4,5]

Licence for Manufacturing

A Licence for Manufacturing is necessary to manufacture Pharmaceuticals, Etc. in Japan. A Licence for Manufacturing may be obtained from the governor of the prefecture or the Director of the Regional Bureau of Health and Welfare designated by the MHLW.[6] The Licence for Manufacturing shall be granted in accordance with the categories of: (i) biological preparations, pharmaceuticals manufactured using a genetically-modified technique, etc.; (ii) radioactive pharmaceuticals; (iii) aseptic pharmaceuticals; (iv) any products other than (i), (ii) and (iii); and (v) only the packaging, labelling and storing of the products set forth in (iii) and (iv). Generally, the Pharmaceuticals and Medical Devices Agency (the "PMDA") designated by the MHLW will conduct an investigation regarding any application for a Licence for Manufacturing.[7]

Additionally, a foreign manufacturer intending to manufacture Pharmaceuticals, etc. that are exported to Japan can be accredited by the MHLW.[8] Generally, the PMDA designated by the MHLW will conduct an investigation regarding such accreditation.[9]

Application for approval for marketing brand name pharmaceuticals

Any person who intends to market pharmaceuticals[10] must obtain approval from the MHLW for each such item.[11] Such person must hold a Marketing Licence[12] and such pharmaceuticals must be manufactured by the holder of a Licence for Manufacturing or imported from an accredited foreign manufacturer.[13] The methods to control manufacturing, or the quality of the pharmaceuticals[14] at that manufacturing facility, must comply with the good manufacturing practice (the"GMP") specified by the Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs.[15,16] In addition, any person engaged in manufacturing, etc. of pharmaceuticals in foreign countries (the "Foreign Manufacturer") may apply for approval for marketing pharmaceuticals from the MHLW through a holder of a Marketing Licence designated thereby.[17]

Such person shall make an application by attaching data concerning the results of clinical studies and other pertinent data to their written applications.[18,19] The type of data that must be attached depends on the type of pharmaceuticals: in the case of brand-name prescription pharmaceuticals, (i) data concerning the results of clinical studies collected by clinical trials,[20] which must be conducted in accordance with the good clinical practice (the "GCP") specified by the Ministerial Ordinance on Good Clinical Practice for Drugs;[21] and (ii) data collected and compiled in accordance with the good laboratory practice (the "GLP") specified by the Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs.[22,23]

Application for approval for marketing generics, biosimilars and non-prescription drugs

The approval process for generic drugs, biosimilars and non-prescription drugs is similar to that for brand-name pharmaceuticals. However, the data that must be attached to such application is different. In case of generic drugs, after such brand-name drugs are re-examined as described later, data concerning bioequivalence are needed instead of most of such data described above.[24] In case of a biosimilar, however, data concerning the results of clinical studies collected by clinical trials must be attached, though certain data regarding toxicity do not need to be attached. In case of non-prescription drugs, excluding those with

new active components, etc., such data do not need to be attached.

Application process for marketing approval

Generally, the PMDA designated by the MHLW will conduct an examination regarding an application for marketing approval.[25] The MHLW may prioritise an examination for orphan drugs, etc.[26] This includes drugs designated under the Precursor Designation Scheme. In order to be designated, the drug must satisfy the following four requirements: (i) it constitutes a breakthrough; (ii) its indication is serious; (iii) it has a very high efficacy for its indication; and (iv) the party has the intention and system to develop and apply for marketing such drug in Japan earlier than the rest of the world, which means that it is advisable to conduct the First-in-Human test and the Proof Of Concept test in Japan. The target periods for examination are nine months for the 80th percentile of orphan drugs, etc. and 12 months for the 80th percentile of other pharmaceuticals with new active components, etc. (the "New Pharmaceuticals").

In cases where the MHLW receives an application for approval for marketing of the New Pharmaceuticals, the MHLW shall hear the opinions of the Pharmaceutical Affairs and Food Sanitation Council in advance.[27]

A person who has received approval for marketing the New Pharmaceuticals shall apply for re-examination by the MHLW within three months after the certain investigation period.[28] In the case of orphan drugs, etc., such investigation period shall be ten years, and in the case of ordinary brand-name drugs, such investigation period shall be eight years.

Licence for Sale

Generally only a proprietor of a pharmacy, or one who has obtained a licence for sale of pharmaceuticals (the "Licence for Sale") may engage in the business of selling pharmaceuticals.[29] As mentioned above, however, a holder of a Marketing Licence may sell pharmaceuticals to a proprietor of a pharmacy, and a holder of a Licence for Sale and a holder of a Licence for Manufacturing may sell pharmaceuticals to a holder of a Marketing Licence.

A pharmacy means a place where a pharmacist is engaged in the dispensing of medicine for the purpose of the sale of such pharmaceuticals,[30] and anyone who establishes a pharmacy must obtain a licence from the governor of the prefecture.

There are three kinds of Licences for Sale: (i) a Licence for Store-based Distribution; (ii) a Licence for Household Distribution; and (iii) a Licence for Wholesale Distribution.[31] The Licence for Store-based Distribution shall be obtained from the prefectural governor for each store.[32] The Licence for Household Distribution shall be obtained from the prefectural governor for each prefecture that includes the area where the intended household distribution will take place.[33] The Licence for Wholesale Distribution shall be obtained from the prefectural governor for each business office. The holder of the Licence for Wholesale Distribution can sell pharmaceuticals only to proprietors of pharmacies, holders of a Marketing Licence, a Licence for Manufacturing or a Licence for Sale, as well as proprietors of hospitals, clinics, or clinics for domesticated animals, etc.[34]

A pharmacy can sell all kinds of pharmaceuticals, though it can sell prescription pharmaceuticals only those who hold a prescription.[35] A holder of a Licence for Store-based Distribution can sell only Pharmaceuticals Requiring Guidance, which means behind-the-counter pharmaceuticals, and over-the-counter ("OTC") Pharmaceuticals.[36] A holder of a Licence for Household Distribution may sell only certain OTC Pharmaceuticals.[37]

Health insurance – who are the payers?

Kinds of health insurance

Under the Health Insurance Act, certain workers employed at certain places of business[38] are insured by the Japan Health Insurance Association (the "JHIA") and health insurance societies.[39] An employer who has one or more certain places of business, regularly employing a certain number or more of such workers or employees, may establish a health insurance society.[40] Employers who jointly employ a certain number or more of such workers at several such places of business can also join together to jointly establish a health insurance society.

Workers who are not members of a health insurance society are insured directly by the JHIA. Such workers may continue to be insured for two years after he/she loses the eligibility therefor.[41] Under certain mutual aid association laws, such as the National Public Servants Mutual Aid Association Act, certain workers are insured by mutual aid associations. Under the National Health Insurance Act, municipalities shall generally insure any other persons domiciled in the area of such municipality other than insured persons under the Health Insurance Act or any mutual aid association laws.[42]

Contributions to health insurance

The above insurance providers receive contributions from the insured persons, employees and the national government. Please note, however, that the elderly aged 75 and over are insured through extended associations for medical insurance specifically for such group under the Act on Assurance of Medical Care for Elderly People.[43] Such insurance through extended associations receive contributions from the insured persons, the national government, prefectures, municipalities, the JHIA, health insurance societies and mutual aid associations.

Use of drug price standard prices for prescription pharmaceuticals

A physician or dentist providing treatment covered by health insurance shall prescribe pharmaceuticals as listed in the Drug Price Standard,[44,45] and a pharmacy providing services covered by health insurance shall fill a prescription with pharmaceuticals listed in the Drug Price Standard.[46,47]

How payment is made under the Drug Price Standard

The pharmaceuticals listed in the Drug Price Standard are paid in the following manner: (i) patients (insured persons and their dependents) partially pay the Drug Price listed in the Drug Price Standard for such pharmaceuticals;[48] and (ii) payment agencies such as the Social Insurance Medical Fee Payment Fund and the Federation of National Health Insurance Associations, pay the rest of the cost to pharmacies upon being billed therefor,[49] and (iii) health insurance providers pay to the payment agency upon being billed therefor.[50]

Please note that the drug price paid between a holder of a Marketing Licence and a holder of a Licence for Wholesale Distribution, or the drug price paid between a holder of a Licence for Wholesale Distribution and a pharmacy, or any drug price other than the price to be paid partially under the health insurance system, is not regulated at all, though the price paid by the pharmacy shall be considered upon revision of the Drug Price listed in the Drug Price Standard as described below.

Patients pay for any other pharmaceuticals, such as OTC Pharmaceuticals and Pharmaceuticals Requiring Guidance, by themselves.

Application for listing in the Drug Price Standard

The MHLW lists pharmaceuticals in the Drug Price Standard, and the holders of a

Marketing Licence of New Pharmaceuticals and generic drugs may apply for listing of such pharmaceuticals in the Drug Price Standard.

An application for listing of New Pharmaceuticals shall be made within one week of the granting of approval for marketing such drugs.[51] As a practical matter, the MHLW hears opinions from the applicant before each application. Thereafter, the MHLW hears opinions from the Japan Medical Association, the Japan Dental Association and the Japan Pharmaceutical Association, and decides whether to list such pharmaceuticals in the Drug Price Standard. Here, it is practically decided whether to list such pharmaceuticals.

Pharmaceuticals inappropriate for health insurance treatment, such as "Viagra", OTC Pharmaceuticals and Pharmaceuticals Requiring Guidance, are not listed. "Re-up", a hair regrowth product of which the active component is Minoxidil, was successfully launched as a Pharmaceutical Requiring Guidance. Therefore, the likelihood of success for an application for listing in the Drug Price Standard is very high.

The MHLW consults with the Central Social Insurance Medical Council (the "CSIMC") regarding the listing of such pharmaceuticals.[52] Then, the MHLW prepares a draft listing of such pharmaceuticals, including the price, and lets the internal organisation of the CSIMC decide upon the draft, and notifies the applicant of the draft. If the applicant is satisfied with the draft, the MHLW lets the CSIMC approve the draft and lists such pharmaceuticals in the Drug Price Standard according to the draft.

Appeal process

If the applicant is dissatisfied with the draft listing, the applicant may make an appeal and the internal organisation of the CSIMC will hear opinions from the applicant and decide regarding the draft again. The MHLW then notifies the applicant of such draft. This time, the applicant cannot appeal.

Length of the application process

It takes about 60 days to 90 days at the latest from the grant of approval for marketing such New Pharmaceuticals to having them listed in the Drug Price Standard.

If marketing generic drugs is approved by either February 15 or August 15, an application for listing of such generic drugs must be made by March 10 or September 10, respectively.[53] Such generic drugs are normally listed in the Drug Price Standard in June and December, respectively.

Decision regarding the drug price for pharmaceuticals newly listed in the Drug Price Standard

In case there is any drug listed in the Drug Price Standard similar to the New Pharmaceuticals newly listed therein, the Similar Efficacy Comparison Method shall be used to determine the Drug Price of such pharmaceuticals. If such pharmaceuticals lack novelty, the Correction Premiums described below shall not be added, and the Foreign Price Adjustment shall not be made. If such pharmaceuticals are novel, the Correction Premiums, such as the Breakthrough Premium, the Usefulness Premium, Premium for Orphan Drugs and Drugs in Small Markets, the Pediatric Premium and the Premium for the Precursor Designation Scheme described above, if any, shall be applied, and the Foreign Price Adjustment shall be made. Finally, the Inter-specification Adjustment shall be applied in order to equalise the ratio of the Drug Price and the active components of such pharmaceuticals and that of similar drugs.

In case there is no drug listed in the Drug Price Standard similar to the New Pharmaceuticals newly listed therein, the Cost Accounting System shall be used to determine the price of such pharmaceuticals. Then, the Foreign Price Adjustment shall be applied.

In case there is no generic drug listed in the Drug Price Standard similar to the generic drug newly listed therein, the Drug Price of such generic drug shall be basically 50% of that of the New Pharmaceuticals. If such generic drug is a biosimilar, its Drug Price shall be basically 70% thereof, and may be increased by up to 10% depending on sufficiency of the clinical testing. In case such generic drug is an oral medicine and more than 10 of the same generic drugs are newly listed in the Drug Price Standard at the same time, the percentage shall be reduced by 10%.

In case there is any generic drug listed in the Drug Price Standard that is identical to the generic drug newly listed in the Drug Price Standard, the Drug Price of such generic drug shall be the same as such identical generic drug. In case that is any generic drug listed in the Drug Price Standard similar to the generic drug newly listed in the Drug Price Standard, the Drug Price of such generic drug shall be the same as such similar generic drug, and the Inter-specification Adjustment shall be applied in order to equalise the ratio of the Drug Price and the active components of such generic drug and that of such similar generic drug.

Revision of the Drug Price

The Weighted Average Market Price Plus Adjustment Range shall be used when revising the Drug Price listed in the Drug Price Standard. Here, the Market Price shall mean the price paid by pharmacies. Such revision is basically made once every two years. The MHLW may conduct a necessary survey to ensure the appropriateness of the Drug Price.[54]

The Drug Price of the New Pharmaceuticals[55] shall be lowered through a certain formula depending on the replacement rate of generic drugs, if such rate is lower than 80% after five years have passed since the first generic drug was listed in the Drug Price Standard. The Drug Price of the New Pharmaceuticals shall be lowered to the Drug Price of the generic drugs 10 years after the first generic drug is listed in the Drug Price Standard.

If any paediatric efficacy or performance, or orphan drugs efficacy or performance, is added or any true clinical usefulness is verified, the Drug Price shall be increased through a certain formula. In certain cases where: (i) the market is expanded; (ii) the principal efficacy or performance has changed; or (iii) the dosage or administration has changed, the Drug Price shall be reduced through a certain formula. In extraordinary cases described in (i) and (iii) above, such reduction shall be made four times a year.

The Drug Price of generic drugs shall be consolidated in three categories through a certain formula. The Drug Price of authorised generic drugs shall be consolidated to the Drug Price of other generic drugs.

There are special provisions to maintain the Drug Price for fundamental pharmaceuticals.

A certain amount shall be added through a certain formula to the Drug Price of certain New Pharmaceuticals listed in the Drug Price Standard before any generic drug is listed therein. Such New Pharmaceuticals include orphan drugs, drugs for which a Breakthrough Premium or a Usefulness Premium was applied when they were listed in the Drug Price Standard, etc.

The Foreign Price Adjustment shall be applied for New Pharmaceuticals: (i) which are imported or which contain active ingredients that are imported; (ii) for which the Cost Accounting System was used when they were listed in the Drug Price Standard; (iii) for which there was no foreign price to be referred to when they were listed therein; and (iv) for which a foreign price is listed after they were listed therein.

Policy issues that affect pricing and reimbursement

Expanding national medical expenditure

The cost of healthcare was 10.9% of GDP in Japan in 2016 – not so high as in the United States and Switzerland, though expenditure on pharmaceuticals and other medical non-durables was 18.8% of expenditure on health in Japan in 2014, which was higher than in the United States and Switzerland. From this perspective, there might seem to be a case to hold down payments to pharmacies under the health insurance system.

But the percentage of elderly Japanese is increasing, even though the Japanese population is decreasing overall. Therefore, the amount of the nation's medical expenditure has been basically increasing. In order to maintain health insurance for elderly people, the new system – which is also contributed to by other insurance providers, as described above – was introduced. In addition, recently, the cost of developing New Pharmaceuticals has tended to increase and accordingly the Drug Prices of New Pharmaceuticals newly listed in the Drug Price Standard has tended to increase. Therefore, the national movement in Japan is toward promoting the following policies.

Promotion of generic drugs

The national government aims to achieve an 80% usage rate for generic drugs by September 2020 or earlier.[56] Therefore, the form of the prescription which a physician or dentist providing health insurance treatment writes must contain a column for generic drugs. If such physician or dentist does not check such column, a pharmacist may, without asking such physician or dentist, change the prescribed pharmaceuticals to generic drugs after consultation with the patient.

Lowering Drug Prices

Recently, the Drug Prices of some New Pharmaceuticals newly listed in the Drug Price Standard are very expensive according to the Cost Accounting System, such as direct-acting antivirals for hepatitis C and the "Opdivo", cancer immunotherapeutic. Therefore, if the markets for such New Pharmaceuticals are expanded, the Drug Prices shall be lowered as described above. On the other hand, in order to facilitate development of New Pharmaceuticals, the Drug Prices for certain New Pharmaceuticals shall be increased as described above.

In addition, the Drug Prices of New Pharmaceuticals which have not been replaced to a large extent by generic drugs shall be lowered, as described above.

Self-medication

The national government promotes self-medication in order to hold down medical expenditure under the health insurance system. Then, the government tries to switch prescription pharmaceuticals to Pharmaceuticals Requiring Guidance, such as pharmaceuticals of which the active component is a histamine-2 receptor antagonist. But there are not so many such pharmaceuticals.

Emerging trends

No new legislation is necessary to modify the Drug Price Standard. The MHLW may flexible enough to make such modifications by itself. Therefore, it is difficult to anticipate any regulation by the MHLW. The following systems might be introduced in the future: (i) a pharmacy would claim from an insurer the purchase price of pharmaceuticals and administration expenses; (ii) a national public corporation would purchase pharmaceuticals

necessary for providing services covered by health insurance; (iii) the reimbursement price would be decided beforehand and if a pharmacy claims more than that, a patient would pay the difference and if a pharmacy claims less than that, the price claimed by such pharmacy would be the price which an insured person would normally partially pay; and (iv) a claim can be made only if the clinical trial effect of a pharmaceutical is approved. Therefore, pharmaceutical companies should be prepared for the possibility of such changes.

Successful market access

Although international harmonisation of the Japanese market is proceeding through such measures as the GLP, the GCP, the GMP, the GQP and the GVP, Japanese pharmaceutical affairs are heavily regulated and the Japanese health insurance system is unique. Therefore, in order to enter the Japanese market, a foreign pharmaceutical company would be well advised to have a subsidiary in Japan and use it to obtain a Marketing Licence.

Actually, most major pharmaceutical companies already have subsidiaries in Japan. Most started by acquiring Japanese pharmaceutical companies or setting up joint ventures with Japanese companies. A foreign pharmaceutical may make a lot of sales in the large Japanese market, but it costs a lot to have a subsidiary with a Marketing Licence in Japan. If a foreign pharmaceutical company does not have a subsidiary in Japan for some reason, it should execute a licence with a Japanese pharmaceutical company with a Marketing Licence.

* * *

Endnotes

1. Article 12 (1) of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)(the "Law") and Article 80 (2) of the Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11 of 1961) (the "Order").
2. Ordinance of the Ministry of Health and Welfare No. 136 of 2004.
3. Article 12-2 (i) of the Law.
4. Ordinance of the Ministry of Health and Welfare No. 135 of 2004.
5. Article 12-2 (ii) of the Law.
6. Article 13 (1) of the Law.
7. Article 13-2 (1) of the Law.
8. Article 13-3 (1) of the Law.
9. Article 13-3 (3) and Article 13-2 (1) of the Law.
10. With certain exceptions.
11. Article 14 (1) of the Law.
12. Article 14 (2)(i) of the Law.
13. Article 14 (2)(ii) of the Law.
14. With certain exceptions.
15. Ordinance of the Ministry of Health and Welfare No. 179 of 2004.
16. Article 14 (2) (iv) of the Law.

17. Article 19-2 of the Law.
18. Article 14 (3) of the Law.
19. Article 40 (1) of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Order of the Ministry of Health, Labour and Welfare No. 1 of 1961) (the "Regulation").
20. Article 2 (17) of the Law.
21. Ordinance of the Ministry of Health and Welfare No. 28 of 1997.
22. Ordinance of the Ministry of Health and Welfare No. 21 of 1997.
23. Article 43 of the Regulation.
24. Article 40 (2) of the Regulation.
25. Article 14-2 of the Law.
26. Article 14 (7) of the Law.
27. Article 14 (8) of the Law.
28. Article 14-4 of the Law.
29. Article 24 (1) of the Law.
30. Article 2 (12) of the Law.
31. Article 25 of the Law.
32. Article 26(1) of the Law.
33. Article 30(1) of the Law.
34. Article 25 (iii) of the Law.
35. Article 49 (1) of the Law.
36. Article 27 and Article 4(5)(ii), (iii) and (iv) of the Law.
37. Article 31 of the Law.
38. Article 3(1) of the Health Insurance Act.
39. Article 4 of the Health Insurance Act.
40. Article 11 of the Health Insurance Act.
41. Article 38 of the Health Insurance Act
42. Article 5 of the National Health Insurance Act.
43. Article 48 of the Act on Assurance of Medical Care for Elderly People.
44. Article 70 (1), Article 72 (1) of the Health Insurance Act, Article 40 of the National Health Insurance Act, Article 19 of the Rules for Health Insurance-covered Medical Facilities and Medical Practitioners.
45. With certain exceptions.
46. Article 70 (1), Article 72 (1) of the Health Insurance Act, Article 40 of the National Health Insurance Act, Article 9 of Rules for Health Insurance-covered Dispensing Pharmacies and Pharmacists.
47. With certain exceptions.
48. Article 74, Article 76 (2) of the Health Insurance Act, Article 42, Article 45 (2) of the National Health Insurance Act.
49. Article 76 (4), (5) of the Health Insurance Act, Article 45 (4), (5) of the National Health Insurance Act.

50. Article 76 (1), (2) of the Health Insurance Act, Article 45 (1), (2) of the National Health Insurance Act.
51. With certain exceptions.
52. Article 82 (1), 76 (2) of the Health Insurance Act.
53. With certain exceptions.
54. Article 77 of the Health Insurance Act.
55. With certain exceptions.
56. Basic Policy on Economic and Fiscal Management and Reform 2015 and 2017.

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Korea

Kyung Shik Roh & Kyungsun Kyle Choi
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Abstract

In Korea, the pricing and reimbursement of drugs is governed by the National Health Insurance ("NHI") scheme, which is a single-payer system operated by the National Health Insurance Service ("NHIS"). NHI premiums are lower than in other developed countries, leading to relatively high patient co-payment rates and a large number of non-reimbursed (unlisted) products and services. Reducing the financial burden on patients that is caused by these features has long been a government policy objective, and the administration of President Jae-In Moon has rolled out the "Mooncare" initiative under which the government will seek to vastly expand NHI coverage, effectively bringing all therapeutic treatments under the NHI coverage.

Once a pharmaceutical product is approved, companies may apply to the Health Insurance Review and Assessment Service ("HIRA") to have the product listed for reimbursement under NHI. For new drugs, reimbursement listing usually involves a two-step process where: (i) HIRA first decides whether or not the product is eligible for NHI reimbursement by evaluating the product's clinical usefulness and cost-effectiveness; and (ii) the company and the NHIS negotiate on the product's maximum reimbursement price ("MRP") based on factors such as the product's price in other countries, the local price of comparable drugs, and the impact on the NHI budget. For certain oncology drugs and orphan drugs regarding which it is difficult to conduct a pharmacoeconomic ("PE") assessment, the PE assessment is exempted or the company may enter into a risk-sharing agreement. The MRP of generics and combination drugs is set according to a set formula and reimbursement listing takes no longer than three months.

Market introduction/overview

As of 2018, 97.2% of Korean citizens were enrolled in NHI; those who are not enrolled receive subsidies in the form of medical benefit payments from the government. NHI is mostly funded by insurance premiums paid by enrollees, and government subsidies (14%) and health promotion funds generated through the tobacco tax (6%) make up the rest.

Although most Koreans are enrolled under NHI, the benefit they receive is restricted due to relatively high co-payment rates (30% to 60% for outpatients, 20% for inpatients) and the large portion of products and services that are not reimbursed (16.5% as of 2016). Patients pay out of pocket with respect to the co-payments and the non-reimbursed drugs. In order to reduce the financial burden on patients, a reduced co-payment rate of 5% and 10% applies with respect to treatments for cancer and orphan diseases, respectively. The relatively high co-payments and low NHI coverage rate also relate to a lower premium rate, which as of 2019 was 6.46% of monthly income.

As of the end of 2017, the population of Korea was 51.77 million and the average age was

41.5 years (based on statistics published by the Ministry of the Interior). As in other developed countries, the population is rapidly ageing – as of 2016, the life expectancy was 82.4 years, higher than the OECD average (80.8 years) and 2.8 years higher than the 2008 life expectancy (79.6 years) (based on statistics published by the Ministry of Health and Welfare). Increasing medical expenses due to an aging population is an issue of concern, and in response, the government is seeking to reduce both the volume of drugs used and drug prices. As of 2016, *per capita* healthcare expenditure was US$2,897 (on a purchasing power parity (PPP) basis), much lower than the OECD average of US$4,069, and total health expenditure as a percentage of GDP was 7.6%, lower than the OECD average of 8.9% (OECD health data 2017); however, healthcare expenditures have been increasing year on year and this trend is expected to continue in the future.

Pharmaceutical pricing and reimbursement

Pharmaceutical products are classified into prescription drugs, which require a prescription from a doctor or dentist, and non-prescription drugs, which can be purchased from pharmacies without a prescription. The regulator responsible for approving pharmaceutical products is the Ministry of Food and Drug Safety ("MFDS").

In order to receive approval for new pharmaceutical products (both chemical drugs and biologics), the company must submit safety and efficacy data, the standards and testing methods used for the product, the Drug Master File ("DMF") and data necessary for the Good Manufacturing Practices ("GMP") certification. For imported products, the company also needs to submit a certificate of manufacture from the country in which the product is manufactured and a certificate of sale from the countries in which the product has already been approved. The MFDS decides whether to approve the product after reviewing the submitted data, and may conduct an on-site GMP investigation.

The statutory processing period for applications to approve a new drug is 120 days, but the period is tolled when the MFDS requests the dossier to be supplemented.

When requesting the approval of generic drugs, the company must, in principle, submit bioequivalence data to substantiate their efficacy; however, depending on the dosage form or active ingredient, it may be possible to submit physicochemical equivalence data or data from a comparative dissolution test. When seeking the approval of biosimilars, the company must submit quality, non-clinical and clinical compatibility data.

Who is/who are the payer(s)?

The Korean NHI is a social insurance scheme under which the payer is the NHIS, a public institution organised based on a statutory mandate. This single payer system was adopted in July 2000 with the enactment of the National Health Insurance Act. The responsibilities of the NHIS include: managing the qualifications of insured persons and dependants; imposing and collecting premiums; and disbursing insurance payments.

Certain healthcare institutions including hospitals and pharmacies have the status of being a "healthcare provider" under the NHI scheme. These healthcare providers are responsible for providing various healthcare services (e.g., health examination, tests) and products (e.g., pharmaceuticals, consumables) in return for payments from the NHIS (up to the maximum reimbursement amount) and patients (co-payments). In some cases, the patient has to pay the entire amount out of pocket.

Pharmaceutical manufacturers and importers that wish to get their products reimbursed under NHI must file an application for drug evaluation (attaching a copy of the product's marketing

authorisation) to HIRA. The decision on whether the product is eligible for reimbursement under NHI will be made after HIRA's Drug Reimbursement and Evaluation Committee ("DREC") reviews matters such as the product's clinical usefulness and cost-effectiveness.

What is the process for securing reimbursement for a new pharmaceutical product?

In Korea, a "positive list" system applies where only those products that are proven to have clinical utility and to be cost-effective may be reimbursed under NHI.

New drugs, in order to be listed for reimbursement, must undergo pharmacoeconomics ("PE") assessment by HIRA, after which the company and the NHIS negotiate the product's MRP, which is the maximum price a healthcare institution may receive for the relevant product. The PE evaluation by HIRA takes many forms, and companies may submit data that shows the product's cost-effectiveness compared to treatment alternatives (mostly based on current standard of care) or accept an MRP calculated based on the weighted average price ("WAP") of comparable products (a company that accepts an MRP that is 90–100% of WAP does not need to negotiate the MRP with NHIS).

To improve patients' access to new oncology drugs and orphan drugs for which comparable treatments do not exist, the regulations exempt such drugs from PE review, or allow the PE review to proceed based on risk-sharing agreements (where NHI listing is based on conditions such as the company refunding a certain portion of the drug price to the NHIS).

The MRP of generics and combination drugs is determined based on a formula set forth in the regulations.

Companies that do not agree with the outcome of HIRA's review may request a re-evaluation by HIRA within 30 days of receiving the review results. HIRA must complete its re-evaluation within 120 days of the request, in principle. However, the chances of obtaining different results through this re-evaluation process are not high.

How is the reimbursement amount set? What methodology is used?

For both new drugs and generics, the MRP is set separately for each product.

In the case of new drugs, the MRP is generally established following PE evaluation to assess the product's cost-effectiveness and negotiation with the NHIS. The NHIS and the company negotiate the MRP based on factors such as the amount recommended by DREC, the reimbursement price in other jurisdictions and the local price of comparable drugs. As discussed above, companies may opt to accept an MRP of 90–100% of the WAP of substitute products, in which case they can receive reimbursement listing quickly without having to negotiate with NHIS.

In the case of generics and combination drugs, the MRP is set based on formulas set forth in the regulations, without negotiation with NHIS, and reimbursement listing takes no longer than three months.

How are drug prices set? What is the relationship between pricing and reimbursement?

When a company files an application with HIRA for NHI reimbursement listing of a new drug, HIRA examines the product's clinical usefulness and cost-effectiveness. HIRA reviews clinical utility first, based on data such as articles on clinical studies, the product's reimbursement status in other jurisdictions and the applicable reimbursement standards, and whether the product is reflected in clinical practice guidelines or mentioned in textbooks for the relevant disease.

If HIRA finds the product to be clinically useful, it then conducts PE analysis to assess whether it is cost-effective compared to treatment alternatives or comparable drugs. When

a drug is clinically superior but expensive, the company has to submit PE data. If HIRA finds such PE data to be insufficient, the company may get the product listed by accepting an MRP that is equal to or below the WAP of treatment alternatives. For certain oncology drugs and orphan drugs for which alternative treatments are not available, the company may choose to enter into a risk-sharing agreement (based on which, for example, the publicly disclosed list price for the product may be set differently from the effective price), or be exempted from having to submit PE data, in which case the "modified price" (ex-factory price plus domestic distribution margin and VAT) of the product in the A7 countries would be regarded as the benchmark.

Once HIRA determines that the product is eligible for reimbursement under NHI, the company will negotiate with the NHIS (except where the company is exempted from negotiation based on its acceptance of the WAP-based MRP). During this negotiation, the price recommended by HIRA will serve as the *de facto* ceiling. Factors that are taken into account during negotiation include the product's price in OECD and other countries, the MRP of treatment alternatives that are already listed under NHI, the relative prices of the product and treatment alternatives in other countries, and the potential impact on the NHI budget. If the negotiations with the NHIS break down, the product would not be listed and the company would need to begin again with the HIRA review stage if it wishes to get the product reimbursed.

Refund/rebate schemes are generally not permitted except for those products that are subject to a risk-sharing agreement, or for which the PE assessment has been exempted. This means the listed and effective price are the same for the vast majority of drugs in Korea.

After the product gets listed under NHI, its MRP may be reduced if the volume of products increases significantly beyond what the company forecast at the time of negotiation with the NHI, or the volume exceeds a certain threshold due to expansion of the product's reimbursement scope or market growth. Once a product goes off patent and generics are listed, the MRP of the brand/original product will be reduced. It is extremely rare for a product's MRP to be increased following reimbursement listing – this would occur only in exceptional circumstances, such as where a company seeks to pull the product out of the Korean market due to the current MRP being significantly lower than the production/import cost.

As discussed, the MRP of generics and combination drugs will be set based on a formula once HIRA completes its review.

Policy issues that affect pricing and reimbursement

According to statistics published by the US Census Bureau, as of 2016, Korea had the most rapidly aging population in the world and was set to become a "super-aged" society (where more than one in five persons are aged 65 or over) by 2026. Korea's 65+ population was expected to reach 35.9% by 2050, making it second only to Japan (40.1%).

This growth in the elderly population has resulted in an increase in chronic diseases associated with old age and in medical expenditures overall. According to data submitted by the NHIS to the National Assembly in 2017, health insurance expenditure more than doubled between 2006 and 2016, from KRW 28.8929 trillion to KRW 65.1874 trillion. During this period, the average annual rate of increase in health insurance expenditure was 8.5%; broken down by population segments, the average was the highest in the 70+ age group (14.8%) and lowest for the 20–29 age group (4.45%). Total healthcare expenditure as a percentage of GDP was 7.6% as of 2017, and has been steadily increasing. This situation

has led to calls to promote and prioritise preventive medicine and reduce reliance on expensive treatment for diseases.

Emerging trends

In August 2017, the government rolled out the "Plan for Strengthening Coverage of National Health Insurance" (commonly referred to as "Moon Jae-In Care" or "Mooncare" after the current President). One of the key goals of Mooncare is to ultimately bring all therapeutic treatments under NHI coverage.

The government is planning to assess the medical validity of various treatments that are not currently reimbursed under NHI and will expand NHI coverage in phases by 2022, when President Moon's term ends. Although Mooncare could potentially boost sales of certain expensive oncology drugs and orphan drugs, the commercial implications are likely to be mixed for most companies, given the increased pressure on the NHI budget and the likelihood that the government may more proactively employ various price control measures.

Successful market access

Early planning is important in order to obtain successful drug pricing in Korea. Companies are advised to plan their pricing and access strategy based on the product's clinical profile before the product is approved. Generally, it can be helpful for the head office to seek input from regulatory personnel involved with the Korean business when planning clinical trials at the global level, to ensure that pricing-related considerations for Korea are adequately reflected. It can also be helpful for head office to review the data that will be requested and reviewed by HIRA in advance and, if possible, to make efforts to include the treatment in global treatment guidelines and/or textbooks.

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Mozambique

Francisca Paulouro & Pedro Fontes
VdA

Mozambique has a very basic Pricing and Reimbursement system. Recent legislative developments show a growing and encouraging concern with access to medicinal products. However, further regulation, as well as improvement of the country's general economic conditions, are required before the system can become more sophisticated and effective.

Market introduction/overview

Mozambique is a large country in East Africa, with an area of 801,590 km^2 and an estimated population of 28,861,863 inhabitants.

The health and pharmaceutical sector in Mozambique is still small and lacking in diversification. However, it is rapidly expanding.

Mozambique is a country with a tropical climate which is prone to natural disasters. Recently this year, on 15th March, the Province of Sofala was severely affected by Cyclone Idai and the country is facing the consequences of this natural disaster.

Cyclone Idai was the strongest tropical cyclone to hit Mozambique since Jokwe in 2008. Idai brought strong winds and caused severe flooding in the entire region, striking not only Mozambique, but also Madagascar, Malawi and Zimbabwe.

Information released by the National Institute of Management of Disasters ("INGC") indicates that Cyclone Idai affected over 800,00 people in central Mozambique, with current casualties estimated at 468.

The number of rescued people has risen from 127,626 to 135,827. They have all taken refuge in 161 shelters.

The National Directorate of Health in Mozambique has sent a team to work on the ground with the afflicted and to identify the main diseases that are arising from this natural disaster. A high rate of water-related diseases was identified, such as diarrhea, due to the consumption of turbid water and malaria. Outbreaks of cholera were also detected in several points affected by the cyclone.

This team has intervened and worked with the local population through the transmission of information on measures to be taken for water treatment, and has distributed chlorine and "Certeza", a product used in Mozambique for water purification.

The international community has spared no effort to support Mozambique, with Unicef estimating that around US$10 million is needed for the most urgent needs of children. The United Nations and its partners have called for US$40.8 million assistance to people affected by Idai in Mozambique.

Healthcare services are provided by: (i) the public sector, under the National Health Service

("NHS"), which is the most geographically extensive and technically advanced; (ii) the private sector, which is divided into a profitable part, with almost exclusive presence in the urban areas, and a non-profitable part, comprising national and international NGOs with strong links to the public sector; and (iii) traditional medicine practitioners (an important part of which is represented by the Association of Traditional Doctors of Mozambique, "AMETRAMO"), widely accepted by local communities, offering non-allopathic and complementary medicine and medications.

The performance of these sectors is still below their potential for growth, due to the various limitations that affect the market, such as undeveloped medical facilities, shortage of medicines, and lack of qualified human resources. Studies carried out in 2014 indicated that the country had only 4.9 physicians and 25.2 nurses per 100,000 inhabitants, a proportion that is among the lowest in the world.

Even though the NHS has benefited from major progress in the last few years, healthcare units still only cover about half of the population, and some of them lack adequate conditions to provide healthcare services, including medicine distribution. In addition, the NHS is under-funded, and heavily dependent on external financing to purchase medicines. In September 2013, the Ministry of Health approved a Strategic Plan for the Health Sector 2014–2019 which defined several strategies and reforms aimed at solving the main problems in the health and pharmaceutical sectors.

Recent improvements in Mozambique's standard of living, and a public commitment to the creation of an enhanced health system, offer promising signs of improvement.

Pharmaceutical pricing and reimbursement

Regulatory classification

Regulation of pharmaceutical products is governed by Law no. 12/2017 of 8th September ("Law 12/2017"), which establishes the rules applicable to the production, distribution, use and marketing of medicines, vaccines, biological products and health products. Medicines are generally subject to medical prescription. Medicines that are not subject to medical prescription are those included in a list that is periodically approved by the Ministry of Health.

Medicines can only be purchased by and used within the NHS if they are included in the National Medicine Form or in the List of Essential Medicines. Both the National Medicine Form and the List of Essential Medicines are periodically revised and published by the Ministry of Health, which is also responsible for ensuring that the medicines included in these documents are, in fact, used. Only private sector providers of healthcare services can prescribe medicines and other health products that are not included in these documents, provided that these products are included in the list of medicines that are registered and authorised in Mozambique.

Reimbursement of medicines is not specifically regulated by Mozambican laws. The applicable legislation does, however, establish situations in which medicines can be provided free of charge. Law no. 2/77 of 27th September ("Law 2/77") establishes that medicines for hospitalised patients should be provided free of charge. Law 2/77 also establishes that "basic medicines" may be provided free of charge for outpatient treatment, and that such medicines would be indicated in a List to be defined by the Ministry of Health and the Ministry of Finances.

The said list was later approved by Ministerial Order no. 24/85 of 3rd July ("Ministerial

Order 24/85"). Ministerial Order 24/85 further established that all medicines distributed by Community Health Workers (a network of healthcare providers in remote areas) would be free of charge, and that medicines dispensed by the primary care network in rural areas would have a single price of 20 MT per prescription (and should be paid by the State in the price exceeding that amount). Medicines provided free of charge pursuant to Law 2/77 and Ministerial Order 24/85 may only be distributed at medicine distribution points and pharmacies of the Government which are attached to the healthcare units where such medicines are prescribed. Medicines which are part of the National Medicines List and which are not included in the list of medicines provided for free pursuant to Ministerial Order 24/85 are purchased at their approved sales price.

Additionally, Decree no. 16/88 of 27th December created a Social Fund for paediatric medicines and food supplements, whereby population groups in need of economic support because they suffer from chronic conditions or because they belong to economically deprived groups (physically handicapped, elderly, unemployed, etc.) have access, in NHS pharmacies, to medicines subsidised by the State (the State contribution to the price of medicines varies between 100%, 80% and 50% of their public sales price).

Who is/are the payer(s)?

The funding of the pharmaceutical and health sector of Mozambique comes from multiple sources and is greatly dependent on external resources, including donations. According to a report from the Medicines and Medical Supplies Department of the Ministry of Health, in 2012, the implementation rate of funding allocated for medicines was 99.9%. The main source of funding is public – the State Budget allocated by the Ministry of Finance, which includes: direct contributions from donor countries to Mozambique's State Budget; funds from Mozambique's Common Fund of Support for the Health Sector (designated in Portuguese as "PROSAÚDE"); and funds from vertical programmes. There are other, less documented funding sources such as private contributions and contributions from families through payments in private clinics and hospitals and co-payments in State hospitals, among others. Apart from the State budget and PROSAÚDE, funds are controlled by the Ministry of Health, including earmarked revenue.

One of the strategies envisaged by the Strategic Plan for the Health Sector 2014–2019 approved by the Ministry of Health in September 2013 is to identify and document the gaps in the funding of medicine and liaise within the Ministry of Health and partner countries in order to obtain more funds. This Strategic Plan further designs a specific Funding Strategy for the health sector, which includes the exploration of more funding mechanisms.

Medicines can also be donated by other countries and foreign organisations to NHS institutions, as well as to other public or private institutions which are not part of the NHS, as provided for in Order of 3rd February 2010. In principle, the Government can only accept donations of medicines included in the National Medicines List.

Public institutions purchase medicines pursuant to public procurement procedures.

What is the process for securing reimbursement for a new pharmaceutical product?

Since the Mozambican legislation does not currently establish a specific regime for reimbursement of medicines, there is no reimbursement procedure to be followed by pharmaceutical companies. When medicines are provided free of charge pursuant to Law 2/77 and Ministerial Order 24/85, the selection and payment of medicines are entirely handled by the Ministry of Health and the Ministry of Finances. The law does not specifically allow companies or suppliers to request that their medicines be included in the

List. As for paediatric medicines and food supplements that are funded through the Social Fund, approved by Decree 16/88, the person belonging to a disadvantaged group is required to submit a request in his/her local pharmacy (or the place where they will retrieve the medicines) to gain access to the applicable co-payment.

How is the reimbursement amount set? What methodology is used?

As we have seen, there is not a specific reimbursement framework or methodology. The criteria for providing medicines free of charge to outpatients pursuant to Law 2/77 is the inclusion in a list of "basic medicines" approved by the Ministry of Health. In the case of funding of medicines pursuant to Decree 16/88, the percentage of funding attributed depends on the condition or status of the person receiving the medicines.

How are drug prices set? What is the relationship between pricing and reimbursement?

Law 12/2017 created a National Regulatory Authority of Medicines (designated in Portuguese as "ANARME"), replacing the Medicines Council created by the previous regime.

A new price regime was also approved by Ministerial Order 21/2017 of 13th March ("Ministerial Order 21/2017"). The former regime established different criteria for price calculation. The methodology differed in accordance with the category of the medicine. A reference prices system was also in force, based on a price comparison with the average price of reference countries, and the price of medicines whose active substance already existed in the market (and generics) depended on the price of medicines that were currently on the market.

The regime enacted by Ministerial Order 21/2017 does not, however, consider these aspects, and is rather focused on simplifying price-setting, and adapting it to the particular costs associated with importing medicines to Mozambique.

Pursuant to Law 12/2017, ANARME is the authority responsible for proposing the pricing of medicines, vaccines and biological products, while the Council of Ministers is responsible for regulating the public sales price of medicines, profit margins and price-revision mechanisms.

The pricing of medicines, as noted above, is regulated by Ministerial Order 21/2017. The Public Sales Price of medicines is set by the Pharmaceutical Department of the Ministry of Health for all national territory, based on a proposal by the Importer-Wholesaler. This proposal should contain the following elements:

(i) indication of the Free on Board ("FOB") Price;

(ii) indication of the Cost, Insurance and Freight ("CIF") Price;

(iii) indication of the Wholesale Price;

(iv) indication of the Retailer Sales Price;

(v) indication of the Public Sales Price; and

(vi) indication of the Sales Price to FARMAC Pharmacies (FARMAC – *Empresa Estatal de Farmácias, E.E.* is the State Pharmacies Company that runs several public street pharmacies).

Ministerial Order 21/2017 further defines the criteria to calculate the Wholesale Price, the Retail Sales Price, Public Sales Price and the Sales Price to FARMAC pharmacies. The Wholesale Price is calculated based on the CIF Price, with the addition of bank, customs clearance and harbour expenses, as well as other direct import fees charged up to the distributor warehouse, until a maximum of 9% of the CIF price.

The Retailer Sales Price is calculated based on the Wholesale Price, to which accrues the Importer-Wholesaler trade margin, which is set at 23.5% of the CIF Price, and the trade margin of the distributor (to cover transportation costs to the entire country), which is set at 5% of the CIF Price.

The Public Sales Price is calculated based on the Retailer Sales Price, to which accrues the retailer trade margin, which is set at 66.3% of the CIF price. The Public Sales Price of medicines dispensed in FARMAC Pharmacies is discounted by 7%. Ministerial Order 21/2017 expressly forbids the sale of medicines at a different price than the prices set therein, except if medicines are dispensed in pharmacies attached to NHS health units. Notwithstanding, importers-wholesalers are entitled to submit a request (to charge higher prices) before the Pharmaceutical Department of the Ministry of Health if they consider that the prices are unacceptably low.

Issues that affect pricing

Several issues affect the pricing of medicines in Mozambique. Lack of control and monitoring of the price throughout the supply chain, as well as the lack of more developed legislation, affects the price of medicines, since it increases the risk of medicines being sold at a higher price than they should, for instance, by the application of random mark-ups or by the adjustment of mark-ups according to the demand for specific medicines.

In addition, disparities in costs can lead to differences in prices based on geographical location, with a tendency for higher prices in urban areas. Surges in prices prevent the population from purchasing medicines at affordable prices, which in turn fosters the black market and counterfeiting of medicines. Furthermore, the lack of a Pharmaceutical Policy, the insufficient revision of the National List of Medicines, and the virtual absence of quality control due to limited capacity, give rise to quality issues. Indeed, only medicines that raise suspicion are monitored. Irrational prescription and consumption also affect the market and negatively influence the prices of medicines.

Policy issues that affect pricing and reimbursement

Demographics, health care costs and political factors may influence the pricing of medicines in Mozambique.

The country suffers from a high incidence of HIV/AIDs and associated diseases, such as tuberculosis, which plagues most Mozambican families. Apart from infectious diseases, the country is also beset by diseases that are characteristic of tropical countries, such as malaria, as well as seasonal, warm weather diseases, such as cholera, which had a serious outbreak in the north of the country at the beginning of 2018. These diseases affect young people in the economically active range. For 2019, the Government foresees an increase in the number of people living with HIV, but also of antiretroviral therapy coverage, from 1,069,593 and 86,508 in 2017, to 1,271,649 and 104,229 in 2019, respectively.

Elderly people represent 5.6% of the population. Most of them suffer from diseases such as hypertension, diabetes, cancer, osteoporosis, among others, aggravated by nutritional problems and physical inactivity.

Access to healthcare is extremely limited, especially in rural areas where the only health care providers are public. In urban areas, there is already a shift in this paradigm of supply, and private healthcare providers are increasing and becoming more visible.

Pursuant to the Strategic Plan for the Health Sector 2014–2019, the total expenditure on health was estimated at 6.2% of GDP and is increasing. Nevertheless, the system is still

underfunded, since the GDP *per capita* spent on health is below regional averages, and below the value that is recommended by the World Health Organization and the World Bank to finance a basic level of care. Politically, the legal and political environment is favourable to the prosecution of health objectives, however, there are still situations of overlap, fragmentation and lack of coordination between laws and policies that hinder the creation and development of laws and policies regarding the pharmaceutical sector, including price and reimbursement of medicines.

Emerging trends

The Strategic Plan for the Health Sector 2014–2019 is still the best indicator of health-related trends in Mozambique. The Plan's main goals and strategies do not concern pricing and reimbursement. Nevertheless, this Strategic Plan did anticipate the revision and approval of a legal framework of medicines regulation. This goal seems to have been achieved with the entry into force of the new Medicines Law, approved by Law 12/2017, as well as the approval of a new pricing regime of medicines by Ministerial Order 21/2017. However, the new pricing regime is strictly based on the costs of freight. There is room for additional sophistication and fine-tuning, namely in the regulation of prices in accordance with the medicine's category or therapeutic indication. There is therefore a chance that the regime will be updated and replaced by a more ambitious regime in the next few years and, when these conditions are met, there may be a shift to reimbursement.

The Parliament's Annual Social and Economic Plan for 2018 recommends an increase in antiretroviral therapies for pregnant women, and an increase in child vaccination coverage.

In 2019, the Government expects a growth of health expenditure to 4.7% of GDP, which should allow an increase in external consultations, institutional births and hospitalisations, as well as an increase in the number of beneficiaries of social protection programmes (children, elderly people, persons with disabilities and female heads of households).

The Government also intends to appoint about 2,126 new health professionals, 80 of whom will be physicians, 100 superior and 1,946 medium healthcare technicians, in order to improve the quality of health services.

The Government's Economic and Social Plan for 2019 also features the strategic objective to expand access and improve the quality of health services. To achieve these goals, the Government sets out to:

(i) introduce new vaccines, namely PCV (Pneumococcal Vaccine), Rotavirus and HPV (Human Papilloma Virus Vaccine);

(ii) enhance the prevention, diagnosis, treatment and fight against malaria throughout the country;

(iii) strengthen medicine supply and improve diet in health units;

(iv) expand the services of prevention and diagnosis and treatment of Tuberculosis, including Multi-resistant ("MDR") and Extremely resistant ("XDR");

(v) expand HIV prevention and diagnosis services;

(vi) increase the number of health units that offer antiretroviral therapy and increase their access; and

(vii) introduce a radiotherapy service at Maputo Central Hospital.

On 19th March 2019 the President of the Republic of Mozambique, Filipe Nyusi, launched the "National Dialogue about Tuberculosis", saying that the major target of this campaign is to prevent and significantly reduce tuberculosis by 2030.

A significant market trend has also recently emerged. A large part of the Mozambican population of the upper middle class has been seeking healthcare in neighbouring South Africa. This cross-border movement is a clear sign that the population's standard of living is increasing, and that demand for quality healthcare is higher than supply. The country is bound to advance in this area, and the creation of private clinics, the construction of hospital infrastructures in rural areas, and the importation of medicines are stimulated by this tendency.

Successful market access

The primary success factors for entering into Mozambique's pricing and reimbursement market are to engage with local stakeholders. Interested parties should also monitor international calls for tender, considering that Mozambique's Government often invites foreign companies to bid for tenders for the supply of medicines, which may provide a relevant opportunity for companies to enter in the market.

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Poland

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The following report outlines basic information on the Polish healthcare system, in particular the pricing and reimbursement issues.

Market introduction/overview

In 2018, the total value of the pharmaceutical market, calculated in retail prices, amounted to PLN 39 billion, which represents an increase of 2% on the previous year.

The Polish healthcare system is multi-layered and its respective segments are subject to rapid change. The healthcare system is generally dominated by public financing schemes. Generally, all insured Polish citizens have guaranteed free access to healthcare services. However, the private sector of healthcare services in Poland is predominant and still growing. Uninsured patients are obliged to cover the full costs of medical services. In general, access to healthcare services is rather difficult.

Pharmaceutical pricing and reimbursement

Reimbursement issues are generally regulated in the Act of 12 May 2011 on Reimbursement of Medicinal Products, Food for Special Nutritional Purposes and Medical Devices, and several regulations laying down more precise requirements and technical rules for the reimbursement process. There are three groups of products that can be covered with reimbursement: (1) medicinal products; (2) medical devices; and (3) food for special nutritional purposes.

Products may be subject to reimbursement if they fulfil the following requirements:

- are authorised for the market or remain marketed;
- are available on the Polish market;
- have an EAN identification code or another code equivalent to the EAN code.

The reimbursement may also cover medicinal products without market authorisation in Poland, imported in accordance with the conditions and procedures provided for in the Pharmaceutical Law Act dated 6 September 2011, and medicinal products where the clinical data on indications, dosage and method of administration differ from those set forth in the Summary of Product Characteristics.

Whereas, reimbursement shall not cover products:

- in clinical conditions in which the medicine can be effectively replaced by a change in the patient's lifestyle;
- belonging to the Rp availability category, which have a substitute belonging to the

OTC category, unless in a given clinical condition they need to be applied for a period longer than 30 days;

- included on the list of products which cannot be reimbursed.

The costs of reimbursed products are divided between the public payer and the patient and depend on the reimbursement limit and the co-payment level. The National Health Fund (the public payer) refunds products if they are on an official list of reimbursed products published by the Minister of Health.

The reimbursement approval process is executed by the Minister of Health (the "MoH"). The MoH decides in administrative proceedings which products will be reimbursed and on what terms. Companies are obliged to file reimbursement applications to the MoH. From January 1, 2018, applications may only be submitted electronically in the Reimbursement List System (SOLR) and must, among others, contain: data identifying the product; requested reimbursement conditions; indication of the maximum and minimum net sales price obtained in Poland and other EU countries; proposed price; HTA analysis – clinical, economic, substantiating; and effects on the budget.

MoH can also determine in the decision (based on the proposal of an applicant) additional terms of financing the medicinal product from public funds, including indicating the risk-sharing instrument (RSS). The catalogue of possible RSS is open, which does not preclude the use of another measure, provided that it will have an impact on increasing the availability of guaranteed services or reducing the costs of these benefits. The MoH should examine the reimbursement application within 180 days. The MoH issues a reimbursement decision for a period of two or three years, taking into account the following criteria:

1. position of the Economic Committee;
2. recommendation of the President of the Agency for Health Technology Assessment and Tariff System;
3. significance of the clinical condition to which the reimbursement application relates;
4. clinical and practical efficacy;
5. safety;
6. relation between health benefits and health risks;
7. cost-to-health-effects ratio of the previously reimbursed medicines, compared to those covered by the application;
8. price competitiveness;
9. effects on the expenses of the entity obliged to finance services from public funds and the expenses of beneficiaries;
10. presence of an alternative medical technology and its clinical efficacy and safety;
11. reliability and precision of estimates of the criteria referred to in subparagraphs (3) to (10);
12. health priorities; and
13. the additional year-of-life cost threshold adjusted by life quality, set as equal to three times the GDP *per capita*, and if it is impossible to determine this cost – the additional year-of-life cost.

Products for which the pricing and reimbursement decision has been issued are dispensed to the patient up to the amount of the financing limit and for a fee equal to the amount of the difference between the retail price and the financing limit amount: free of charge, on a flat-rate basis or for a fee of 30% or 50% of its financing limit.

The reimbursed products fall into one of the following reimbursement categories:

- available at a pharmacy on prescription (in the full scope of registered indications and intended uses, or in an indication determined by a specific clinical condition);
- used as part of a therapeutic programme;
- used in chemotherapy (in the full scope of registered indications and intended uses, or in an indication determined by a specific clinical condition); and
- as part of the provision of guaranteed health care services other than indicated above.

The MoH also defines the limit groups of products for which the limit basis is determined. With respect to medicinal products, they are qualified to the same limit group in case of having the same international name or different international name but similar therapeutic action and a similar mechanism of action. The limit basis for a given limit group of medicinal products is constituted by the highest of the lowest wholesale prices for a defined daily dose (DDD) of a medicinal product which complements 15% of the quantitative volume, counted on the basis of the DDD, sold in a given limit group in the month preceding the announcement of the Reimbursement List by three months.

The main factors determining the price of reimbursed products are: limit basis; retail price (official sales price increased by the official wholesale and retail margin, and VAT payable); and payment rates. Those factors are determined officially by the MoH. Additionally, there are restrictions regarding medicinal products for which there is at least one reimbursed substitute in a given indication. In the case of another substitute reimbursed in the given indication, the official sales price, taking into account the quantity of DDDs in a unit package, shall not be higher than:

- 75% of the official sales price of the only substitute reimbursed in a given indication; or
- the official sales price of a substitute determining the limit basis, or the cheapest substitute if the limit basis in a given limit group is determined by a medication with another active ingredient.

Other factors affecting pricing include: indications; product manufacturing costs; patent protection; and the size and profitability of a pharmaceutical company.

Policy issues that affect pricing and reimbursement

In the Polish system, the official sales prices and the official wholesale and retail margins are fixed. In accordance with Polish regulations, in order to provide guaranteed health care services, the health care provider is obliged to purchase reimbursed products:

- at a price not higher than the official sales price, increased by a margin not higher than the official wholesale margin, and – if the health care provider makes a purchase from an entity other than a wholesale trader – at a price not higher than the official sales price.

Also, the health care provider is obliged to purchase reimbursed products (available at a pharmacy on prescription, used as part of a therapeutic programme and used in chemotherapy):

- at a price not higher than the official sales price of a product constituting the limit basis, taking account of the DDD of the medicinal product, the quantity of units of the foodstuff intended for particular nutritional uses in a package, the number of single medical devices or the quantity of medical device units; and

- increased by a margin not higher than the official wholesale margin, and – if the health care provider makes a purchase from an entity other than a wholesale trader – at a price not higher than the official sales price.

Politics in Poland has a significant impact on pricing and reimbursement policy. The factors limiting the development of the reimbursed medicinal product market were:

- the transfer of some drugs used in oncological treatment to the hospital market; and
- falls in drug prices in selected limit groups, most often associated with the appearance of the first counterparts of original medicines in the refund.

Decisions of the MoH regarding the entry – or lack of it – on the list of reimbursed medicinal products are much more important for pharmaceutical companies than economic phenomena. The previous practice of the MoH shows that the RSS are mainly used to reduce public spending while fully controlling the NFZ budget for financing new therapies. Currently RSS are highly required by the MoH. Additionally, political trends in Poland indicate that generic products are more likely to be refunded. Also MoH strives to maintain the lowest prices in the EU.

The latest lists of reimbursed products issued by MoH show that MoH covers fewer and fewer products with reimbursement and has increased prices of reimbursed products, in some cases from 1 grosz to nearly 45 zlotys. This is most often connected with entering a list of another, cheaper equivalent of the reimbursed medicinal product.

Emerging trends

Currently there are two proposed amendments to the reimbursement act, which are in the legislative phase. Proposed amendments are likely to significantly change the pricing and reimbursement system for, among others, medicinal products. Proposed changes include: relaxing the strict reimbursement criteria for ultra-orphan drugs; introduction of compassionate use; simplified reimbursement procedure for well-established off-label indications; and prolonged duration of reimbursement decisions and reimbursement lists.

The UK's decision regarding leaving the EU has had a great impact on the Polish pharmaceutical market. In accordance with Polish regulations, with respect to medicinal products only a marketing authorisation holder (MAH), MAH's representative, or an entity authorised to carry out parallel import activities, may be an addressee of a reimbursement decision and may apply for it. Current Polish regulations regarding reimbursement do not directly specify special provisions, allowing for a change of the addressee of a valid reimbursement decision.

Changing of the applicant in the ongoing reimbursement procedure was not a problem. The provisions of the Code of Administrative Procedure expressly provide such a possibility in cases concerning transferable rights. However, a problem arises when the addressee of the valid decision is a British-based company which is losing the status of MAH to the benefit of another company from another EU country.

In connection with the potential Brexit, the Polish MoH took a position that in the event of MAH change (being also the addressee of a valid reimbursement decision), there is no possibility to change the addressee of a decision in a simplified procedure. According to the MoH, the correct procedure would be to submit a request to shorten the period of a valid reimbursement decision, and a new application for covering a medicinal product with reimbursement by the new MAH. This interpretation was extremely unfavourable for all the companies having MAH based in UK.

Successful market access

Lately the MoH has not been as focused on promoting risk-sharing schemes as additional arrangements being attached to reimbursement decisions, as it was a while ago. The pressure of minimal reimbursement price policy is the critical success factor for market access. In general, preparing for various scenarios regarding price negotiations of reimbursed medicinal products is highly recommended.

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Portugal

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Following a recent reform in 2015, the Portuguese pricing and reimbursement system is now sophisticated and comprehensive. Nevertheless, substantial discretion is extended to the competent national authority, and this is the source of most challenges for innovators.

Market introduction/overview

Portugal is a relatively small country, with about 10.3 million inhabitants. The main indicators of public health have registered a positive and steady evolution over the last decade. According to the most recent data (2016), average life expectancy at birth is 80 years old, and increasing, just like life expectancy at 65 years old, while the infant mortality rate is 2.9 per 1,000.

Adjustments in the health system have yielded life-year gains in respiratory, digestive and infectious diseases. Some indicators, however, raise concerns.

Portugal suffers from the ailments that are associated with an ageing and declining population. Healthy life years are steadily decreasing. Chronic diseases are growing factors of mortality. Heart disease, cancer, respiratory, nutritional, endocrine and metabolic diseases are the greatest causes of premature mortality, and still play a significant role in later deaths. Risk factors, such as inadequate eating habits, hypertension, smoking, and high body mass greatly contribute to this outcome.

The Portuguese health system is thus a mature, complex, and rather successful structure that – as with many other developed countries – is now faced with the consequences of its success.

Higher life expectancy is associated with an ageing demographic, and to an increase in health-related costs. The better the system becomes, the harder it is to ensure its sustainability.

Policies are headed towards preventing diseases rather than curing them. While innovation is commendable, the State is not focused on rewarding innovative therapies, but rather on taking steps to guarantee that they are not necessary.

Pricing and reimbursement of medicines is therefore perceived as a double-edged sword: while it satisfies the basic needs of citizens, and fulfils fundamental duties from the State, it needs to be achieved without excessive sacrifices from a declining Public Budget. Public regulators very much agree that this paradox should not be settled at the taxpayer's expense. Pressure on innovators has therefore never been higher.

As far as the legal regulatory framework is concerned, the Portuguese legal framework follows the EU legislation closely. Consolidated in a single piece of legislation, Decree-

Law 176/2006, of 30th August, the regime is applicable to, among others, the marketing authorisation, manufacture, import, export, marketing, classification, labelling, promotion and pharmacovigilance of medicines, transposing into Portuguese Law several directives, including Directive 2001/83/EC, as amended (the Directive).

Pricing and reimbursement, in contrast, are exclusively dealt with at national level, being beyond the scope of EU legislation, with the exception of transparency measures and procedural requirements provided for in Council Directive 89/105/EEC, of 21st December 1988, relating to the transparency of measures regulating the pricing of medicinal products for human use ("Transparency Directive").

The general regime applicable to pricing and reimbursement is provided in Decree-Law 97/2015, of 1st June, as amended. This diploma approved SiNATS, the National System of Evaluation of Health Technologies, congregating in a single piece of legislation topics related to pricing and reimbursement of pharmaceuticals. This general framework is complemented by several Ministerial Orders and densified by the Practice and Informative Notes of the Portuguese agency *Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.* ("Infarmed").

In addition to its competence for technical health regulation, Infarmed's powers cover pricing and reimbursement. Price approval of prescription products, including products for hospital use, is also attributed to this agency. Infarmed plays a significant role in the reimbursement of medicines, being the entity responsible for conducting the relevant procedures and proposing decisions to the Ministry of Health.

Pharmaceutical pricing and reimbursement

Regulatory classification

The classification of medicines is identical to that arising from EU legislation.

Two major classifications exist: prescription; and non-prescription products.

Medicines are subject to medical prescription where they: (a) are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision; (b) are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health; (c) contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation; or (d) are to be administered parenterally.

Prescription medicines are then divided into sub-categories, including, for renewable delivery, special medical prescription and restricted medical prescription for use in certain specialised areas. Concerning this last subcategory, products will be classified as subject to restricted prescription when, in general terms, their respective use is reserved for a hospital setting or requires special supervision throughout the treatment.

Prescription products can only be sold in pharmacies or, in the case of a restricted medical prescription, dispensed and/or exclusively at a hospital setting (including hospital pharmacies).

In turn, all medicines which do not meet the criteria to be classified as subject to medical prescription, are classified as non-prescription products.

Under this broad classification of medicines – subject to medical prescription or not – medicines can be of several types, depending essentially on the marketing authorisation (hereinafter "MA") procedure followed and composition of the product.

The following types may be identified:

Branded medicines

Branded medicines are divided into six sub-categories: (a) full application; (b) well-established use applications; (c) fixed combination applications; (d) informed consent applications; (e) hybrid applications; and (f) biosimilar applications.

Full application products are commonly known as "reference medicines", i.e. medicines which have been granted an MA by a Member State or by the European Medicines Agency ("EMA") based on a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data. These medicines may be biological or not, depending on their composition.

Products arising from well-established use applications are those regarding the results of preclinical and clinical trials which are replaced by detailed references to published scientific literature, if it is demonstrated that the active substances of the product have been in well-established medicinal use within the community for at least 10 years, with recognised efficacy and an acceptable level of safety.

Fixed-combination applications are those related to medicines containing active substances used in the composition of authorised medicines, but not hitherto used in combination for therapeutic purposes. In these cases, the results of new pre-clinical tests or new clinical trials relating to that combination must be provided, it not being however necessary to provide scientific references relating to each individual active substance.

There are also the so-called informed consent applications, in which following the granting of an MA, the authorisation holder allows use to be made of the pharmaceutical, non-clinical and clinical documentation contained in the dossier of its medicinal product with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

Hybrid applications, which rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data, differ from generic applications in that the results of appropriate pre-clinical tests and clinical trials need to be submitted. This occurs in the following circumstances: where (i) the strict definition of a generic is not met; (ii) bioavailability studies cannot be used to demonstrate bioequivalence; and (iii) there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic compared to the reference medicine.

Finally, there are the biosimilars, i.e. biological medicines, similar to a reference biological product but which do not meet the conditions of the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in the manufacturing processes of the similar biological medicine and the reference biological medicine, and, therefore, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

All the above categories are considered as "branded products" for the purposes of pricing and reimbursement rules, with the exception of biosimilars in respect of which a specific regime exists.

Generics

Generics are products which have the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicines, which is or has been authorised for no less than eight years in a Member State or in the community. The applicant is not required to provide the results of pre-clinical tests and clinical trials, provided

bio-equivalence with the reference medicinal product must further be demonstrated by appropriate bio-availability studies.

In terms of pricing and reimbursement, the following categories are relevant, the rules differing depending on which category the product falls under: (a) branded products (which include: full applications; well established use applications; fixed combination applications; informed consent applications; and hybrid applications); (b) generics; and (c) biosimilars.

Generics are subject to specific pricing and reimbursement rules.

The critical distinction for the purposes of reimbursement is whether the product is subject to medical prescription or not.

Whereas non-prescription medicines are not subject to price control and, as a rule, are not eligible for reimbursement, save in exceptional circumstances, prescription medicines are subject to a price control regime and are eligible for reimbursement. This principle applies to all types of products identified above (i.e. branded, generics, biologic and biosimilar).

Who is/are the payer(s)?

The payer varies depending on the product's classification.

Non-prescription products and medicines subject to common medical prescription, renewable and special medical prescription, may be purchased directly by individuals – if they are sold in street pharmacies – and by private hospitals and National Health Service hospitals ("NHS Hospitals") for internal use. Restricted medical prescription products are only purchased by hospitals, be they private or NHS hospitals, with patients having access to these products via the hospital pharmacies.

Should the product be reimbursed, part or the whole of its sales price is borne by the Health Ministry's share of the State Budget.

What is the process for securing reimbursement for a new pharmaceutical product?

A distinction should be drawn between products which are to be sold and dispensed at street pharmacies and those which are to be sold to NHS Hospitals.

The first follows a reimbursement procedure. The second follows a very similar procedure with a view to being sold in NHS Hospitals – the so-called prior evaluation procedure.

The *ratio* underlying both procedures is, in essence, the same: evaluating whether, in light of the therapeutic alternatives, it is justifiable from an economic and therapeutic perspective for the State to purchase the product – be it via *reimbursement* or through the budget of NHS Hospitals.

The reimbursement procedure is initiated by the MA holder, or its representative, before Infarmed. The MA holder must demonstrate that the product fulfils the criteria for reimbursement: i.e. that the medicine is innovative, or therapeutically equivalent to current alternatives, and presents an economic advantage. This being the general principle, the law further lists the situations which can give rise to reimbursement and specifies the criteria which should be met – particularly to demonstrate the economic advantage.

The reimbursement request should be accompanied by a comprehensive set of documents, comprising both technical and scientific information about the product that demonstrates its efficacy, safety, and effectiveness for the claimed therapeutic indications and an economic evaluation study. Such a study is not required for generics, which follow a simplified procedure.

In fact, reimbursement of generics is subject to specific rules strictly linked to the respective price – be it by comparison with the reference medicine or other reimbursed generics,

depending on how many generics are already present on the market.

The same logic applies to the reimbursement of biosimilars: a price is also set for reimbursement purposes. The first biosimilar will be reimbursed if its price does not exceed 80% of the price of the reference biologic product. The said percentage decreases to 70% if there are more biosimilars on the market representing at least 5% of the market share of the respective active substance.

The reimbursement procedure is conducted before Infarmed. The Ministry of Health, however, is responsible for the reimbursement decision, although said power may be delegated to Infarmed.

Reimbursement may be subject to the execution of a contract between the MA holder and Infarmed which sets forth the terms and conditions to which a reimbursement is subject. These conditions may include:

(a) a maximum amount of public expenditure on the product, considering the number of patients and applicable therapeutics;

(b) consequences of exceeding this maximum amount, such as the MA holder being required to: (i) pay back the amounts in excess; (ii) lower the price of the product concerned or of other products;

(c) existence of a limited period of time, on expiry of which the amount of reimbursement is reduced, with a consequent reduction of the price of the product or the product is delisted; and

(d) risk-sharing arrangements.

Even though the execution of a reimbursement contract is not mandatory, in the case of innovative products, Infarmed typically chooses to execute a contract with the MA holder. If Infarmed proposes to enter into a reimbursement contract, negotiations should be concluded in 30 days. In practice, however, contract negotiations take significantly longer.

Although contracts are bilateral, reimbursement is a unilateral decision, almost entirely at the discretion of Infarmed. Accordingly, Infarmed has an exceptional edge in contract negotiations.

While MA holders may try to influence the reimbursement decision or contract – especially, the maximum amount of public expenditure on the product – through negotiation, the decision ultimately depends on Infarmed and its assessment of the market and the product's expected performance, taking into account available public funds and budgetary concerns.

The MA holder should be able to demonstrate that the medicinal product complies with the reimbursement criteria at all times.

Infarmed can exclude medicines from reimbursement, or change their reimbursement conditions upon re-evaluation of market conditions – especially if new medicines emerge that are either therapeutically innovative or economically advantageous in relation to the reimbursed medicine.

Situations that may trigger exclusion from reimbursement or a change in reimbursement conditions are provided for in the law. Amongst these we find, for instance: the medicine becoming less effective in relation to other reimbursed medicines with the same therapeutic purpose; consumption data demonstrating that the medicine has been used off-label, in indications that are not covered by the reimbursement; the price of the product becoming 20% higher than non-generic reimbursed alternatives; and the medicine no longer being subject to medical prescription or changing its classification to restricted medical prescription.

Illegal promotional practices may also determine exclusion from reimbursement.

As noted above, prescription medicines must undergo a prior evaluation procedure with a view to being bought by NHS Hospitals – unless otherwise decided by the Ministry of Health or Infarmed, should the Ministry delegate the competence to take this decision. Non-prescription products may also be subject to such a procedure if their sales volume to NHS Hospitals is very significant.

The purpose of the prior evaluation procedure is very similar to that of the reimbursement procedure: the applicant must demonstrate that the medicine is innovative, or therapeutically equivalent to current alternatives and presents an economic advantage. Also, and similarly to what happens with reimbursement, the law specifies the criteria which should be met for a favourable decision to be awarded – particularly so as to demonstrate the economic advantage.

If favourable, the prior evaluation decision sets a maximum price of acquisition for NHS Hospitals and entails the execution of a contract between the MA holder and Infarmed. These contracts, further to being entered into for a fixed term, can provide for conditions similar to those we have seen above for reimbursement. The most common ones are the establishment of obligatory discounts over the maximum sales prices and the setting of a maximum amount of public expenditure with the purchase of the product which, if exceeded, should be paid back by the MA holder.

Medicines subject to prior evaluation cannot be purchased by NHS Hospitals until a favourable decision is issued and a valid contract executed. In exceptional circumstances, for example, in the absence of a therapeutic alternative and should the patients' life be at risk, and on a case-by-case basis, Infarmed may, on a case-by-case basis, authorise the purchase of these products.

Rules of procedure specify clear deadlines for issuing a reimbursement and a prior evaluation decision: (a) 30 business days, for generics and biosimilars; (b) 75 business days, for new therapeutic indications of an active substance which is already reimbursed; and (c) 180 business days, for new active substances. These deadlines are suspended and extended if, during the process, Infarmed asks for additional elements from the applicant, or opinions from independent committees.

Decision deadlines are merely indicative, with no consequences arising from non-compliance therewith. Should a decision not be issued within these timeframes, the applicant cannot assume that its product has been reimbursed or approved – neither can it assume that it is not. Unfortunately, reimbursement and prior evaluation procedures of innovative products, both new active substances and new therapeutic indications, take far more time than is provided for in the law.

Negative decisions in the context of reimbursement and prior evaluation procedures are subject to appeal.

MA holders are entitled to file an administrative appeal before Infarmed or the Ministry of Health – depending on who issued the final decision. This appeal, which is not mandatory for recourse to judicial action, has extremely limited chances of success. A judicial challenge before administrative courts is also admissible, even though the court's powers are limited to judicial review. A judicial claim can take as much as two years to be decided in the first instance.

How is the reimbursement amount set? What methodology is used?

The general rule is for reimbursement to be set as a percentage of the maximum public sales price of the product.

The reimbursement amount is set in one of four tiers, ranging between 15–90% of the product's maximum public sales price (15%, 37%, 69%, 90%). A Ministry of Health Order provides the pharmacotherapeutic groups that correspond to each reimbursement tier – so the reimbursement tier in which medicines are included depends on the diseases they are indicated to treat. The reimbursement tier rises in accordance with the priority the Government assigns to the treatment (or access to treatment) of a certain disease.

In addition to this general regime, medicines can be included in special or exceptional reimbursement regimes, which may follow specific rules and set specific reimbursement amounts. Specially or exceptionally reimbursed medicines are usually reimbursed in full, and concern specific diseases which raise significant health concerns. HIV and hepatitis medicines, for instance, benefit from a special reimbursement regime and are dispensed at no cost to patients at NHS Hospital pharmacies.

How are drug prices set? What is the relationship between pricing and reimbursement?

Medicines subject to medical prescription (yet not restricted medical prescription), both generics and non-generics, must undergo a price approval procedure before Infarmed prior to being launched in the market. Price approval – contrary to reimbursement – is a condition to market the product.

In the context of the price approval procedure, a maximum sales price is approved, which, in the case of branded products, is determined by reference to the wholesale price applied in four reference countries. The reference countries are defined annually (in 2019: Spain; France; Italy; and Slovenia). The maximum sales price cannot exceed the average of the wholesale price applied in the reference countries (with exclusion of applicable margins and taxes). If the medicine does not exist in the reference countries, the price cannot be higher than the price of identical or essentially similar medicinal products in those markets (excluding generics). If such a product does not exist, the price should not be higher than the price of identical or essentially similar products in the national market. If similar medicines are not marketed in Portugal or the reference countries, the price cannot be higher than the price in force at the country of origin. This maximum sales price is subject to annual revision according to the same criteria.

Branded medicinal products subject to medical prescription which are not reimbursed and are sold before NHS Hospitals are also subject to a price approval and annual revision procedure. The logic, similarly to what happens with retail pharmacy products, is that in comparison with the price applied in three reference countries, it is the same as that defined in a pharmacy setting. However, in the case of these products, the maximum sales price to hospitals cannot exceed the lowest wholesale price applied in three reference countries.

The maximum sales price of generics, in turn, is set by reference to the price of the reference medicine. The price of the generic cannot exceed 50% of the maximum sales price of the reference medicine or 25% of that price, should the reference product's wholesale price be lower than €10. Generics are also subject to an annual price revision. Under the said revision, the price of the generic should continue to maintain the same price difference *vis-à-vis* the reference product.

The price of the generic may, however, be affected for reimbursement purposes.

In fact, the placement of a generic in the market gives rise to the creation of a "homogenous group", composed of branded medicines and generics (with the same active substance, dosage, method of administration and pharmaceutical form). The creation of the "homogeneous group" triggers the approval of a reference price for the products which

make part of said group. The reference price corresponds to the average of the retail sales price of the five lowest-priced products included in the group.

Following approval of the reference price, the maximum amount of reimbursement for products included in the group will be determined by applying the applicable reimbursement percentage to the reference price. With a view to being reimbursed, the maximum sales price of generics entering the market after the group's creation must be at least 5% lower than the price of the cheapest generic already in the group (up to a limit of 20% of the reference medicine's maximum sale price). This successive lowering of the price of generics and of the reference price leads to significant savings in expense with reimbursement, but also to a substantial gap between over-the-counter prices of generics and branded medicines.

Finally, generics which are not reimbursed and are sold to NHS Hospitals are also subject to a price approval and revision procedure. Under this regime, the price of the generic should be at least 30% lower than the price of the reference product.

While biosimilars are not subject to a specific price-approval procedure, price control of these products is set within the context of the reimbursement procedure. As noted above, reimbursement of a biosimilar can only be approved if the respective price does not exceed 80% of the reference medicine's price.

Similarly to what happens with generics, a biosimilar entering the market also triggers the creation of a "homogeneous group", and of a reference price as well. Two differences occur. Reimbursement of similar biological medicines can only be approved if their price does not exceed 80% of the reference medicine's price and, in case a "homogeneous group" with at least one biosimilar medicine already exists, the price of the following biosimilar cannot exceed 70% of the reference medicine's price.

Lastly, discounts can be granted throughout the medicine's marketing circuit (manufacturer, wholesaler and pharmacy). However, discounts can only be granted in relation to the non-reimbursed part of the sales price of the medicinal product.

Issues that affect pricing

As noted above, Portugal follows a referencing system as far as price definition is concerned.

Limiting public expenditure is therefore done, on the one hand, through price control and, on the other, through reimbursement or prior evaluation procedures – in general terms, market access. The major factor influencing market access is cost. Rather than assessing the medicine's performance and market behaviour independently, public authorities are compelled to lower maximum amounts of public expenditure, based almost exclusively on the budget that is allocated for the expense of medicinal products.

Although the launching of a generic in the market does not directly affect the price of the reference medicines, competition of generics and therapeutic alternatives – particularly if cheaper – greatly influence the sales of the branded products.

This is achieved through several means:

- Firstly, through the renegotiation of the maximum public expenditure levels provided for in reimbursement/prior evaluation contracts.
- Secondly, because of substitution. In fact, the general rule, in which generics are concerned, is for mandatory substitution.

Prescription of medicines should be done by the International Non-proprietary Name ("INN") – although the brand of the product may be added. Once generics are placed on

the market, the rule is one of substitution, and the physician is only allowed to prevent substitution in the limited and exceptional cases provided for in the law. Similarly, pharmacists, when confronted with a prescription, are required to inform patients of the existence of products with an identical active substance, pharmaceutical form, dosage and presentation of the prescribed product, as well as whether these are reimbursed and those which have the lowest sales price.

Pharmacies should have available for sale at least three products with the same active substance, pharmaceutical form, dosage and presentation, between the five products with the lowest sales price. Unless the patient chooses otherwise, the pharmacist should dispense the medicine with the lowest price. The patient is further entitled to replace the prescribed product with one with that has the same active substance, pharmaceutical form, dosage and presentation unless the physician has prevented substitution. Even in the latter case, the patient may choose to replace the product for a cheaper product if the circumstance on the basis of which the physician prevented substitution was due to the fact that the product was designed for long-term treatment (i.e. that which is anticipated to last over 28 days).

On the other hand, and concerning NHS Hospitals, medicines are purchased pursuant to mandatory public procurement procedures. Supply contracts awarded through these procedures are overwhelmingly awarded to the bidder with the lowest price – meaning that generics and biosimilars are expected to take over the market as soon as they begin marketing. Several instructions have also been directed to NHS Hospitals with a view to increasing the purchase of biosimilars.

Finally, the Ministry of Health has taken measures to ensure that NHS Hospitals and Services can begin purchasing generics and biosimilars as soon as they enter the market.

Policy issues that affect pricing and reimbursement

Portugal's population has stagnated and is not expected to grow in the coming years. The elderly population is growing steadily and significantly. According to the latest census (2011), the population of all age groups up to 30 years old decreased between 2001 and 2011, while the population of older age groups increased in all tiers. Significantly, the 75+ age group increased from 701,366 to 961,925 between those years, and other senior age groups substantially increased their population (source: www.pordata.pt).

While no aggregate data is immediately available, the authorities recognise that the growth in the elderly population considerably contributes to growth in prevalence of chronic diseases, and that these are responsible for more than 80% of disease-related mortality.

As of 2017, the cost of State-funded healthcare was estimated at 4.5% of GDP and the cost of drugs covered by the State Budget was €1.2135m. (source: www.pordata.pt). In this same year, total NHS expenses were €8,757.70m, the cost of drugs amounting to approximately 13.8% of the Health Budget (source: www.pordata.pt).

These demographic and financial data strongly suggest that public authorities will be faced with great pressure to lower the prices of medicines.

Aside from pricing policies and budget-oriented evaluations, the most significant political influence over pricing and reimbursement policy is a shift of priorities, from treatment to prevention. Public authorities are focusing on disease-deterrence programmes that concern lifestyle and nutrition changes, and essentially seek to prevent the appearance of chronic diseases. Health authorities are favouring this approach over counting on the approval of innovative medicines. This naturally involves a transfer of State Budget funds towards prevention. Notwithstanding this growing inclination in policy, an increase in the

prevalence of chronic diseases has generated a need to create disease-specific programmes, which may involve the increase of reimbursement for diseases that are becoming more frequent (such as cancer and cardiovascular and respiratory diseases).

Emerging trends

Considering that the pricing and reimbursement system was completely overhauled in 2015, with the approval of SiNATS (the National System of Evaluation of Health Technologies), which was later revised in 2017, no significant changes in legislation are currently anticipated.

The enactment of this new legislation did not, however, remedy the challenges with which innovative pharma companies are confronted. Delays in deciding prior evaluation and reimbursement procedures have not been dealt with. Even though legal deadlines exist, the delay of the procedure significantly exceeds these deadlines, as far as branded medicines are concerned, with practically no consequences attached to it.

Another recent trend following the approval of SiNATS is the increased imbalance between Infarmed and MA holders in reimbursement and prior evaluation contracts. Such imbalance is particularly evident when Infarmed has the power to unilaterally change the contract and the maximum amounts of public expenditure with the medicine – which, if exceeded, trigger payback of the excess.

Reimbursement contracts have lately seen an important development. Infarmed usually sets the maximum public expenditure cap by product and indication. Recently, the agency proposed reimbursement contracts that provide a maximum expenditure cap for an entire therapeutic indication, covering all products indicated for treatment of the said disease. In this case, if there is an excess, companies will pay it back *pro rata*, based on their market share.

Despite recent improvements, there are still concerns about transparency in reimbursement and prior evaluation procedures. The regime is far from compliant with the EU Transparency Directive which clearly provides that measures regulating the pricing of medicinal products should use objective and verifiable criteria.

The entry of biosimilars in the market is still surrounded by some uncertainty. While a regime – largely based on what is applicable to generics – has been approved, it is too soon to tell whether this will be effective.

Successful market access

The top factor in securing successful market access is to protect the MA holder's credibility before Infarmed. During the submission of reimbursement or prior evaluation requests, the negotiation of contracts, or the re-evaluation of the medicine's compliance with the applicable criteria, the MA holder may feel tempted to overstate the product's economic advantage or therapeutic added value – which may happen, for instance, if the economic evaluation study submitted with the request heavily relies on less tangible or probable economic advantages.

This strategy will often backfire, and lead Infarmed to disregard the information submitted by the MA holder and delay the procedure, focusing solely on price. Lack of consistency of the data submitted with the reimbursement request may therefore result in poorer conditions than those that could be approved if the MA holder resorted to more agreeable estimates and projections.

Credibility is also an asset in subsequent re-evaluations and negotiations. If effective consumption is very wide of the mark of a former estimate of consumption, the Agency will feel strongly compelled to ignore the MA holder's revised estimates and sharply lower the expenditure limits.

Flexibility can also be accounted a success factor. Considering the frequent changes in regulation and policy orientation, MA holders should be open to several scenarios, and have sufficient strategic insight to negotiate contracts in a fast-changing environment, where several reimbursement or payback solutions are theoretically possible.

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Spain

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Abstract

Spain is a very attractive market for pharmaceuticals within the European Union. However, it is also a very regulated market and the decisions are taken by different authorities at different levels. This is why market access can appear complex. In the following chapter we will try to explain the most important rules which must be taken into account in order to understand the process of pricing and reimbursement in Spain.

Market introduction/overview

In 2018, the pharmaceutical market in Spain reached €17.5 billion, of which €6.8 billion corresponds to the hospital market, and €10.7 billion to products dispensed through retail pharmacies. Growth was above 4.5%, with expenditure in hospital products exceeding 7.67% over 2017, whilst growth in retail pharmacies was under 3%. In the near future, one may expect further increases in the hospital market as a result of the appearance of innovative medicinal products, especially in the area of oncological products and orphan drugs. Because of this, cost containment measures may appear in various forms, as we shall explain in this chapter.

As in many other EU countries, the Spanish pharmaceutical market is highly dependent on public policies, given that approximately 73% of health expenditure comes from the public sector. Spanish public pharmaceutical expenditure is said to account for 0.9% of gross domestic product, and 14.5% of all public healthcare financing. According to data of Farmaindustria (the association of the Spanish innovative pharmaceutical industry), the Spanish pharmaceutical industry is the most productive sector of Spain (double the industry average); it is one of the leaders in exports (exceeding €10 billion per year); and by comparison with other sectors in Spain, it has a higher concentration of more stable, qualified and diverse employment (more than 95% of its workers are permanent, 50% have university studies, and 50% are women).

As regards demographics, at the beginning of 2019, 46.9 million inhabitants lived in Spain, with a gross birth rate of 7.8 births per 1,000 inhabitants and an average maternal age of 32 years. Life expectancy at birth reached 83.2 years. Since 2017, Spain has the classical pyramid of population of a developed country where the number of deaths increases more than the number of births. Data from *Instituto Nacional de Estadística* ("INE")[1] show that steady growth in births may be expected during the next 10 years at rates that may be near 0.5%; but a decline in population of almost 50,000 persons each year. The percentage of the population aged 65 years and over may reach 25% in 2033, and the number of persons that are dependent on others will continue increasing up to almost 60% in 2033.

In relation to the Spanish healthcare system, Article 43 of the Spanish Constitution establishes the right to healthcare as one of the basic principles that must inspire action by all public administrations, and this has been interpreted to recognize universal access to healthcare.[2] However, measures[3] taken by the Spanish government during the economic crisis that Spain suffered from 2008 to 2014 have affected such universal access to healthcare, setting forth some limits as regards the condition of beneficiaries of the system.

These limitations consisted basically in the establishment of some prerequisites in order to access healthcare benefits, such as: contributing to the Spanish Social Security system; having an authorised residence in Spain; holding pensioner status in the Social Security System; or being the beneficiary of any other periodic Social Security benefit, including unemployment benefits and subsidies. Those who have exhausted their benefit or unemployment subsidy and appear registered in the corresponding office as a job-seeker will also have access. Other than that, the measures taken determined that nationals of Spain, or of any Member State of the European Union, the European Economic Area or Switzerland residing in Spain, and foreigners holding an authorisation to reside in Spanish territory, may hold the status of insured provided they can prove they do not exceed an income limit determined by regulation.[4]

Put into practice, these measures implied that some population would not access the healthcare provision. The Constitutional court declared that these limitations to the healthcare provision were valid but many regions in Spain have declared that right to healthcare is universal in their territory, and the matter has been very controversial in Spain in recent times. Many of the restrictions resulting from Royal Decree-Law 12/2016 were reversed by another Royal Decree-Law adopted on 27 July 2018, on Universal Access to the National Health System.[5]

During the year 2016, 1,257 presentations of medicinal products were included in the provision of the National Health System (NHS).[6] Furthermore, Spain is a market which has numerous innovative therapies included within the provision of the NHS.

In Spain, market access has two stages: (i) the granting of the marketing authorisation by the regulatory agency (Spanish Agency of Medicinal Products and Medical Devices, "AEMPS") or the inscription at AEMPS registry of products approved under the EU centralised procedure; and (ii) the resolution on pricing and reimbursement by the Ministry of Health ("MOH"). AEMPS also intervenes to some extent in the pricing and reimbursement procedure by issuing a so-called Therapeutic Positioning Report, on which the MOH relies when deciding on pricing and reimbursement.

Furthermore, an aspect which needs to be taken into account is that Spain is a decentralised country and the regions have an important role in market access because, even though the MOH decides which therapies are financed, the regions are the ones that allocate the budget for financing such therapies. This means that in the case of high budgetary impact products, companies must expect that access to market be subject to agreements with regional authorities (or sometimes with local hospitals) regarding the conditions under which the product will be available in such region or hospital.

Pharmaceutical pricing and reimbursement

Regulatory classification

According to Article 19 of the Spanish Law on Medicinal Products (Royal Legislative-Decree 1/2015), when the AEMPS authorises a medicinal product, it will determine its

prescription conditions by deciding whether the product is subject to medical prescription or not.

The same Article establishes that certain medicinal products which meet certain conditions will be always subject to a medical prescription. This is the case for those medicines which may present a danger, either directly or indirectly (even under normal conditions of use), when they are used without being under medical supervision. The same happens with those medicinal products which are used frequently under abnormal conditions of use, and this may involve, directly or indirectly, a danger to health. Spanish law also sets forth that those medicinal products which contain substances (or preparations based on these substances) whose activity and/or adverse reactions need to be studied in more depth, must also be classified as subject to a medical prescription, and the same happens with those medicinal products which are administered parentally.

AEMPS may also establish some subcategories, for medicines that can only be dispensed under medical prescription. This would apply to products subject to a special medical prescription regime; or to medicinal products which can only be dispensed by certain means (such as medicinal products for hospital use). It is also important to note that the MOH may also establish restrictions as regards the prescription, dispensing and financing of some medicinal products within the NHS. These may include the need to go through a special visa procedure before the patient may get a given product under reimbursement by the NHS. Under Spanish law, the regions are not entitled to establish local measures restricting prescription, dispatching or financing of medicines or devices that have been accepted for reimbursement at a national level.

AEMPS may classify as medicinal products which are not subject to medical prescription those that are destined for processes or conditions that do not require an accurate diagnosis, or those whose toxicological, clinical or use evaluation data and route of administration do not require medical prescription, and these medicines will be dispensed by a pharmacist who will inform, advise and instruct about their correct use.

Spanish law also contemplates the classification of medicines between brand medicinal products, generic medicinal products, biologic medicinal products or biosimilar medicinal products.

Article 2 of Spanish Law on Medicinal Products (Royal Legislative-Decree 1/2015) defines generic medicinal products as any medicinal product that has the same qualitative and quantitative composition in active ingredients and the same pharmaceutical form, and whose bioequivalence with the reference medicine has been demonstrated by adequate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active ingredient will be considered the same active ingredient, unless they have considerably different properties in terms of safety and/or efficacy. Biosimilar products are not defined under Spanish law, although there exist provisions under which all biological products are considered as non-eligible for substitution without the prior approval of the prescribing doctor.

Under Spanish law, the distinction between over-the-counter medicines and non-prescription medicines does not exist, because the law only distinguishes between prescription and non-prescription medicines.

Who is/Who are the payer(s)?

Spain's Autonomous Regions pay for all healthcare services out from their own budgets and,

subject to certain conditions which may derive from European and Spanish rules on public procurement, they enjoy a large degree of autonomy to decide how they purchase goods and services which they may require in order to provide healthcare services to patients.

The MOH is the department of the central government responsible for approving reimbursement of medicinal products. As explained, the public funds that may be used to finance this reimbursement come out of the budget of the 17 Autonomous Regions into which Spain is divided. Because of this, the regions participate in the specific committee at the MOH responsible for assessing applications for deciding on the maximum ex-factory price for reimbursed products. This committee is called the Interministerial Committee for the Price of Medicines ("ICPM").

This generates a complex situation where the basic content of the pharmaceutical provision is set forth at a state level (because the MOH makes the decision on pricing and reimbursement) but where the Autonomous Regions are responsible for the financing of these medicines without being allocated a specific budget for each medicinal product, but having to administer their budget and complying with the basics of the pharmaceutical provision.

On the other hand, products that patients obtain at retail pharmacies are subject to co-payment rules under which the patient has to pay part of the price of the product. The co-payment percentage depends on the type of product and also on the type of patient.

What is the process for securing reimbursement for a new pharmaceutical product?

The reimbursement process starts *ex officio* and it is compulsory, meaning that the marketing authorisation holder ("MAH") does not have the right to say that it is not interested in reimbursement and that it will launch the product right away. Under Article 92 of the Spanish Law on Medicinal Products (Royal Legislative-Decree 1/2015), the MAH has to go through this process, so that the MOH may decide whether the product shall be reimbursed and covered by the NHS or not.

The process regarding pricing and reimbursement in Spain of a medicinal product that is centrally approved begins when the AEMPS gives final clearance to the packaging materials that are to be used in Spain. Once the AEMPS has approved the final packaging materials of the product, it shall record this decision and notify it to the MAH and to the General Directorate of Pharmacy and Medical Devices, which is the body within the MOH which is competent to rule on reimbursement. As explained, the reimbursement process then starts *ex officio*. The General Directorate of Pharmacy and Medical Devices shall send a letter to the MAH or to its local representative, informing it that the process has begun and granting the company a period between 10 and 15 working days to make any submission it deems convenient on the reimbursement of the product.

Under the law, the process to decide on pricing and reimbursement may take up to 180 days. Furthermore, the authorities usually request additional information, and these requests may stop the clock of the procedure. In practice, companies may well expect the reimbursement approval to run for a minimum of six months. Sometimes, we have seen procedures take up to a year.

Who influences the decision?

The most important decision-maker in the reimbursement process is the central government. AEMPS has a very important role when issuing its therapeutic position report, and the MOH, through the General Directorate for Pharmacy and the ICPM, decides on reimbursement and

then on price. In theory, the General Directorate for Pharmacy is the first to decide on whether the product is reimbursed or not; and the ICPM then decides on the maximum reimbursed price. In practice, however, the two procedures run in parallel and overlap, because the decision of the General Directorate for Pharmacy regarding reimbursement is also based on the price that the ICPM would set for the product.

The General Directorate for Pharmacy, on the other hand, takes care of process management, preparing the rulings that the ICPM shall adopt; it is also the *de facto* leader of the negotiations with the MAH, and coordinates the work done by evaluation teams who handle the dossiers prior to the meeting of the ICPM.

It is also very important to note that authorities of the Autonomous Regions have a very important role in this decision, because they are the ones funding the dispensing of the product to the patient. This is also why three of the Autonomous Regions are members (on a rotating basis) of the ICPM. At present, representatives of all other Autonomous Regions may participate as observers at all ICPM meetings. On the other hand, whilst the central Spanish legislature and government have exclusive competence to enact legislation on medicinal products, the Constitutional Court has established in several cases[7] that this applies to the rules related to the evaluation, approval and surveillance of medicinal products, but not necessarily to the ones having to do with aspects related to how individual patients may get access to medicines. This is important because the Autonomous Regions are thus competent to establish the specific procedural rules that may apply to how the patients may get access to reimbursed products.

It is also important to note that other relevant stakeholders may include doctors, medical and hospital pharmacy societies and patient associations, who may try to exercise some influence. Anyhow, the procedure is a bilateral one between the interested company and the MOH. Other entities (including associations, competitors, etc...) do not have legal standing to intervene as interested parties, and they have no right to make allegations, nor the right of access to the information provided by the interested company.

What pharmaceutical products are eligible/ineligible for reimbursement?

Under Article 92 of the Spanish Law on Medicinal Products, the inclusion of a medicinal product in the financing of the National Health System is decided according to a selective funding system and taking into account general objective and published criteria, more precisely, the following:

a) the seriousness, duration and sequels of the pathologies for which the product is approved;
b) the needs of special groups of people;
c) the therapeutic and social utility of the product as well as its incremental clinical benefit, taking into account its cost and effectiveness;
d) the need to limit and rationalise public pharmaceutical expenditure and the impact of the medicinal product on the NHS;
e) the existence of medicines already available and the existence of other alternatives for the same illnesses, which have a lower price; and
f) the degree of innovation of the product.

This being said, Royal Decree-law 16/2012 introduced new rules stating that when deciding on whether a product must be accepted for reimbursement or not, the MOH shall also consider, specifically:

a) The impact that financing such product may have on the public budget.

b) A cost-efficiency analysis. For the purposes of this analysis, the MOH shall rely on a Therapeutic Position Report ("IPT" for "*Informe de Posicionamiento Terapéutico*" in Spanish) that the AEMPS shall prepare, and on the opinion of the Advisory Committee on Pharmaceutical Coverage. Any studies that the MAH may present may also be considered.

c) The innovation of the product; whether it provides an indisputable therapeutic advance for altering the course of an illness or easing the course of such illness; and its prognostics, results or contribution to the NHS.

d) The contribution of the product to Spain's gross domestic product. This is awkward because it could indicate that local manufacturing or development operations have an influence on pricing and reimbursement; something which would be totally contrary to EU law principles.

e) The return mechanisms which may be proposed by the marketing authorisation holder (discounts, price reviews). This is the result of the increasing relevance that risk-sharing schemes are having in Spanish practice nowadays; many companies, especially for high-budgetary-impact products, are required to offer specific arrangements to obtain reimbursement. These may be in various forms, including caps on the number of units that will be reimbursed by the NHS and chargebacks in the event that some established therapeutic results are not achieved.

The medicines which are directly excluded from the pharmaceutical provision are those which are not subject to medical prescription; those medicinal products which are not addressed at healing a concrete illness; and products which are considered cosmetics, dietetics, mineral waters, elixirs, dentifrices and other similar products. Spanish law also specifies that those medicinal products which are indicated for syndromes or illnesses of minor severity, and those which do not respond to current therapeutic needs, shall also be excluded from the pharmaceutical provision.

What is the relationship between pricing and reimbursement?

Under Spanish law, the ICPM determines the maximum price for the units of the products that are reimbursed by the Spanish NHS. The MOH will also take note of the so-called "Notified Price". The notified price is the price at which the MAH intends to market the product if it is not reimbursed by the NHS. This may apply to products that are not eligible for reimbursement and also to units of reimbursed products that are marketed outside the NHS (i.e. private patients or products that wholesalers may parallel-export from Spain to other EU Member States). The MOH, when receiving notice of the notified price, may only oppose it on the grounds of protecting public interest.

It is also important to note that the decision on financing a product does not have to affect all the therapeutic indications of a product. It is viable that only certain indications of products are financed. In these cases, it is customary that the MOH makes prescription of these products subject to a visa system.

How are drug prices set?

As regards setting the price of medicinal products, Spain has always been said to follow a 'cost plus' system, under which the maximum ex-factory price should respond to the cost of the product plus a given profit margin. This is what Royal Decree 271/1990 contemplates in accordance with the provisions of Directive EC 89/105.

The cost of the product is to be determined through the analytical application of the "Complete Cost", including R+D, manufacturing costs, and allocations corresponding to commercial and administration costs. In determining the Complete Cost, three groups of variables are established: variables which are considered; variables which are not considered; and variables which are subject to intervention and may be limited:

(i) Variables which are considered:
- Level of activity of the company.
- Evolution of costs of the company.
- Evolution of sales of the company.
- Sales estimates.
- Impact that manufacture of the product may have on overhead costs of the company.

(ii) Variables which are not considered since they are treated as unjustified or unnecessary costs:
- Overvaluation of active substances in comparison with market prices.
- Excessive royalties (trademarks or technology).
- Promotion or advertising expenses which are not adequate to the characteristics of the product.
- Expenses which are not necessary to the normal development of the activities of the company.

(iii) Variables which are subject to intervention and which may be limited by the Government Delegate Commission for Economic Affairs:
- Research and development.
- Promotion and publicity.

Under Order of 17 November 1990, R+D expenses are not subject to any limitation. R+D expenses may therefore be incorporated into the cost of the product if they are justified, and prior deduction of all public aids granted to the company under R+D programmes. The R+D percentage which may be incorporated to the cost of the product is the equivalent to the percentage that the total expenses of R+D represent of the company's total sales.

As to promotion and advertising expenses, they may only be incorporated to the cost of the product within a range of 12–16% of such cost.

As regards the profit component, the rule is that the target profit of each company shall be within a range of 12–18% on capital allocated to exploitation, including own resources (share capital, update and revaluation accounts, reserves, and others) and external resources with financial cost.

Issues that affect pricing

As a matter of practice, it has always been known that the price-approval process entails a negotiation with the authorities where the cost and the profit margin are not really the variables which are considered.

Companies should be prepared for prices mainly to be determined by the following two issues:

a) A comparative pharmaco-economic evaluation of the medicine in which the advantages of the new product should be quantified.

b) The price of the product in other EU Member States.

Other than these, companies need to be ready for the authorities to consider other issues such as the activities performed by the company in Spain (R+D, manufacturing, etc.) and the relationship with a local company through a co-marketing or licensing arrangement.

It is also important to note that under the Spanish Law on Medicines and Medical Devices, the authorities, when dealing with the price-approval process, need to take into account the criteria we have mentioned above when discussing reimbursement approval. It is also true that in case a similar product is commercialised in the Spanish market, the authorities may use it in order to determine the price. The price of any competing product inside Spain will undoubtedly serve as a reference for the MOH when discussing the price of a new product.

What is the process to appeal a decision?

Companies may file an administrative appeal against the decision taken by the ICPM once this is notified. The appeal must be filed within one month of the date on which the decision is considered to have been notified. These decisions are notified electronically, and companies have a period of 10 days to download the notice once they receive the alert that it is ready to be downloaded.

If the administrative appeal is rejected, the company may file a court action seeking a declaration that the ICPM acted wrongly. However, in pricing and reimbursement cases, the chances of a court action being successful are rather limited, given that the MOH has wide discretionary powers on these matters. In general, companies have more chances of being successful at the administrative appeal level if they are able to provide evidence of some major mistake in the administrative decision.

The administrative appeal does not suspend the application of the decision taken by the ICPM. The suspension may be requested when filing the administrative appeal and this request must be answered within one month. In this case, failure to respond by the MOH acts in favour of the appellant, because in such event the suspension is deemed to have been granted. Afterwards, however, the MOH may lift such suspension when deciding on the substance of the appeal. In order for the suspension request to have any chance of success, the applicant must provide evidence that the immediate entry into force of the decision of the ICPM will result in irreparable harm. The threshold is thus rather high; and this is why we normally consider that the chances of succeeding in a request for suspension are rather low.

One issue which often arises when dealing with administrative procedures in Spain refers to the general climate, and to whether companies that may be strict enforcing their rights, and even filing administrative or court appeals, may suffer some sort of negative reaction by the MOH. Our opinion, based on over 20 years of experience dealing with these matters, is that neither AEMPS, nor the MOH nor the ICPM, penalise companies by defending their position – provided this is done under general good faith principles. In some cases, special diplomacy may need to be exerted to ensure that the position of the company is not misinterpreted – it is important to play fair – but in general terms, this is not something to be too concerned about.

Reference pricing

It is also very important to bear in mind that in Spain the public financing of medicines is subject to a reference price system. Once a generic version of a medicinal product is approved, or even in other circumstances if no generic exists in Spain but the main active ingredient of a product has been generally available in the EU for the last 10 years, the MOH may make it subject to a reference price, which will apply to all financed product

presentations containing the same active ingredient and identical administration route.

The reference price is the maximum price which the Spanish authorities will pay for these products when they are prescribed and dispatched through an official prescription at a pharmacy, and such price is fixed on the value represented by the lowest cost of the treatment per day of the presentations of the medicinal products included in each group. The reference price system, as an instrument designed to guarantee the sustainability of the public pharmaceutical provision, uses the appearance on the market of competing products for a certain active ingredient to establish a maximum price for the dose necessary for a day of treatment with this active ingredient, which is the maximum price that the NHS will satisfy when the presentations with this active ingredient are dispensed or administered to the patient charged to public funds.

In general terms, when a medicinal product is included in the reference price system, one may expect a reduction between 40% and 50% in the price of the reference/s product/s (the price of generics are likely to be within this range).

In 2018, Spanish courts have had to rule on various cases where plaintiffs have argued that the MOH was inadequately including, in the same reference price group, products that did not have the same active ingredient. In the majority of these cases, the issue was whether products, having as their active ingredient different salts or esters, should be considered the same for reference price purposes. The courts have ruled that if the MOH wished to include all these products in the same reference price group, it should provide evidence that the differences between the various salts or esters included in the same group did not have enough significance from an efficacy or safety perspective.

On another note, in 2018, the Spanish MOH took special measures to protect some products that could be impacted by reductions of their reference price in cases where such reduction could result in the products not being available any more.

Compulsory discounts

For many products, compulsory discounts or chargebacks apply. The general rule, in this respect, is that products for which no generic competition exists, will be subject to a discount of 7.5% on their maximum ex-factory price (4% in the case of orphan drugs). If a product has been on the market for more than 10 years, the discount will apply even if there is no generic competition, unless the product is still covered by product patent protection in any EU Member State.

Annual reviews

MAH of products with high budgetary impact may expect that decisions on pricing adopted by the ICPM will be subject to annual review, which may be triggered *ex officio* by the MOH. As one may expect, the annual review procedure will aim to lower the price of the product. Within the procedure, the MOH shall grant the company a period of 10 working days to file documents and allegations in support of its position.

May patients have access to an approved drug while the pricing and reimbursement process is still open?

Under Royal Decree-Law 1/2015, a medicinal product which has received a marketing authorisation ("MA") valid in Spain cannot be placed on the market in Spain until the pricing and reimbursement process has been completed. However, under Royal Decree 1090/2015,

in these situations the product may be available for patients under the rules that apply to products for which a valid MA exists in Spain but which are not commercially available.

These rules allow access to the product if the prescribing doctor, under his/her own responsibility, considers that the use of such product is indispensable for the treatment of an individual patient because no other equivalent product is available in Spain. An equivalent product is one having the same composition and the same pharmaceutical form. The patient – or the patient's representative – must consent in writing to the prescription, after having been informed about the benefits and risks of the treatment, and the written approval of the management direction of the healthcare centre where the patient is treated must be obtained. The law also states that prior administrative approval from AEMPS for each individual case must be obtained; that the prescribing doctor must respect any special restrictions resulting from the protocols approved at the healthcare centre; and that he/she must also report to AEMPS the results of the treatment and any suspected adverse events.

The units of the product supplied under either of these routes can be charged to the healthcare centre requesting such medicinal product. The price is fixed by the importer, normally after negotiation with the pharmacy service of the healthcare centre. The common practice is to stick to the "international" price of the product. However, there are some caveats to this: first, as a matter of practice, it is not uncommon that some units provided under this route be supplied free of charge. At present, there is no legal obligation to do so in Spain, but this is not uncommon. Second, if the product is for a patient who has previously participated in a clinical trial with this product in Spain, and the sponsor continues to receive information from the doctor/healthcare centre as regards the treatment results of such patient, then the supply must be free of charge until the product is effectively marketed in Spain after receiving all relevant approvals (art. 31 of Royal Decree 1090/2015 on clinical trials).

What happens with products for which reimbursement is denied?

Up to very recently, there was consensus in Spain in the sense that if the MOH decided to deny reimbursement, the MAH could still place the product in the market for patients or hospitals who would wish to acquire it at the notified price. The only regulatory requirements would be two. First, to inform AEMPS about the fact that the product would be commercially available. Second, for hospital use products, the purchase of these by hospitals would require approvals from the regional authorities where the hospital is located, such approvals to be granted as per the process determined by each region.

This consensus has been in danger since May 2019, when the General Director of Pharmacy issued a report stating that medicines for which a ruling expressly denying reimbursement has been adopted cannot be paid for by hospitals or Regional Authorities. This report is now the subject of major controversy. Our position is that it is null and void because the General Director of Pharmacy is not competent, under Royal Decree 1047/2018 which defines her authority, to issue a report that creates a new category of products (those for which a ruling expressly denying reimbursement has been adopted), and which is drafted under terms that restrict the ability of the regions and of hospitals to purchase those products, and the right of patients to have access to them.

Furthermore, we sustain that article 17.6 of Royal Decree 178/2010 states that hospitals may buy products that are not reimbursed subject to some special approvals and procedures handled by the regional healthcare services. The report states that article 17.6 of the Royal Decree 178/2010 refers to medicines not included in reimbursement by the NHS, but not to those medicines which have received, expressly, a resolution of no reimbursement.

We think that there is no passage of Royal Decree 178/2010, or of any other law or regulation in Spain, which supports the idea that when Royal Decree 178/2010 refers to medicines not included in the reimbursement of the NHS, it intends to differentiate between products that are not reimbursed because the law excludes them from reimbursement and those that are not reimbursed because a ruling expressly denying reimbursement has been adopted. This is a case where the general principle of law *ubi lex non distinguit nec distinguere debemus* (no differences should be made when the law does not establish them) applies.

Confidentiality and transparency

Companies involved in a pricing and reimbursement procedure may need to disclose confidential information to Spanish authorities. Spanish law, in this respect, contemplates that the MOH may request the company to provide information about technical, economic and financial aspects related to the product and to the activities of the company. Article 97 of the Spanish Law on Medicinal Products (Royal Legislative-Decree 1/2015) states that all information that the authorities may obtain from the company in these procedures is confidential. On the other hand, under Article 52 of Law 7/2007, which is the general law on public employees, all civil servants are obliged to act in conformity with the law and to abide by the principle of confidentiality.

The decisions of the MOH on pricing and reimbursement are acts of a public authority, taken in the ordinary course of its activity, and as such they are subject to the rules on transparency and freedom of information contained in Law 19/2013 on Transparency, Access to Public Information and Good Government. Under this Law 19/2013, any person, without the need to prove any special interest, may have access to documents that a public authority has created in the ordinary course of its activity, and the reasons for which such access may be denied are rather limited.

In cases where the Spanish Council on Transparency has received complaints against the MOH denying access to pricing and reimbursement rulings, it has decided that the MOH should deliver these rulings to the party that has requested them, only allowing those parts of the ruling the transparency of which could cause unfair or disproportionate damage to the company. In these decisions, the Spanish Council on Transparency has taken this position relying on the fact that Spanish law contemplates that the information that a company provides to the MOH when applying for pricing and reimbursement of a drug is confidential. Our view is that, relying on these decisions, and unless there is any change in future developments, any citizen would be able to obtain, from the MOH, information on the maximum reimbursed price for any medicinal product in Spain. It is clear that both the administrations and the bodies in charge of settling claims arising from requests for access have an important challenge ahead in order to find the right balance between the protection of commercial, economic and strategic information of companies and the principle of transparency that should govern the activity of the public administration.

In addition to the above, it is relevant to consider that under Spanish rules on public procurement, public contracting bodies are under an obligation to make public the main terms of any contract they enter into with any supplier of any good or service. In the event that the public contracting body understands that such publication may harm legitimate private or public interests, it may only redact the documents and avoid publishing some data after having obtained permission to do so from the Spanish Council on Transparency (which is probably going to be reluctant to agree to not publishing information on the prices at which a hospital is buying a given product).

On the other hand, it is important to note that it is common practice in Spain that contracting bodies do not publish information about supply agreements that they may negotiate individually with companies when there is no invitation to tender because there is no competition in a given market. In these cases, where the supply agreement is entered into following the process known as "negotiated procedures without prior publication of a contract notice", it is common that the agreement is not published at all. We cannot exclude that this administrative practice changes in the future because, as a matter of law, even these agreements should be publicised. But for the time being, this is where things stand.

Policy issues that affect pricing and reimbursement

The general political environment in Spain has affected the pricing of medicinal products. Over the last few years, budget constraints have been constant, and authorities have been very strict and careful as regards pricing decisions.

It is relevant to mention that in late 2015, Farmaindustria reached an agreement with the Spanish Government, under which pharmaceutical expenditure is not to grow more than real GDP growth. The agreement contemplates chargebacks to be paid by pharmaceutical companies in the event that the expenditure exceeds the agreed ratio. The agreement also contemplates that if the expenditure exceeds the agreed ratio, special measures to rationalise the use of medicinal products may be adopted. These measures, in essence, shall imply barriers for prescription of high-budgetary-impact drugs.

As regards more specific groups of medicines, we would also like to mention the special situation for rare disease medicines in Spain. In 2009, the Spanish MOH launched the Rare Diseases Strategy of the Spanish NHS. This Strategy was approved by the Interterritorial Council of the Spanish NHS, a committee on which the MOH sits together with representatives of all the Autonomous Regions. The Rare Diseases Strategy of the Spanish SNS was therefore a document supported by the central Spanish Government and also by all the Autonomous Regions. One of the objectives of the Strategy was to secure prompt access to treatments, and the recommendation to such effect was to shorten the periods for pricing and reimbursement approval once an orphan drug has obtained the relevant marketing authorisation. This recommendation was confirmed when the Strategy was updated in June 2014.

Emerging trends

Stability Program 2019–2022

The Stability Program 2019–2022 submitted by the Spanish Government to the EU refers to various measures aimed at obtaining savings in public expenditure of medicinal products dispensed in pharmacy offices. Furthermore, some proposals on hospital expenditure are expected to be formulated by the Government in the near future.

a) *Medicine selection processes at the national level*

The most relevant proposal among those announced in the Program is the introduction of a national medicine selection system for medicinal products dispensable in pharmacy offices. The objective of this measure is to allow the MOH to benefit from the margins currently received by pharmacies when dealing with these products. Recommendations in this area point towards a purchase model based on tenders, with only one bid per laboratory, at a uniform price, and with an invitation to tender at European level (rather than a national level). The proposed model takes inspiration from Andalusia's medicine selection system, but with corrective mechanisms such as the elimination of exclusive

supply, or the use of the system only for medicinal products for minor pathologies and with high economic impact.

b) *A new reference price system*

The Program contemplates a review of the current reference price system. In this regard, the Government proposes a system considering therapeutic indications (ATC 4) and active ingredients (ATC 5). The Program does not contemplate the introduction of an "avoidable co-payment system" that would allow patients to choose between branded and generic products by paying a higher price for the branded product if the patient wanted to do so.

c) *Decision-making and sustainability*

The Government proposes specific measures on the application of cost-effectiveness criteria in decisions related to reimbursed products, such as the introduction of a pharmacoeconomic evaluation method for medicinal products, and the measurement of health outcomes.

The Program also foresees the performance of *ex officio* reviews of the prices of products for treating chronic diseases with a high impact on the NHS. The need to reach sustainability agreements with the industry is also stressed in the Program. In this regard, the Program endorses the agreement already subscribed with Farmaindustria regarding this matter and shows a strong position in favour of its renewal.

d) *Measures to monitor prescriptions and expenditure*

Although this is a matter that mainly falls within the scope of the Regional Authorities' competences (and therefore not the central Government ones), the Program includes the following proposals: (a) the implementation and improvement of protocols for the supervision and follow-up of prescriptions; (b) the enhancement of electronic prescription and incentive systems; (c) the introduction of periodic control systems over certain kinds of medicinal products or groups of patients to mitigate consumption variations; (d) the interoperability of databases from different authorities; as well as (e) the development of educational plans aimed at the general public. All of the above seem reasonable measures as long as they do not inappropriately interfere with the freedom of the physician to prescribe the medicinal product that he or she deems appropriate.

Other trends

The rules contained in Royal Decree 271/1990 have been under review for a long time now, and at the end of 2015, the Spanish MOH was working on a Royal Decree project that would have governed reimbursement of medicines, but which was never approved. In 2019, the MOH has finally formed an Advisory Council on Pharmaceutical Coverage of the NHS, and works on the renovation of these rules may be expected to resume soon.

Successful market access

Reimbursement and pricing procedures in Spain entail a lot of negotiation. As in any negotiation, defining a strategy will be very important. When doing so, companies must not forget that budgetary constraints in Spain are important, so they must be ready to be confronted with very strong positions by the authorities which intervene in the process.

Successful market access depends on many aspects, but the basics in order to access pharmaceutical provision are: to prove additional therapeutic value over the existing medicines which are already being financed (for which the therapeutic positioning report will be essential); and to be open to entering into risk-sharing agreements with the MOH.

Endnotes

1. https://www.ine.es/prensa/pp_2018_2068.pdf.
2. "*Financiación pública y fijación del precio de los medicamentos*", J. Vida, Administrative Law professor at Universidad Carlos III of Madrid, chapter 22 of the *Tratado de Derecho Farmacéutico* by Jordi Faus and José Vida (Thomson Reuters Aranzadi, 2017).
3. Those measures were established by means of Royal Decree 16/2012, of urgent measures to guarantee the sustainability of the Spanish National Health System and improving the quality and security of the provisions contained in it.
4. This limitation was later annulled by the Spanish Constitutional Court in its Judgement of 21 July 2016.
5. Royal Decree-Law 7/2018 of 27 July 2018, published in the Official Journal on 30 July 2018.
6. https://www.mscbs.gob.es/estadEstudios/estadisticas/sisInfSanSNS/tablasEstadisticas/InfAnSNS.htm.
7. See, for all, the case of 18 December 2014 on Law 12/2010 on medicines that may be dispensed in the Autonomous Community of Galicia.

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Sweden

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Abstract

This article provides an overview of the model for pricing and reimbursement of pharmaceutical products in Sweden, including brief notes on reimbursement of medical devices.

In 2002, Sweden abandoned the reference price system for pharmaceutical reimbursement used since the 1990s, which is still widely adopted in European countries, and introduced a new value-based pricing and reimbursement scheme. Thereby and since, to a large extent Sweden has led the way on value-based pricing for pharmaceutical products. The main features of the value-based model are the use of cost-effectiveness analysis for determining the reimbursement status of pharmaceuticals, and mandatory substitution for the lowest-cost generic alternative. The use of cost-effectiveness analysis in reimbursement decisions aims to relate and balance the reimbursement price to the social value of the product, but does not necessarily result in (or intend to result in) the lowest possible price.

The county councils are solely responsible for the funding of in-patient pharmaceutical expenditure and the costs are covered by taxes.

Costs for subsidised out-patient pharmaceutical products included in the reimbursement scheme are formally financed by the county councils but are covered by government grants. Patients only pay a limited part of the price for such pharmaceuticals and a patient's maximum costs during a year are subject to high-cost protection.

Market introduction/overview

Swedish healthcare is a shared responsibility of the state, county councils and municipalities. The state is responsible for the overall health and medical care policy, while the county councils are responsible for providing healthcare. The Ministry of Health and Social Affairs (Sw. *Socialdepartementet*) is responsible for issues concerning the welfare of society by implementing the objectives set by the Swedish Parliament and the Government. Several independent agencies answer to the ministry.

According to the Health and Medical Services Act (2017:30) (Sw. *hälso- och sjukvårdslagen*) (HSL), the goal of healthcare is good health and healthcare on equal terms for the entire population. Furthermore, the care should be given with respect to the equality of all human beings and to the individual's dignity. Those who have the greatest need for care shall be given priority. The national health service covers all Swedish residents. According to Statistics Sweden (Sw. *Statistiska centralbyrån*), the population in Sweden will continue to increase within all age groups. The percentage increase is greater in the older age groups. In addition to the increasing number of elderly, immigration constitutes the largest demographic change and primarily increases the population that is of working age.

Manufacturing of medicinal products and medical devices is one of the largest industries in Sweden, accorded a high priority by the Swedish Government, and Sweden is the 2019 EU innovation leader according to the European Innovation Scoreboard. During 2018, the Swedish pharmaceutical market had a turnover of SEK 47.7 billion, an increase of 9% compared to 2017. In 2018, 205 million pharmaceutical packages were sold in Sweden. Approximately 50% of these packages were prescription pharmaceutical products, while approximately 44% were non-prescription pharmaceutical products.

The Swedish pharmacy market was deregulated in 2009. Since then, the number of pharmacies has increased by almost 500. Currently, there are over 1,400 outpatient pharmacies in Sweden. The industry is dominated by five pharmacy chains and there are just over 30 companies with one or a few pharmacies. In addition to out-patient pharmacies, there are hospital pharmacies, dose-dispensing pharmacies and distance pharmacies. The total sales for out-patient and distance pharmacies amounted to approximately SEK 45.4 billion in 2018, of which approximately three-quarters consisted of prescription pharmaceutical products and other products, while the remainder of the sales mainly consisted of non-prescription pharmaceutical products and merchandise.

Since the deregulation, pharmacies have increased their opening hours. This, as well as the emergence of e-commerce, has contributed to improved accessibility than before the deregulation.

Pharmaceutical pricing and reimbursement

Regulatory classification

Legal framework

Being an EU Member State, Sweden's legal framework on pharmaceutical products is to a large extent based on relevant EU directives and subject to EU regulations. The national legislative basis for regulatory issues (including marketing authorisation and substitutability), supervision and enforcement of pharmaceutical products in Sweden is primarily stipulated in the Medicinal Products Act (2015:315) (Sw. *läkemedelslagen*) and the Medicinal Products Ordinance (2015:458) (Sw. *läkemedelsförordningen*) and, for medical devices, in the Medical Devices Act (1993:584) (Sw. *lag om medicintekniska produkter*) and the Medical Devices Ordinance (1993:876) (Sw. *förordning om medicintekniska produkter*). The Medicinal Product Act and the Medicinal Products Ordinance are based on Directive 2001/83/EC. The Medical Devices Act and the Medical Devices Ordinance are based on Directives 90/385/EEC, 93/42 EEC and 98/79/EC. There are also regulations and guidelines issued by the Swedish Medical Products Agency (MPA).

Notably, on 26 May 2017, the new EU regulations on medical devices entered into force within the European Union; Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices. However, the new rules will only apply after a transitional period of three years after entry into force for the regulation on medical devices (spring 2020), and five years after entry into force for the regulation on *in vitro* diagnostic medical devices (spring 2022).

The legal framework concerning the granting of marketing authorisation of a pharmaceutical product differs from the framework concerning pricing and reimbursement. While the former is based on EU rules as described above, the latter is substantially regulated at a national Swedish level, with little influence from the EU.

The Swedish Dental and Pharmaceutical Benefits Agency (TLV), which is an expert state

agency, decides to what extent a pharmaceutical product shall be reimbursed, according to the Pharmaceutical Benefits Act (2002:160) (Sw. *lag om läkemedelsförmåner m.m.*) (PBA) and the Pharmaceutical Benefits Ordinance (2002:687) (Sw. *lag om läkemedelsförmåner m.m.*) (PBO). TLV also issues regulations and general advice.

In addition, Sweden has a system for substitution of generically equivalent medicinal products. The MPA (and/or the European Medicines Agency) approves all medicinal products, including generics and parallel imported products, with regard to their quality, safety and efficacy. The MPA decides which medicinal products shall be substitutable at the pharmacies and publishes a list of groups that includes such products.

The basic principles for substitution are that products that have the same active substance in the same amount, and are otherwise medically equivalent, shall be substituted. Only products that are included in the benefits scheme may be substituted. The system demands that pharmacies dispense the least expensive generic product available to the patient, regardless of the prescribed product, unless the prescribing doctor has opposed substitution for medical reasons in writing. The patient may also refuse 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 resulted in several court cases regarding the MPA's decisions on the equivalence of different medicinal products.

Prescription vs. requisition

Pricing and reimbursement procedure and regulation of pharmaceutical products primarily depends on whether the specific product is a *prescription pharmaceutical* or a *requisition pharmaceutical*.

Prescription is the case when a pharmaceutical product is prescribed to a patient and based on which a pharmacy may provide the specific pharmaceutical product to the patient. The price of prescription pharmaceuticals included in the reimbursement scheme is determined by TLV, while the pricing of prescription pharmaceuticals outside this system can be set freely (see below).

Requisition, on the other hand, means the requisition of pharmaceutical products by and to healthcare professionals, to be administered to patients in institutional or non-institutional healthcare. *Institutional care* refers to treatment given to patients in a hospital or other type of institution, and *non-institutional care* refers to any other treatment of a patient that is not defined as institutional. Requisition pharmaceutical products are procured and priced pursuant to public procurement procedures carried out by the Swedish county councils.

It is possible for a specific pharmaceutical product to be subject to both prescription and requisition. In such case, two different systems of regulation will apply – which can lead to different pricing of the same product.

Prescription-only vs. non-prescription pharmaceuticals

Pursuant to Chapter 4 of the Medicinal Products Act, a pharmaceutical product will, in connection with being granted marketing authorisation, be classified either as a prescription-only or a non-prescription pharmaceutical product. The MPA will decide the classification for the pharmaceutical product depending on its intended use and characteristics. A prescription-only pharmaceutical product must be subject to either the prescription or requisition regulation in order to reach the patient. Non-prescription pharmaceuticals, on the other hand, are not required to be subject to either the prescription or requisition regulation; however, nothing prevents non-prescription drugs from being prescribed or requisitioned.

Products eligible for reimbursement

Pharmaceutical products prescribed for certain purposes and to a specified group of people may be covered by the pharmaceutical reimbursement scheme in accordance with the PBA. The general rule is that only prescription-only pharmaceutical products are eligible for reimbursement, as set forth in Section 15 of the PBA. However, pursuant to Section 17 of the same act, and further by the PBO, TLV has been authorised to issue regulations regarding the prerequisites for non-prescription pharmaceutical products being eligible for reimbursement. According to the TLV regulation TLVFS 2003:2 (regarding non-prescription pharmaceutical products in accordance with Pharmaceutical Benefits Act) (last amended by TLVFS 2012:3), non-prescription pharmaceuticals are eligible for reimbursement. In addition to pharmaceuticals, there are also other products that are eligible for reimbursement.

As stipulated in Section 18 of the PBA, only some medical devices are eligible. Medical devices eligible for reimbursement, called *consumables*, only includes products used: (i) in connection with stoma; (ii) to induce a pharmaceutical product into the human body; and (iii) for self-monitoring of medication. Stoma-consumables are covered by the same rules regarding reimbursement as pharmaceutical products in general, while consumables used to induce pharmaceuticals, and for self-monitoring of medication, are entirely reimbursed and are free of charge for the patient.

Even food may, under certain circumstances, be eligible for reimbursement. According to Section 20 of the PBA and as further regulated in Sections 6 and 7 of the PBO, foods that have been prescribed to a child (aged below 16) may be reimbursed provided that the child suffers from any of the specific conditions stipulated in the PBO.

Who is/are the payers?

Pricing of medicinal products that are included in the reimbursement system is regulated and the cost of such medicinal products dispensed in pharmacies to patients is to a large extent subsidised by the state. The patient pays some of the costs for subsidised prescription pharmaceuticals, but according to the PBA, a patient's maximum costs are subject to high-cost protection valid for 12 months at a time starting from the date of the first purchase. As of the date of this chapter, the maximum amount is SEK 2,300 (approx. €220). The high-cost protection is calculated based on the base amount set out in the Social Insurance Code (2010:110) (Sw. *socialförsäkringsbalken*). A patient pays the entire cost up to a maximum amount (as of the date of this article SEK 1,150 (approx. €110)), after which the patient only makes a co-payment according to a scale of discounts until the high-cost protection is reached.

All children under the age of 18 are offered free prescription medicinal products and medical devices included in the reimbursement scheme. The purpose of this is to reduce inequality of children's health between groups in society with different financial conditions. Also, prescribed contraceptive drugs included in the reimbursement scheme are free for all women under the age of 21.

As stated above, the prices for requisition pharmaceutical products used in institutional and non-institutional healthcare are negotiated in public procurement processes, and the patient only pays the standard patient fee that applies for the healthcare treatment concerned.

Most non-prescription (over-the-counter) medicinal products are not subject to regulated pricing and are not reimbursed by the state. As a result, such medicinal products purchased in pharmacies (or other authorised retail stores) are typically paid for entirely by the end customer.

What is the process for securing reimbursement for a new pharmaceutical product?

TLV decides to what extent a medicinal product shall be reimbursed, according to the PBA. For a medicinal product to be covered by the reimbursement scheme, a written application shall be submitted to TLV. The company applying for reimbursement is responsible for demonstrating that the medicinal product meets the applicable legal requirements. In the application, the applicant shall state the requested price of the product and provide reasoning and adequate documentation to support the requested price (see below how the price is determined), e.g. a health economic analysis.

An application is granted if the pharmaceutical product is eligible for reimbursement and all the material requirements in the PBA are fulfilled, and if TLV finds that the requested price is justified in consideration of the value that the medicinal product brings to society in terms of improved health (i.e. it is cost-effective and brings marginal benefit to the market).

Medical devices that are eligible for reimbursement are subject to the same reimbursement rules as medicinal products, as long as the devices are to be used by patients and prescribed by a physician. However, the rules regarding substitution of medicinal products do not apply to medical devices.

Decisions made by the MPA, TLV and other governmental authorities can be appealed to the Swedish Administrative Courts. The Administrative Procedures Act (1971:291) (Sw. *förvaltningsprocesslagen*) governs the procedure of such appeals. Decisions and judgments from the Administrative Courts may, in most cases subject to granting of leave to appeal, be appealed to one of the Administrative Courts of Appeal, whose decisions and judgments may further be appealed to the Supreme Administrative Court. Proceedings in the administrative court system are primarily conducted in writing, but oral hearings are possible if requested by a party or if the court finds it appropriate.

Appeals of decisions by authorities (e.g. the MPA and TLV) are submitted directly by the company to the authority. The main rule is that an appeal must be submitted so that it is received by the authority no later than three weeks from the date on which the appellant received the decision, or it may be inadmissible. Only if the authority does not amend its original decision as claimed by the appellant, will the appeal be forwarded to the relevant Administrative Court. If all formal requirements of appeal are fulfilled, and the appeal is not dismissed on formal grounds, the Administrative Courts are authorised to assess an appealed decision in its entirety. The main possible outcomes are, depending on the circumstances in each case, either: rejection of the appeal; material change of the appealed decision; or referral of the case back to the authority for reassessment in accordance with any statements of reason from the court. It is possible to claim that the court should issue an interlocutory order regarding the appellant's claims (in full or in part), to be in effect during the court proceedings.

How is the reimbursement amount set? What methodology is used?

The main rule is that only prescription-only pharmaceutical products may be included in the pharmaceutical reimbursement scheme. In general, all pharmaceuticals, including over-the-counter pharmaceuticals, may be reimbursed and included in the reimbursement scheme, provided that the conditions stipulated in the PBA are fulfilled. According to the PBA, the requirements for a prescription-only pharmaceutical product to be included in the reimbursement scheme are that: (i) the costs of using the pharmaceutical product appear

reasonable from a medical, humanitarian and socioeconomic perspective; and (ii) there are no other available pharmaceutical products or treatments, which, when balancing the intended effect and potential harm, are deemed to be significantly more suitable.

TLV shall determine whether the price requested by the applicant is reasonable by making a total assessment, taking into consideration three ethical principles of healthcare that are included in the HSL to guide priority-setting in the health service. These ethical principles are:

(i) the *human dignity principle*, which implies that the care should be given with respect to the equality of all human beings and with consideration of the individual's dignity;

(ii) the *needs and solidarity principle*, which entails that the person with the greatest need for healthcare shall be given priority; and

(iii) the *cost-effectiveness principle*, which means that one should strive towards a reasonable relationship between cost and effect, measured in improved health and an increased quality of life, when considering different activities and measures.

A decision on reimbursement is thus based on value, which is often described in terms as applying '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.

There are two main types of reimbursement: general and restricted reimbursement. In the case of general reimbursement, the pharmaceutical product is eligible for reimbursement for its entire approved area of use, while a restricted reimbursement means that the pharmaceutical product is included in the pharmaceutical reimbursement scheme only for a certain area of use or a specific patient group. TLV may also stipulate special conditions for a reimbursement decision, e.g. that the applicant, after some time, must present new data on the use of the pharmaceutical product in the healthcare system. One of the reasons why TLV grants a restricted reimbursement may be that the pharmaceutical product is only considered to be cost-effective for one limited and specific group of patients.

There are no additional provisions specifying the criteria that TLV applies when taking a decision on a subsidy and price, at the legislative level. Instead, the idea is that TLV provides more detailed guidance through regulations and general advice. The administrative courts also continuously develop legal precedent on the conditions for determining subsidy and price.

In order to estimate the cost for the use of the pharmaceutical product, TLV requires information regarding the relevant patient group and volume; for instance, the number of patients that will need the pharmaceutical product and for how long. Furthermore, TLV considers whether there is a risk that the pharmaceutical product is used outside a potential limitation of the subsidy – which, in that case, risks being a usage that is not cost-effective. TLV has developed a practice on how to apply the criteria for subsidy and pricing. In 2003, TLV issued general guidelines (LFNAR 2003:2, last amended by TLVAR 2017:1) which are intended to guide pharmaceutical companies that plan to apply for subsidy and pricing of a pharmaceutical product, and describes how TLV believes that a health-economic analysis should be conducted. The guidelines are worth considering in the planning and implementation of health economics studies to be used in upcoming applications for subsidy and pricing.

How are drug prices set? What is the relationship between pricing and reimbursement?

There are various pricing procedures for pharmaceutical products; for example, through decisions by TLV, the county councils' procurement procedures, or free pricing. The pricing of products differs in out-patient and in-patient treatment.

Out-patient care

In out-patient care, the difference between price and reimbursement for pharmaceutical products included in the reimbursement scheme is the patient's co-payment (see section "*Who is/are the payers?*", "Pharmaceutical Pricing and Reimbursement" above). This means that the state reimburses almost the entire cost.

TLV determines the pharmacies' trade margin for pharmaceutical products included in the reimbursement scheme, which means that the pharmacies' purchase price (AIP) as well as selling price (AUP) are regulated. The county councils and pharmaceutical companies may enter into managed entry agreements, which is one of several factors considered when TLV takes decisions on price and reimbursement. Risk-sharing through managed entry agreements has become an increasingly valuable tool to manage uncertainties for certain new pharmaceutical products. Furthermore, they may ensure cost-effectiveness and reduce the increasing costs for new pharmaceuticals. Consequently, the discussions between county councils, pharmaceutical companies and TLV can enable the use of such pharmaceuticals, even when there is significant uncertainty concerning their medical effect and cost-effectiveness. Furthermore, the pharmacies have a right of negotiation, which means that they may use prices other than those determined by TLV, for some pharmaceutical products, mainly parallel imported pharmaceutical products.

The pricing of non-prescription (over-the counter) pharmaceutical products can be set freely. The patient pays the entire cost for these medicinal products. Prices are regulated for non-prescription drugs that are included in the reimbursement system, and the patient makes a co-payment. It should be noted that most over-the counter pharmaceutical products are not included in the reimbursement system. The reason is that pharmaceutical companies usually do not apply for reimbursement for over-the-counter pharmaceuticals, since pharmaceutical products outside the reimbursement scheme are unregulated and subject to free pricing.

The MPA decides which medicinal products that shall be substituted at the pharmacies and publishes a list of groups that includes such products. Only products that are reimbursed may be substituted. Sweden also has a 'product of the month' system for substitutable products. The product of the month within the groups of substitutable products is decided by TLV and appointed through a monthly auction. The substitution is mandatory and consequently, the pharmacies are obligated to dispense the least expensive pharmaceutical product included in the reimbursement scheme that is available on the market, regardless of the prescribed product.

In-patient care

The prices for in-patient care (hospitals) medicinal products are negotiated in the county council's public procurement processes, which are regulated by the Swedish Public Procurement Act (2016:1145) (Sw. *lagen om offentlig upphandling*). The patient only pays the patient fee that applies for the in-patient treatment concerned, and except such flat fee, the entire price of pharmaceutical products used in in-patient case is reimbursed by the county councils.

Pharmaceutical products used in in-patient care are not covered by the national reimbursement scheme and there is no nationwide reimbursement list for in-patient

pharmaceuticals, since county councils decide on which treatments to use and finance them at the regional level.

Issues that affect pricing

Generic substitution

As stated above, the MPA approves all medicinal products with regard to their quality, safety and efficacy, and the MPA also decides which medicinal products shall be substituted at the pharmacies and publishes a list of groups that includes such products. The basic principles for substitution are that the products have the same active substance in the same amount, and are otherwise medically equivalent. Only products that are reimbursed can be substituted. This means that pharmacies are obligated to dispense the least expensive pharmaceutical product included in the reimbursement scheme that is available on the market – regardless of what product is prescribed. Physicians and pharmacists at the pharmacies may only prohibit substitution on medical grounds, as stipulated in Section 21 of the PBA. The purpose of this substitution system is to safeguard the lowest possible cost for both the patient as well as the society.

Ceiling prices

Generic substitution leads to lower prices due to competitive market forces, which may result in significant price differences between generic substitutes arising. In this situation, TLV may decrease the maximum accepted selling price within the reimbursement scheme by setting a lower ceiling price for substitutable pharmaceuticals. This is most relevant for the branded original pharmaceutical product that has lost its patent protection.

Each month, TLV analyses prices and sales volumes in order to find groups where the criteria for setting a ceiling price are met. When the prices of a group of substitutable generic pharmaceuticals have dropped by at least 70% of the price that the pharmaceuticals had before generic competition arose, and when generic competition has been ongoing for at least four months, TLV sets a ceiling price. The ceiling price may not enter into force until at least six months after the introduction of generic competition within the substitution group.

The new fixed ceiling price is normally 35% of the highest price in the relevant substitution group when generic competition arose. Setting the ceiling price in this way thus reduces the differences in price between substitutable generic pharmaceuticals within the reimbursement scheme, but it also has the effect of further decreasing costs in addition to the cost-decreasing effect of generic substitution itself, by forcing a lower price of original pharmaceuticals within the reimbursement scheme. After TLV has determined a ceiling price, pharmaceutical companies have the options of either applying for a new price that meets the set ceiling, or withdrawing from the reimbursement scheme.

Price reduction after 15 years

From 1 November 2014, there are new rules for the pricing of some older drugs (see TLV's regulation TLVFS 2014:9). The change is based on changes in the PBA and means that TLV will reduce the price of pharmaceutical products by 7.5% when they are older than 15 years. The 15-year threshold is determined based on the date of first marketing authorisation in each relevant so-called *substance/form group*. This means that TLV can decide to reduce the price of pharmaceutical products that have recently been approved for reimbursement, if the first marketing authorisation in the same substance/form group is older than 15 years. TLV's decisions to reduce the price can be appealed to the administrative courts (see section "What is the process for securing reimbursement for a new pharmaceutical product?").

The first price reductions under the new rules came into effect on 1 January 2015. The intention is to contribute to a more cost-effective use of pharmaceuticals in Sweden. The changes were initiated by an agreement on lowering the prices of some older medicinal products, between the Swedish Government and the trade organisation for the Swedish research-based pharmaceutical industry (LIF) in 2013.

Policy issues that affect pricing and reimbursement

According to Statistics Sweden, the population in Sweden will continue to increase within all age groups. The percentage increase is greater in the older age groups. In addition to the increasing number of elderly, immigration constitutes the largest demographic change and primarily increases the population that is of working age.

A recently reported public inquiry appointed by the Swedish Government (see further "Emerging trends" below), *inter alia* concluded that shared resources available for financing pharmaceuticals are insufficient to meet all needs and therefore priorities must be set. As the population grows, gets older and suffers from more chronic diseases, while innovation within the pharmaceutical industry increases and drugs become more expensive, the need for priorities will also increase. These issues are likely to affect pricing and reimbursement policy, at least in the long term.

Emerging trends

The Swedish Government has a major focus on the pricing and reimbursement of pharmaceutical products and in 2016 the Government appointed a public inquiry to investigate and analyse the current system of funding, subsidising and pricing of pharmaceutical products. It is the first review since 1998, when the cost responsibility for pharmaceutical products benefits passed from the state to the county councils. Since the introduction of the system, the conditions in the healthcare system have changed, as well as the types of pharmaceutical products that reach the market. Many parties, such as patients, companies and county councils, have described the current system for financing, pricing and reimbursement of pharmaceutical products as complex, difficult to grasp and, in some respects, not sufficiently transparent.

The public inquiry was concluded in December 2018, and the final report was submitted to the Government in January 2019 (SOU 2018:89). The inquiry proposes several changes to the current system, including increased responsibility for county councils to fund pharmaceuticals (with a decreased responsibility for the state). A new special subsidy to support use of drugs within certain areas, e.g. cell and gene therapies, has been proposed. The inquiry also proposes several new responsibilities for existing competent authorities, with the purpose of increasing the state's ability to facilitate a more equal and cost-effective use of pharmaceuticals, while making new innovative drugs and therapies available to patients quicker.

The inquiry report has been heavily criticised by several important and influential parties on the market, including the Swedish Association of the Pharmaceutical Industry, which is of the opinion that the inquiry must be fundamentally reworked, and large patient organisations which believe the inquiry focuses too heavily on costs and moving funds between different parties, but without paying sufficient attention to patient need or enabling timely access to new treatments (which was an express objective of the inquiry). Time will have to tell whether the inquiry report will result in any governmental bill for new and amended legislation.

In 2014, a three-party negotiation process between the county councils' negotiation delegation, TLV and the pharmaceutical company in question, as well as managed entry agreements for pharmaceutical products covered by the reimbursement scheme, were introduced. The idea of the three-party negotiations is to give companies yet another opportunity to receive reimbursement for their products, if they do not receive reimbursement immediately, as well as facilitate access to new, innovative treatment options for patients while maintaining a general price control and reduction for the society. The three-party negotiations typically involve discussions concerning risk-sharing between the companies and TLV, e.g. by considering the possibility of granting reimbursement only for a limited amount of time. The three-party negotiation model has so far been tested and used in connection with the introduction of new pharmaceutical products as well as in the case of established drugs, such as particularly costly medicines and biological drugs for which the patent has expired. The public inquiry report mentioned above (SOU 2018:89) proposes a few changes and clarifications of the three-party negotiation process, including that the framework for such negotiations should be regulated by law.

Managed entry agreements are used to an increasing extent and now encompass products with a total annual turnover of approximately SEK 4 billion. More than half of the sales of newly introduced unique drugs are covered by managed entry agreements. The public inquiry report mentioned above (SOU 2018:89) proposes changes to the organisation for managed entry agreements, including, e.g. introduction of a new county council joint public authority. For the purposes of, among other things, increasing transparency and legal certainty, the new public authority is proposed to *inter alia* take over the responsibilities of the current New Therapies Council (Sw. *NT-rådet*), which is a group of experts that supports the county councils on matters concerning new drug therapies, including making recommendations on the use of new drug therapies, with the aim of enabling equal drug treatment for patients throughout the country.

Successful market access

For successful market access in Sweden, it is crucial to obtain an understanding of the Swedish value-based pricing model and the considerations involved in assessing applications for inclusion of pharmaceutical products in the reimbursement scheme. This is true for marketing of original drugs, generics and parallel imports alike. An understanding of the model will also facilitate effective participation in public procurement by the county councils for in-patient use.

If an application for listing in the reimbursement scheme is rejected by TLV, the company may consider attempting to enter into three-party negotiations with the county councils' negotiation delegation and TLV in order to get another opportunity for reimbursement of its products. For such a negotiation process to be successful, it is beneficial to understand the different factors that will be considered by the county councils and TLV. As an alternative, or if the three-party negotiation fails, companies may also appeal the rejected decision to have the case tried by the administrative courts, or set about putting the drug on the market without reimbursement (an option that is always available) or resubmit the application to TLV (e.g. including a more comprehensive health economic analysis) for a second-round evaluation.

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Switzerland

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Abstract

Every resident in Switzerland is mandatorily obliged to be covered by basic healthcare insurance which provides for a wide range of services. Persons with lower incomes are, in principle, granted reductions on the premiums payable for such basic healthcare insurance. Thus, every resident in Switzerland is granted access to affordable healthcare.

In general, therapeutic products are only reimbursed if they are listed on the so-called specialty list. In order to be listed thereon, a medicinal product must be admitted by the competent Swiss authority, and has to satisfy the criteria of effectiveness, functionality and economic efficiency, based on which the maximum price for the therapeutic product in question is determined.

Market introduction/overview

Size and demographics

Switzerland has one of the world's most expensive healthcare systems. For example, in 2016, healthcare costs amounted in total to 80.7 billion Swiss francs (an increase of 3.8% compared to 2015), of which approximately 13.2 billion was paid for healthcare goods, including therapeutic products in hospitals. Compared to the general domestic product (GDP), healthcare spending represented 12.2% in 2016 (an increase from 11.9% in 2015). Every resident in Switzerland paid on average 803 Swiss francs per month for the healthcare system in 2016 (*cf*. www.bfs.admin; last visited on 5 April 2019). The corresponding numbers for 2017 and 2018 are not yet available.

In 2018, the total value of goods and services exported from Switzerland amounted to 304 billion Swiss francs (provisional result), whereas the value of imported goods and services amounted to 273 billion Swiss francs (provisional result). A positive balance of 31 billion Swiss francs (provisional result) in favour of Switzerland resulted therefrom. The most important part of Switzerland's exports were chemical and pharmaceutical products, which constituted 34.3% of the exports (104 billion Swiss francs). Chemical and pharmaceutical products further constituted the second-largest group of imported products (18.4% of the imports, respectively 50 billion Swiss francs). It has to be noted that all numbers stated above are provisional results (*cf*. Key figures 2018, available under the following link: www.ezv.admin.ch; last visited on 5 April 2019).

According to the Association of research-based pharmaceutical companies in Switzerland (Interpharma), in 2017, reimbursable therapeutic products represented more than 84% (compared to 83% in 2016) of the total pharmaceutical market. This corresponds to 67% of all packs of therapeutic products sold in 2017 in Switzerland. Most of these reimbursable

therapeutic products' packs were prescription-only products. (*cf.* Interpharma, Pharmaceutical Market Switzerland, 2018, p.40).

Over 435,000 people in Switzerland worked in the healthcare industry and the pharmaceutical sector. This corresponds to approximately one in twelve of the working population (*cf.* Interpharma, Swiss Healthcare and Pharmaceutical Market, 2018, p.18).

In Switzerland there is a very high density of hospitals which offer a wide range of medical services. In 2017, 281 hospitals and maternity units (38,157 beds) and 1,561 homes for elderly and care (99,242 places) were registered in Switzerland (*cf.* www.admin.bfs.ch; last visited on 5 April 2019). The density of general practitioners is, however, relatively low compared to other countries. For a million inhabitants in Switzerland there are only 1,143 general practitioners. The same applies with respect to pharmacies, whose density is comparatively low, as in certain cantons doctors are allowed to dispense medicines themselves (*cf.* Interpharma, Swiss Healthcare and Pharmaceutical Market, 2018, p.18). Contrary to certain countries, such as the USA, most therapeutic products cannot be sold via supermarkets.

Switzerland is one of the world's leading players in the domain of biomedical research and technology. Given the high importance of the pharmaceutical market, the Swiss Federal Council has endeavoured to strengthen the international position of Switzerland with several initiatives, such as the 'Masterplan for the promotion of biomedical research and technology' of 2013 (for further information, *cf.* www.bag.admin.ch and below section "Emerging trends"). Also, the costs of research and development are taken into account for the determination of the price of therapeutic products and a supplement for innovation may be granted (*cf.* below section, "What is the process of securing reimbursement for new pharmaceutical products and how are drug prices set?", in "Pharmaceutical pricing and reimbursement".

Healthcare system and access to care

The Swiss Federal Office of Public Health ("**FOPH**") is responsible for public health in Switzerland. In particular, the FOPH coordinates Switzerland's health policy and supervises the compulsory health insurance. Further, the FOPH is involved in decision-making with respect to pricing and reimbursement of pharmaceutical and medicinal products.

The Swiss Agency for Therapeutic Products ("**Swissmedic**") is the national authorisation and supervisory authority for therapeutic products. Swissmedic aims to ensure that only high-quality, safe and effective therapeutic products are made available in Switzerland.

The responsibility for the provision and funding of healthcare lies mainly with the 26 cantons of Switzerland, even if regulated on a federal level. Together with the compulsory health insurance, cantons also co-finance hospitals and nursing homes, which are mostly owned or controlled by the cantons and municipalities, and promote the prevention of disease. The responsibility for these tasks lies primarily with the cantonal and municipal departments of health (*cf.* also Interpharma, Swiss Healthcare and Pharmaceutical Market, 2017, p.4).

Health insurance is regulated by the Swiss Federal Act on Health Insurance of 18 March 1994 ("**HIA**"; *Bundesgesetz über die Krankenversicherung, KVG*) and the Swiss Federal Act on the Supervision of Health Insurance of 26 September 2014 ("**SHIA**"; *Bundesgesetz betreffend die Aufsicht über die soziale Krankenversicherung, KVAG*) and various associated ordinances.

In principle, every person domiciled in Switzerland is mandatorily obliged to conclude basic health insurance within three months of moving to Switzerland or from the birth of a child (article 3 para. 1 HIA). Any such person may freely choose among insurers, which are authorised pursuant to the SHIA to offer basic health insurance (article 4 HIA). The SHIA

defines insurers as legal entities organised pursuant to private or public law which do not pursue a profit-making purpose and offer basic health insurance. According to the FOPH, approximately 60 approved non-profit insurance providers currently offer basic mandatory insurance and optional loss of earnings insurance.

The insurers offering compulsory health insurances must treat all insured persons equally. In particular, they are not allowed to decline a request for basic health insurance and must offer to all insured persons the same range of benefits. Insureds are free to change insurer by giving notice three months before the end of a calendar semester (article 7 para. 1 HIA).

The cantons are required to ensure compliance with compulsory insurance. If a person domiciled in Switzerland does not timely conclude a basic health insurance, the canton of its domicile has to allocate such person to one of the insurers (article 6 HIA). Consequently, every resident in Switzerland has basic health insurance.

Compulsory health insurance reimburses the costs for the services of healthcare providers regarding diagnosis and treatment of diseases and their consequences (articles 25 para. 1 and 35 HIA). This includes all examinations and treatments carried out by doctors or physicians as well as chiropractors. Further services include, inter alia, laboratory analyses, therapeutic products, aids and equipment prescribed by medical doctors (article 25 para. 2 HIA). The aforementioned shows that the catalogue of services covered by compulsory health insurance is quite extensive.

In case of congenital diseases, basic health insurance pays the same costs as in case of disease, if such costs are not covered by invalidity insurance (art. 27 HIA). As regards accidents, the corresponding healthcare costs will be covered by basic health insurance, provided that no accident insurance is in place (articles 28 and 1a para. 2 lit. b HIA). Furthermore, healthcare costs related to maternity are also borne by health insurance (article 29 HIA).

In addition to compulsory basic health insurance, insurers may provide for supplementary health insurance. Such supplementary coverage may include additional services, such as, for example, homeopathy, and usually provides for more freedom with regard to the choice of doctor or hospital.

Compulsory health insurance is funded by the monthly premiums payable by the insured, the deductible, the insured's contribution to the costs of a hospital stay and public subsidies.

The tariffs for mandatory basic health insurance have to be approved annually by the supervising authority, which is the FOPH (articles 16 and 56 of the SHIA). The monthly premiums payable by the insured persons are not dependent on the income of such insured, but they vary between the cantons and between the insurers. The amount of the premium depends on the deductible chosen by the insured: the higher the deductible, the lower the premium. As regards insured persons with low revenues – children and young adults – they often benefit from a reduction in premiums, guaranteeing that every resident in Switzerland is given access to affordable healthcare.

Incidence and prevalence of disease

Since 1992, the Federal Statistical Office ("**FSO**") conducts every five years a public consultation regarding the health status of the population, health determinants, diseases and their consequences, the healthcare system, including the number of doctor appointments, and health insurance (the so-called Swiss Health Status Consultation). The sixth consultation took place in 2017, the results of which may be seen online under the following link: www.bfs.admin.ch (last visited on 5 April 2019).

According to the FSO, 84.7% of the overall population assess their health as being good or

very good. At the age of 75 and older, 67.1% still assess their health as being good or very good; 32.7% of the population declare having a chronic health problem; 75.7% are sufficiently physically active; 27% smoke; 4% have consumed cannabis during the 30 days preceding the public consultation; and 10.9% drink alcohol on a daily basis (*cf*. www.admin.bfs.ch; visited last on 5 April 2019).

Persons taking medication in the course of the week preceding the FSO consultation further increased from 46.3% in 2007, to 48.6% in 2012, and to 50.3% in 2017. This means that half of people aged 15 years and over take at least one medicinal product per week in Switzerland. Further, the number of persons using alternative medicine is increasing. In 2017, 28.9% used alternative medicine in the course of the 12 months preceding the FSO consultation, compared to 24.7% in 2007. Generally speaking, more female than male, and more elderly than young people, take medicinal products, and far more females than males use alternative medicine (*cf*. www.admin.bfs.ch; last visited on 5 April 2019).

The hospitalisation ratio per 1,000 residents was 119.3.0, while infant mortality stood at 3.5‰, in 2017. The most common causes of death in Switzerland are cardiovascular diseases (approx. 32% of the deaths in 2016) and cancer (approx. 26% of the deaths in 2016). According to the Swiss Cancer Report 2015 published by the FSO, cancer has become a chronic illness. In 2015, 317,000 people in Switzerland were living with a cancer diagnosis. This is twice as many as 25 years ago. Every year, approximately 17,000 people living in Switzerland die from the consequences of cancer. Pursuant to said report, it is expected that around 40% of the Swiss population will be diagnosed with cancer at any point in their lifetime.

The main reason for this increase is due to the fact that the population is getting older. However, in comparison to the other European countries, Swiss incidence rates are still average for men and even low for women, except for melanoma, which have a high incidence rate in Switzerland (nevertheless, mortality rates for melanoma are very low). As regards survival rates across all types of cancer, Switzerland's five-year survival rates are among the highest in Europe (*cf*. for more details, Swiss Cancer Report 2015 of the FSO, available under the link: www.bfs.admin.ch; last visited on 5 April 2019).

Pharmaceutical pricing and reimbursement

Regulatory classification

Pharmaceutical products are regulated in the Swiss Federal Act on Medicinal Products and Medical Devices of 15 December 2000 ("**TPA**"; *Bundesgesetz über Arzneimittel und Medizinprodukte,* HMG) and several ordinances. The purpose of the TPA is to protect human and animal health and to guarantee that only high-quality, safe and effective therapeutic products are brought to the market.

Pursuant to article 23 para. 1 of the TPA, therapeutic products are classified into categories according to whether (categories A and B) or not (category D) they are subject to prescription. Further, over-the-counter therapeutic products are classified into category E. More specifically, pursuant to articles 40 *et seqq*. of the Swiss Federal Ordinance on Medicinal Products of 21 September 2018 ("**OTP**"; *Verordnung über die Arzneimittel, VAM*), therapeutic products are classified as follows:

- single delivery prescription drugs (category A);
- prescription drugs that may be delivered several times with the same prescription (category B);

- non-prescription drugs that require previous consultation (category D); and
- non-prescription drugs that may be bought without further consultation (category E).

Previously, category C encompassed non-prescription drugs that required previous medical consultation. However, this category was abrogated as per end of 2018.

Irrespective of whether therapeutic products are subject to prescription or not and save for a few exceptions, they can only be brought to the market if authorised by Swissmedic. Any person applying for a marketing authorisation for a therapeutic product must have a registered address, registered office or a branch office in Switzerland. Swissmedic can impose restrictions and conditions to the marketing authorisation, such as the obligation to deliver further clinical-experimental data or other post-marketing obligations, the existence of which should be verified by due diligence.

The marketing authorisation is, in principle, valid for five years (article 16 para. 2 TPA). Swissmedic may at any time examine, adapt or revoke such marketing authorisation (article 16c TPA). On request, Swissmedic renews the authorisation if the requirements are still fulfilled (article 16b TPA). In principle, the renewed marketing authorisation is valid for an unlimited term. However, Swissmedic may put a time limit on it (article 16b TPA).

Who is/are the payer(s)?

In order to benefit from the reimbursement of therapeutic products by the compulsory health insurance, the respective products must be listed by the FOPH on the so-called specialty list (article 52 para. 1 lit. b HIA). The specialty list may be consulted online under the following link: www.spezialitätenliste.ch (last visited on 5 April 2019).

If a therapeutic product is more than 20% more expensive than a third of all therapeutic products listed on the specialty list with the same composition, the insured has to pay 20% of the costs exceeding the deductible (article 38a of the Ordinance on the Benefits of the Mandatory Health Insurance of 29 September 1995 ["**OBHI**"]; *Verordnung des EDI über Leistungen in der obligatorischen Krankenpflegeversicherung, KLV*).

Furthermore, reimbursement may be obtained from invalidity insurance. Pursuant to article 13 para. 1 of the Federal Act on Invalidity Insurance of 19 June 1959 ("**IIA**"; *Bundesgesetz über die Invalidenversicherung, IVG*), insured persons are entitled up to the age of 20 to obtain the medical measures necessary to treat congenital diseases. Such medical measures include, inter alia, medical treatment and the dispensing of prescribed medicinal products (article 14 para. 1 IIA). The congenital diseases giving rise to such entitlement are listed in the Annex of the Ordinance on Congenital Diseases of 9 December 1985 ("**OCD**"; *Verordnung über Geburtsgebrechen, GgV*). In order to obtain funding from invalidity insurance, the insured person has to file an application to the invalidity insurance.

Consequently, non-listed therapeutic products have to be paid for by consumers themselves.

What is the process of securing reimbursement for new pharmaceutical product and how are drug prices set?

First of all, an application for a therapeutic product to be listed on the specialty list has to be filed with the FOPH. In order to be listed thereon, a therapeutic product must be approved by Swissmedic and must satisfy the criteria of effectiveness, functionality and economic efficiency (article 65 para. 1 and 3 of the Ordinance on Health Insurance of 27 June 1995 ["**OHI**"]; *Verordnung über die Krankenversicherung, KVV*). Based on these criteria, the FOPH determines the maximum price for the therapeutic product in question. The approval process has recently been expedited and should not exceed 60 days from the date of marketing authorisation (article 31b OBHI).

In order to assess the effectiveness of a therapeutic product, the FOPH relies in principle on the same documents which were used by the applicant for the approval of Swissmedic. However, the FOPH may demand that further documents are submitted (article 32 OBHI). As regards the criteria of functionality, the FOPH examines the impact, composition and possible side effects of the therapeutic product in question (article 33 OBHI). Finally, a therapeutic product is deemed economically efficient if the indicated therapeutic effect is reached most cost-efficiently (article 65b OHI).

The FOPH bases the evaluation of a therapeutic product's economic efficiency on two aspects: on the one hand, on a comparison with the prices in foreign reference countries – which are Germany, Denmark, Great Britain, Netherlands, France, Austria, Belgium, Finland and Sweden (so-called *Auslandpreisvergleich*) – and on the other hand, on an assessment with respect to other therapeutic products (so-called *therapeutischer Quervergleich*). As regards the comparison with other therapeutic products, the FOPH examines the efficiency and costs of the therapeutic product in question compared with other drugs used for the treatment of the same disease (article 65b OHI and articles 34a et seqq. OBHI).

The costs for research and development are taken into account for the examination of the economic effectiveness of a product, unless the original therapeutic product in question is a successor product that brings no therapeutic progress. Further, a so-called innovation supplement is granted for a maximum of 15 years for therapeutic products providing a significant therapeutic progress (article 65b para. 6 and 7 OHI).

The therapeutic products on the specialty list are re-examined every three years, as well as after the expiration of the patents in question. As a result of this re-examination, the FOPH may order a reduction of the price for the therapeutic product in question (article 65d and 65e OHI).

Policy issues that affect pricing and reimbursement

Population growth (growth in size of elderly population/growth in populations with chronic diseases)

Life expectancy in Switzerland is among the highest in the world. A newborn in 2017 is expected to reach the age of 81.4 (men) or 85.4 (women). According to a study conducted by the FSO, it is to be expected that the Swiss population will significantly and rapidly grow older. In particular, between 2020 and 2035, the baby boomer generation will reach retirement age (*cf.* Media Release of the FSO of 22 June 2015). Given that among the population over 80 years, 15.7% lived in retirement homes per 31 December 2017 and 28.1% needed care at home, and that the total costs of retirement homes alone amounted to 10.128 billion Swiss francs in 2017 (*cf.* www.bfs.admin.ch; last visited on 5 April 2019), the costs for healthcare will most presumably further rise.

As already discussed herein above, the most common causes of death in Switzerland are cardiovascular diseases and cancer (*cf.* above, "Incidence and prevalence of disease", in "Market introduction/overview"). Since the costs of certain therapeutic products for the treatment of cancer are very high, a further increase of healthcare costs is to be expected in this respect too.

The extremely high costs for the healthcare system and, in particular, the financing of these costs are currently a highly controversial political topic in Switzerland (*cf.* also above, "Size, demographics" in "Market introduction/overview"). Also, costs and benefits of very

expensive treatments, in particular when carried out with regard to old persons, are debated increasingly vehemently.

Prohibition of benefits and kick-back

Pursuant to article 33 TPA, it is prohibited to grant, offer or promise material benefits to persons who prescribe or dispense medicinal products, or to the organisations which employ them. Further, it is prohibited for persons who prescribe or dispense medicinal products as well as for the organisations which employ them, to solicit or accept material benefits. However, material benefits of modest value, which are related to medical or pharmaceutical practice, as well as commercially and economically justified discounts on the price, are permitted.

In the context of the current revision of the TPA (*cf.* below section "Emerging trends"), it is planned to further increase transparency and integrity with respect to therapeutic products (*cf.* below section "Emerging trends") by clarifying the legal provisions regarding pecuniary benefits and strengthening the implementation of these provisions.

Previously, pharmaceutical companies would sponsor events and congresses for practitioners. The increasingly stringent regulations have already resulted in a substantial reduction of such sponsorship. It is to be expected that this trend will be favoured by the entering into force of the new ordinance mentioned above.

Emerging trends

As part of the master plan of the Confederation for strengthening biomedical research and technology, the TPA and the corresponding ordinances are currently under revision. The revision aims at improving the population's access to therapeutic products and the conditions for biomedical research and industry. The Federal Council transferred the dispatch on the revision of the TPA to the Parliament on 7 November 2012, which accepted the core elements of the Federal Council's draft, amended part of it, and adopted the revised TPA on 18 March 2016.

Certain provisions have already entered into force on 1 January 2018. With regard to the remaining implementing provisions, a consultation process was conducted in 2017. Thereupon, most of the revised provisions of the TPA and the corresponding ordinances entered into force on 1 January 2019. However, as a result of the consultation process, the implementing provisions relating to integrity, transparency and the obligation to pass on discounts needed to be amended: the new ordinance on transparency and integrity in the context of therapeutic products will enter into force on 1 January 2020.

Successful market access

In our opinion, the following factors are key to successfully entering the Swiss national market:

- in-depth knowledge of the healthcare legislation in Switzerland;
- taking into account that for certain questions the cantons are competent and not the federal authorities;
- considering that most therapeutic products cannot simply be sold via supermarkets;
- rigorous documentation of the process from research to marketing;
- requests for authorisation in a timely manner and within the time limits; and
- high efficiency and quality.

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Ukraine

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In Ukraine, reimbursement is effectuated by full or partial compensation to business entities acting in the retail trade for medicines, if such medicines are sold on prescription.

Market introduction/overview

The Ministry of Healthcare of Ukraine is a central executive body, the activity of which is directed and coordinated by the Cabinet of Ministers of Ukraine. The Ministry of Healthcare of Ukraine is the principal body in the system of central executive bodies, ensuring the formulation and realization of state policy in the sphere of healthcare.

Reimbursement applies to all medicines included in: "the National List of Essential Medicines", approved by the Ruling of the Cabinet of Ministers of Ukraine, No. 333 of March 25, 2009; the list of international nonproprietary names of medicines, approved by the Ruling of the Cabinet of Ministers of Ukraine, No. 135 of February 27, 2019; and the Register of medicines that are subject to reimbursement approved by the Order of the Ministry of Healthcare of Ukraine.

These are the medicines required for ambulatory treatment on an outpatient basis in the following medical states: cardiovascular diseases; type II diabetes; and bronchial asthma.

Other registered medicines that are not on the List may be purchased by healthcare establishments and financed from the budget, provided the budget allows and covers the need in essential medicines.

Apart from the above, purchases can be made based on the agreement of the Ministry of Healthcare of Ukraine with the specialised procurement organisations.

The Register of medicines that are subject to reimbursement is renewed twice a year and announced on the official website of the National Service of Health of Ukraine. The owner/representative of the owner of the registration for medicine files a statement to the National Service of Health of Ukraine within 10 days of the announcement, with a proposition for the inclusion of its medicine into the Register. The National Service of Health of Ukraine takes a decision on inclusion into the Register of medicines that are subject to reimbursement on the basis of propositions received.

It is generally agreed that the mechanism for the reimbursement of the cost of medicines should continue to be reformed if the mechanism is to fully contribute to the proper provision of patients with medicines and achieve the end result of effective treatment.

Pharmaceutical pricing and reimbursement

The healthcare system of Ukraine has been in a state of constant transformation under the

reform in recent times. As a result, more than 1 billion hryvnyas (approx. US$ 37,936,250) has been compensated by the state under 18 million prescriptions within the reimbursement programme, "Budget-friendly medicines".

Since September 26, 2018, the Concept for reform of the procurement of medicines and medical products, of the Cabinet of Ministers of Ukraine, No. 582-p has been approved, which will improve and accelerate the reimbursement process with the involvement of specialist organisations.

Reimbursement of the cost of medicines is made on the basis of the agreements on reimbursement between the National Service of Health of Ukraine and business entities, under the programme of state guarantees for medical services for the public. The principal administrator of reimbursement funds is the Ministry of Healthcare of Ukraine.

According to data from the Auditing Chamber, the budget programme for expenditure in 2017 was UAH 627.2 million (approx. US$ 22,352,100), and for UAH 1038.4 million (approx. US$ 37,828,779) comprising respectively 90% and 96% of open assignments.

The reimbursement programme "Budget-friendly medicines" has given the opportunity for the budget to compensate the cost of the medicines for treatment of cardiovascular diseases, type II diabetes and bronchial asthma for a total amount of UAH 1.7 billion (approx. US$ 64,885,500) since April 2017.

The pricing mechanism is formed in consideration of the margin supply and sales and retail price increase.

The reimbursement is calculated according to the formula Ar = M x Q (1 + Io/100) x (1 + Ir/100) x (1+VAT/100),

where Ar is the amount of reimbursement for the package of medicines:

- M – minimum wholesale price;
- Q – quantity of the daily dose of the medicine in the package;
- Io – margin supply and sales increase in price;
- Ir – margin retail increase in price; and
- VAT – value-added tax.

State registration of the medicine is made by the Ministry of Healthcare of Ukraine on the basis of the statement and the results of the expertise of the registration dossier, conducted by the State Expert Center of the Ministry of Healthcare of Ukraine.

In case the medicine is registered by the European Medicines Agency, state registration of the original medicine is made without the mentioned expertise on the basis of the statement, registration materials, the report of assessment of the registration dossier by the European Medicines Agency, and the report of the State Expert Center of the Ministry of Healthcare of Ukraine, regarding compliance of the product instruction and methods of medicine quality control with the registration materials.

Registration of a medicine takes approximately 1.5 to 2 years.

Policy issues that affect pricing and reimbursement

Apart from the common policy issues affecting increases in the prices of medicines (such as cost of research & development and innovation), we may note an assessment of a 7% VAT rate for operations relating to the supply of medicines to Ukraine.

Emerging trends

From the second quarter of 2019, an electronic prescribing programme, "Budget-friendly medicines", is being introduced, networking 436 pharmacies as legal entities (each third pharmacy has joined the programme), allowing access by those pharmacies having an agreement with the National Service of Health of Ukraine to prescribing practice data, thus significantly impacting the mechanism of reimbursement in the pharma sector.

The programme will be administered by the National Service of Health of Ukraine and will make the reimbursement of medicines simpler.

Also on the agenda is development of the strategic procurement of medications and medical products.

Realisation of the Concept for reform of the procurement of medicines and medical products envisages:

- development and implementation of an information system for the management of centralised procurement of medications;
- the creation of respective regulatory procedures for participation in tenders for producers/non-residents, as well as the realisation of an international exhaustion regime;
- providing opportunities for the joining of Ukraine with other countries for the procurement of medicinal products and related services; and
- use of existing mechanisms of the world practice for procurement, etc.

As determined by the Law of Ukraine "On State Financial Guarantees of Medical Services for the Public", before December 31, 2019 reimbursement is made pursuant to the list of medical states in the order, established by the Cabinet of Ministers of Ukraine. From 2020, reimbursement of the cost of medicines stipulated by the programme of medical guarantees is introduced.

Successful market access

In planning market access with new medicines, we recommend making sure that such actions will not infringe the intellectual property rights (trademark and patent rights) of third persons.

In addition, the company entering the market should take into account the above tendencies and AMC requirements.

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United Kingdom

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Abstract

The UK has a large and complex healthcare system, under which the National Health Service ("NHS") funds the vast majority of medicines prescribed to patients.

The complexities of the system mean there is no single pathway to NHS reimbursement for a medicinal product, nor a universal reimbursement list. If and how the NHS funds a product often depends on the setting in which the NHS uses it. However, guidance from the National Institute for Health and Care Excellence ("NICE") plays an important role in determining whether the NHS will support the use of a product. The UK has price control policies for branded medicines but, in general, leaves the price of generic products open to market forces.

NHS drug expenditure continues to increase, albeit growth rates vary significantly depending on product-type. Reasons for this include a growing and ageing population, with specific needs, as well as the launch of costlier high-tech and rare disease medicines into the UK. Currently, the healthcare system faces significant financial pressure and this creates a challenging environment for product pricing and reimbursement. In light of this, there is a trend for the NHS and other state organisations to involve themselves directly and indirectly in drug pricing. Another trend is for suppliers and healthcare organisations to enter into innovative or bespoke commercial arrangements to facilitate the availability of a product in the NHS.

Market overview

The UK comprises four constituent nations: England; Wales; Scotland; and Northern Ireland. The UK has a population of approximately 66 million people, with the vast majority (approximately 55.6 million) resident in England. There is a well-developed healthcare market in the UK, dominated by a large and sophisticated public healthcare system, the NHS. The NHS is almost entirely state-funded and mostly free to patients at the point of need.

When considering pricing and reimbursement in the NHS, it is important to keep two points in mind. Firstly, the structure and organisation of the NHS varies across the four nations of the UK, though many key concepts are similar. For the sake of simplicity, this chapter focuses primarily on the NHS in England, which is by far the largest market. Secondly, the way the NHS pays for medicines differs considerably between those supplied in "primary care" (i.e., prescribed by General Practitioners or other community prescribers and dispensed in a community pharmacy or by a dispensing doctor) and "secondary care" (i.e., in hospitals, clinics and similar settings). This distinction is relevant throughout this chapter.

In England, the NHS spent an estimated £18.2 billion on medicines in 2017/18, without taking discounts into account. That represents a 4.6% increase on the prior year and is broadly

consistent with an average 5% annual growth rate since 2010/11. That growth is almost entirely attributable to medicines dispensed in hospital settings (i.e., secondary care), the cost of which has more than doubled since 2010/11. The 2017/2018 year was the first on record in which hospital medicines consumed more than half of NHS England's total drugs budget.

By contrast, spending on medicines in primary care fell by 1% in 2017/18. The gross amount spent has broadly remained the same since 2010/11, despite the fact that the volume of medicines dispensed in primary care has risen by an average of 3.3% each year. This demonstrates the downward pressure on prices for medicines that are mainly dispensed by community pharmacies to non-hospitalised patients.

Historically, the NHS in England spends approximately three-quarters of its drugs budget on branded products.

Pharmaceutical pricing and reimbursement

Regulatory classification

Classification of medicinal products

The Human Medicines Regulations 2012 create three broad regulatory classes of medicines:[1]

1. Prescription-only Medicines ("POMs");
2. "General Sale Medicines," which consumers may purchase without a prescription; and
3. "Pharmacy Medicines," which consumers may purchase without a prescription but only from a pharmacy.[2]

The regulatory classification of a new medicine will depend on a number of factors, including whether: (i) the marketing authorisation designates it as a POM, a General Sale Medicine or a Pharmacy Medicine; (ii) by statute the product must fall into a particular category; or (iii) the Medicines and Healthcare products Regulatory Agency ("MHRA") or the European Commission has allocated the product to a particular category.

In principle, NHS reimbursement is available to all three classes of medicines. However, the NHS increasingly focuses its expenditure on POMs and to that end, NHS England aims to dissuade clinicians from prescribing medicines available over the counter.[3]

Eligibility for reimbursement

In primary care, any medicinal product commercially available in the UK is, in principle, eligible for reimbursement (i.e., the NHS agrees to refund the cost of the medicine to the dispensing pharmacist/doctor). The main exceptions to this are where the NHS has "black-listed"[4] a product in the Drug Tariff (the monthly list of reimbursement prices in primary care) or has placed conditions on reimbursement (e.g., through the so-called "Selected List" in the Drug Tariff).[5]

In secondary care, eligibility for reimbursement is more localised and there is greater scope for variation. Prescription, treatment and supply often take place within a single NHS organisation (e.g., a hospital), which gives that organisation a degree of autonomy over the medicines it chooses to fund. CCGs (as defined in section "Who is/are the payer(s)?" below), NHS Hospital Trusts and other stakeholders often have their own policies and formularies setting out which products are and are not available to a clinician to prescribe. Prescribers in secondary care settings usually only deviate from these policies for clinically justified reasons, such as an individual patient's exceptional circumstances or requirements.

In both primary and secondary care settings, guidelines issued by NICE play an important role in determining whether the NHS funds a product and, in practice, whether clinicians

would prescribe the product to NHS patients (see section, "How is the reimbursement amount set?" below, which discusses NICE guidelines).

Who is/are the payer(s)?

The NHS ultimately funds the vast majority of POMs supplied to patients in the UK. In England only, it recovers a small fraction of its costs through flat-rate prescription charges, payable only by some patients (usually, adults aged under 60 in employment and earning over a certain threshold). The UK has a smaller – but growing – private healthcare market, funded by patients themselves or through private insurance.

Which NHS organisation is responsible for funding ("commissioning") a medicine and how it arranges that funding are complex questions, which often hinge on the type of treatment provided and the treatment setting (primary or secondary care). The main payers and payment structures in England are as follows:

- NHS England has responsibility for commissioning primary care in England, though these days many Clinical Commissioning Groups ("CCGs") (discussed further below) co-commission primary care services with NHS England. The reimbursement mechanism in primary care is largely centralised, under the Community Pharmacy Contractual Framework. Essentially, contractors who dispense products in primary care will receive a fixed reimbursement price for a particular product.
- Commissioning in secondary care is effectively the responsibility of approximately 200 local CCGs.[6] CCGs receive funding from the NHS and it is for them to obtain value for money in terms of the products and services they make available.
- NHS England commissions Specialised Services (which include treatments for certain cancers, genetic disorders or complex medical or surgical conditions) and Highly Specialised Services for rare diseases (typically to treat around 500 patients per year). These mechanisms allows NHS England to provide centralised funding for high-cost products that CCGs may be reluctant to fund.
- NHS England is also responsible for commissioning certain "public health" services (such as vaccination programmes).

What is the process for securing reimbursement for a new pharmaceutical product?

As noted above, the NHS funds treatments in a number of different ways. This means there is no single pathway to securing NHS reimbursement for a new product.

Nonetheless, NICE is often considered the gatekeeper to reimbursement, because a positive recommendation for a product or treatment from NICE obliges NHS England to make funding available for it, usually within three months of the recommendation.[7] A negative recommendation from NICE does not necessarily mean a product is ineligible for reimbursement. However, unless other funding arrangements are in place, it provides commissioners with a basis to resist or delay funding. As a matter of practice, NHS clinicians usually prescribe products according to NICE guidelines.

NICE topic selection

NICE does not appraise each and every new product. Its current aim is to evaluate all new significant drugs and indications launched in the UK. Manufacturers of new products may make suggestions for an appraisal though UK PharmaScan (an industry horizon-scanning directory).

From April 2019, NICE charges companies up to £126,000 for conducting technology appraisals.

NICE assessment

NICE evaluates whether the NHS should fund products or treatments (which NICE refers to as "technologies") based on clinical and cost-effectiveness assessments. As part of the Voluntary Scheme Agreement (see "How are drug prices set? What is the relationship between pricing and reimbursement?"), NICE has committed to reviewing its methodologies, with a public consultation expected in 2020.

Currently, NICE has a standard assessment methodology as well as variants for specific types of products (such as certain cancer or highly specialised drugs, see "NICE's Methodology for Certain Products – Cancer Drugs and Highly Specialised Technologies", below). The common thread is NICE's focus on a technology's incremental cost-effectiveness ratio ("ICER") against an existing reference based on the quality-adjusted life year ("QALY"). These are established health economic concepts that seek to quantify the relative utilities of a technology.

NICE's Standard Assessment Methodology

In most cases, NICE will issue a positive recommendation if it assesses a product to have an ICER, usually against an existing reference, of less than £20,000. NICE may apply its discretion to recommend technologies with ICERs between £20,000 and £30,000, where justified on certain grounds, such as the innovative nature of a drug. Under its standard methodology, it is rare for NICE to give a positive recommendation to a technology whose ICER exceeds £30,000. However, NICE has additional discretion where products are used in end-of-life scenarios. Nevertheless, NICE has yet to recommend a product using its standard methodology where the incremental cost-per-QALY was significantly in excess of £40,000.

NICE's cost-per-QALY thresholds have remained fixed for a number of years. Inflationary pressures, and an increased industry focus on rare diseases and other high-cost treatments, mean that it is increasingly difficult to bring certain new products below the thresholds in order to receive a positive recommendation.

NICE's Budget Impact Test

Introduced in April 2017, the "Budget Impact Test" is an additional step for NICE assessments. Any product that NICE has assessed to be cost-effective but is likely to cost the NHS more than £20 million in any of the first three years of its use must be subject to further negotiations between the supplier and NHS England to bring the overall cost down. If these negotiations are unsuccessful, NHS England may apply to NICE to delay funding the product by up to three years, or longer in exceptional cases. This has proven to be a controversial measure: in the second half of 2017, the Association of the British Pharmaceutical Industry ("ABPI") launched unsuccessful court proceedings to challenge the legality of the test.

Patient Access Schemes

When a product does not meet NICE's cost-effectiveness criteria, NICE may still give a positive recommendation subject to an agreed Patient Access Scheme. These are formal pricing agreements, provided for under the Voluntary Scheme (see section, "How are drug prices set? What is the relationship between pricing and reimbursement?", below) between a supplier and NHS England that make a product more affordable (e.g., by way of a price discount, rebates, free-stock or outcome-based pricing). The commercial details are usually kept confidential. NICE's Patient Access Scheme Liaison Unit advises NHS England on the feasibility of any proposed scheme.

Managed Access Agreements

Where the clinical data supporting a NICE application are uncertain, NICE may recommend a product subject to a Managed Access Agreement. These agreements enable NHS patients to access treatment, while allowing the company to collect real world data for a NICE re-appraisal. The commercial terms of these agreements are usually confidential, though they often contain an overall budget-impact cap.

NICE's methodology for certain products – Cancer drugs and highly specialised technologies

When evaluating specialist and high-cost technologies, NICE may depart from its standard methodology. For example:

- There is a specific assessment pathway for "Highly Specialised Technologies" ("HST"), which treat rare and specialist conditions. The HST process is only available to products that satisfy certain requirements, including:
  - The target patient group is distinct for clinical reasons and sufficiently small that treatment will usually be concentrated in very few centres in the NHS.
  - The condition is chronic and severely disabling.
  - The technology has the potential for lifelong use.

  For these products, the conventional NICE appraisal builds in certain allowances to accommodate likely higher-cost, and often more limited, clinical data. NICE will usually recommend HSTs that have an ICER of less than £100,000. It has discretion in certain circumstances to recommend products above that threshold, usually up to ICERs of £300,000. NICE has assessed a small number of products using the HST process and to date, has issued nine pieces of final guidance in more than five years.
- The Cancer Drugs Fund ("CDF"), is in place to enable faster access to promising new cancer treatments. Following its relaunch in 2016, the CDF aims for all new systemic cancer drugs to receive a fast-tracked NICE appraisal. NICE will recommend a product to receive funding from the CDF, at a negotiated price, if it has the potential to satisfy the criteria for routine commissioning, but there is clinical uncertainty that needs further investigation (i.e., through data collection in the NHS or clinical studies). The drug will remain available within the CDF while more evidence becomes available, at which point NICE will subject it to one of its standard technology-appraisal processes. A recent coup for the CDF was the landmark approval of certain CAR-T therapies through the fund.

NICE appeals

Generally, the manufacturer of the product under review, patient groups or clinician organisations who have participated in the assessment may appeal the outcome of a NICE assessment to the NICE Appeal Panel. There are three possible grounds for appeal, which mirror the grounds for judicial review in the English Courts:

1. that NICE has failed to act fairly;

2. the recommendation is unreasonable in light of the evidence submitted; and/or

3. NICE has acted unlawfully or has exceeded its legal powers.

Most appeals are under the first two grounds but, in recent years, some successful appeals against NICE determinations have invoked novel human rights' considerations of the affected patient groups (e.g., children), which are essentially claims that NICE has acted unlawfully.

If an appeal to NICE's Appeal Panel is unsuccessful, a party may challenge the decision by way of judicial review in the High Court.

How is the reimbursement amount set?

In primary care, the NHS usually reimburses products: (i) for the amount set out in the Drug Tariff (if the product is listed there); (ii) at the "NHS list price"; (iii) or in other cases for the net price at which the dispensing pharmacy/doctor purchased the product. The Drug Tariff lists the reimbursement amount for commonly used, mostly generic products. The NHS reviews Drug Tariff prices each month, based on a survey of the market. The NHS list price applies mainly to branded products and is set in accordance with the Voluntary or Statutory Schemes (see section, "How are drug prices set? What is the relationship between pricing and reimbursement?" below).

The concept of a "reimbursement amount" is less relevant in secondary care because the NHS operates a *payment by results* model. Under this model, providers receive an amount per patient treated, based on the treatment provided, the length of a patient's stay, the complexity of their needs, etc. In most cases, this does not take the price of individual products directly into account.

How are drug prices set? What is the relationship between pricing and reimbursement?

The Secretary of State for Health has a statutory power to limit the price of medicines supplied to the NHS (section 262, NHS Act 2006). However, significant price control mechanisms only really exist for branded products and not generics (whose prices are broadly controlled by market forces). Branded medicines supplied to the NHS are subject to one of two price control schemes: the Voluntary Scheme for Branded Medicines Pricing and Access ("Voluntary Scheme"), or the so-called "Statutory Scheme".

Voluntary Scheme

As the name suggests, the Voluntary Scheme is an opt-in arrangement, agreed between the innovative pharmaceutical industry body, the Association of the British Pharmaceutical Industry ("ABPI") and the Department of Health. In one form or other, the Voluntary Scheme has been running in the UK since 1957. The current scheme came into effect on 1 January 2019 and will run for five years. The current Voluntary Scheme builds on many of the principles set out in the previous "Pharmaceutical Price Regulation Scheme", which expired at the end of 2018.

The Voluntary Scheme contains complex arrangements for price and profit control. Below are some key features:

- The Voluntary Scheme aims to cap increases in the amount the NHS spends on branded medicines, which companies that have opted into the Scheme ("Members") supply, to 2% growth per annum. To stay within this cap, Members must pay the Department of Health a fixed percentage of their net sales of branded medicines supplied to the NHS ("Scheme Payments"), with certain exceptions. Scheme Payments are designed to offset anticipated growth above the agreed 2% limit. The fixed percentage applies scheme-wide and is 9.6% for 2019. For future years, the percentage will depend on the difference between the agreed growth rate and projected growth in sales (it is expected to be 14.2% in 2020).
- Members who are small companies (i.e., essentially, those whose sales of branded products to the NHS total less than £5 million in the previous year) are exempt from making Scheme Payments. For medium-sized companies (i.e., essentially, those whose sales of branded products to the NHS total between £5 million and £25 million in the previous year), the first £5 million of sales may be exempt from Scheme Payments.
- Importantly, not all branded medicines supplied by Members are subject to Scheme

Payments. Medicines containing new active substances sold to the NHS within 36 months of their marketing authorisation are outside the net of Scheme Payments. However, sales of those products will still contribute to calculating expenditure grown across the scheme.

- The Voluntary Scheme also contains pricing controls. A Member may not increase the list price of a product without the prior approval of the Department of Health, which (amongst other things) requires a justification for the increase and an assessment of the Member's profits. In order to avoid stifling innovation, Members have the freedom to set the list price of medicines containing new active substances launched in the UK within 36 months of the grant of a marketing authorisation. However, this still requires a Member to confirm that its intended selling arrangements to the NHS will take cost-effectiveness into account. In other words, very high prices would go hand in hand with significant NHS discounts.

As part of the Voluntary Scheme agreement, NHS England has made a number of commitments aimed at improving access to medicines. These include the aim that from 2020, all new innovative medicines will receive NICE appraisals unless there are clear reasons not to assess them. There is commitment to review NICE's methods for conducting assessments – albeit NICE's cost-effectiveness thresholds will not change for at least five years. There is also a commitment to increase commercial flexibility, giving NHS England scope to engage with industry and agree bespoke pricing and access deals with companies.

Statutory Scheme

Manufacturers or suppliers of branded medicines to the NHS who do not participate in the Voluntary Scheme are, by default, subject to the so-called "Statutory Scheme" (per sections 262–264 of the NHS Act 2006).

The Government revised the Statutory Scheme significantly in 2018 through the Branded Health Service Medicines (Costs) Regulations 2018 (the "2018 Regulations"). The 2018 Regulations came into force on 1 April 2018 and were subject to further significant amendments, which took effect on 1 January 2019. The re-cast Statutory Scheme includes the following features:

- Manufacturers or suppliers must pay a percentage of their net sales of branded products to the NHS on a quarterly basis. The percentage payable was 7.8% for the 2018 calendar year, 9.9% for 2019 calendar year, and will be 14.7% for 2020 and 20.5% for 2021.
- There are also pricing controls, such as:
  - The maximum price of a product that was on the market on 1 December 2013 is capped to the price at that date, subject to any agreed increases.
  - Price increases and the price of new presentations require the agreement of the Secretary of State, who must take into account factors including: (i) the clinical need for the product; (ii) the cost of therapeutically equivalent or comparable products (including in other European Economic Area countries); (iv) if the product contains a new active substance; and (v) estimated profits and other financial parameters, etc.
- From 1 January 2019, unless the Voluntary Scheme applies, the Statutory Scheme will encompass all biologic medicines supplied to the NHS, including biosimilars.

The revisions to the Statutory Scheme bring it more closely in line with the Voluntary Scheme, though there are some differences. Arguably, pricing arrangements for products containing new active substances are more straightforward under the Voluntary Scheme than the alternative.

Factors that affect pricing

A number of factors affect drug pricing in the UK, ranging from Government and NHS policies, commercial arrangements between companies and the NHS, and marketplace competition. Note, the UK list price is often a benchmark for countries that operate reference pricing systems. This can be an important consideration for companies, which encourages providing discounts to the NHS under agreements that do not affect the reference price.

As noted above, companies must price branded products in accordance with the Voluntary or Statutory Schemes. The schemes tightly control increases in the price of established branded medicines but provide more (though unlikely complete) flexibility when pricing new products. New, innovative products are very likely to be subject to a NICE appraisal and companies try to meet NICE's cost-effectiveness criteria, if at all possible. If that is not feasible, companies often consider methods to provide better value for money to the NHS, such as through Patient Access Schemes or Managed Access Agreements.

Even after companies have agreed a price under the Voluntary or Statutory schemes and a NICE appraisal has taken place, there are various forces within the NHS that can further reduce the price that a company actually charges for its products.

For example, NHS Hospital Trusts, CCGs and other NHS bodies rely heavily on tenders, rebate agreements and other commercial arrangements to purchase generic and branded products with additional discounts. In particular, the NHS increasingly uses Framework Agreements (structured agreements in which a consortium of NHS "buyers" can purchase products for centrally contracted prices), which can significantly affect the price a supplier receives. "Framework Agreements" are regulated under the UK Public Contracts Regulations 2015.

The NHS in England increasingly takes a joined-up approach to procurement and medicines optimisation. For example, the NHS has established several national and regional procurement groups to co-ordinate and support medicines procurement, sharing information and expertise. Similar groups exist to align local formularies and prescribing policies to the most cost-effective options available, which can stimulate companies to offer keener prices to remain locally recommended or on a preferred formulary.

As in most other markets, competition from generic and biosimilar products also affects the price of innovator products on the market. The NHS' policy, for some time, has been to encourage clinicians to prescribe most products by their International Non-proprietary Name (INN) to encourage generic prescribing and dispensing. Many NHS organisations (such as CCGs or Hospital Trusts) also run programmes to switch patients from innovative to generic or biosimilar products. These factors mean that once generic or biosimilar products enter the market, suppliers of innovative products can rapidly lose market share unless they reduce prices. Note, however, that the UK prohibits generic or biosimilar substitution in pharmacies for a brand-name prescription (save in certain hospitals). That situation may change, on an emergency basis, if the UK exits from the EU in a "no deal" scenario.

The NHS generally avoids intervening in the market for generic products, relying on market forces to regulate it. However, over the last two years, the NHS has experienced severe shortages in the supply of certain generic medicines. Reportedly, this is the result of a weakened currency affecting imports and a variety of other supply-side issues. These shortages have led to price increases and the NHS has, in some cases, reflected this by offering a higher reimbursement amount in the Drug Tariff, often on a temporary or *ad hoc* basis.

Policy issues that affect pricing and reimbursement

The NHS' medicines policies aim to balance a number of interests, including:

- obtaining value for money for taxpayers;
- ensuring there is equitable access to treatment for NHS patients; and
- stimulating innovation in the life sciences industry by reimbursing new products that demonstrate clinical and cost-effectiveness.

However, demographic change, an increase in spending on prescription medicines, and budgetary pressure, make it increasingly difficult to maintain this balance.

The UK's population is growing as well as becoming older. The Office for National Statistics projects the UK's population to increase from approximately 65.6 million people in 2016 to approximately 69.8 million people by 2026. In that time, the proportion of the population over the age of 65 would increase from 18% to 20.5%. The rising number of older people has increased the demand for healthcare and the volume of products dispensed, particularly those to treat age-related conditions, such as cardiovascular disease and diabetes.

As noted above, the volume and cost of drugs used in and/or reimbursed by the NHS is on a steady upward trajectory. Population and demographic changes are major contributing factors. Another reason is an increase in high-cost innovative medicines available in the NHS (such as medicines for orphan and ultra-orphan conditions). It is unsurprising that while price-control mechanisms such as the Voluntary and Statutory Schemes have delivered savings and depressed prices of established medicines, the NHS has struggled to contain its overall drugs bill.

While NHS spending on medicines has risen by approximately 5% per annum over the past decade, investment into the NHS has struggled to keep pace, growing by approximately 1.5% *per annum* over the same period. Much of that is because of Government austerity and a challenging economic climate. In June 2018, the Government announced a plan to increase NHS spending by 3.4% *per annum* in real terms from 2019 to 2024. Despite this, many commentators still consider there to be an unsustainable funding gap.

Emerging trends

The NHS is constantly evolving and there are a number of emerging trends that may affect pricing and reimbursement. Some of these are below:

- NHS budgets are likely to face continued pressure, which may lead to further measures to cut drugs spending. The newly re-cast Voluntary Scheme, combined with NICE's fixed cost-effectiveness criteria and Budget Impact Test, mean that some companies launching new products in the UK may need to offer the NHS sizeable discounts to achieve meaningful levels of uptake. NHS England's strengthened mandate to negotiate pricing deals with industry will probably make Patient Access Schemes and similar agreements more common. NHS England points to its reimbursement of CAR-T oncology therapies sooner than in most other EU countries as an example of its new access-oriented approach. However, not all cases have proven as successful, with NHS England and Vertex Pharmaceuticals deadlocked over the access price of Orkambi.
- The NHS is committed to speeding-up access to promising technologies in specific treatment areas, such as cancer, dementia and diabetes. The NHS has recently made improvements to its Accelerated Access Collaborative ("AAC"), which identifies

game-changing innovations and provides their manufacturers with advice and strategic support to ensure rapid uptake within the NHS. Recently, the AAC identified tumour-agnostic oncology drugs as a particular area of interest.

- The NHS is likely to continue using co-ordinated procurement (particularly Framework Agreements) to drive better value for money. This could lead to more medicines procurement litigation. A recent example from early 2019 involved an unsuccessful attempt to overturn an NHS procurement programme for products to treat and eliminate Hepatitis C, the largest drug tender the NHS has ever undertaken.
- The NHS' internal policies are likely to reinforce the cost-effectiveness message to clinicians. For example, NHS-organised Regional Medicines Optimisation Committees now provide targeted guidance to CCGs and clinicians about savings associated with switching to specific biosimilars. The overall aim is to switch 90% of new patients and 80% of existing patients to the cheapest available biological product within 3–12 months of its UK launch. NHS organisations that fall short of delivering value for money are potentially vulnerable to financial penalties or disincentives.
- Linked to this is the growing tendency for the NHS to support using unlicensed products (or licensed products off-label) for reasons of cost. Historically, the NHS respected the principle of using licensed products within their label wherever possible, which is consistent with the MHRA's position and professional guidelines for doctors. Similarly, NICE's position is that it cannot positively recommend unlicensed products or off-label use of licensed medicines in an assessment (though it sometimes takes this into account for cost-comparison purposes). Despite this, the NHS has in certain high-profile cases advocated using lower-cost, unlicensed or off-label products. This is highly controversial, having been the subject of recent High Court litigation in respect of reformulated bevacixumab for intra-ocular use. At the time of writing, the case is awaiting a Court of Appeal hearing.
- NHS organisations continue to seek increasing amounts of information from internal and external sources about product pricing (e.g., discounts). The Health Service Medical Supplies (Costs) Act 2017 gives the Secretary of State wide-ranging powers to demand a variety of information from all stages in the medicines supply chain. Authorities could use this information to derive better value for money in areas where there has traditionally been price opacity (e.g., generics). The controversy surrounding a Vertex product, Orkambi, has led to a Parliamentary enquiry and discussions about forcing companies to reveal their EU-wide prices. Similarly, there is a growing expectation that NHS bodies that enter into commercial agreements with suppliers will share this information within the NHS with a view to deriving the best value nationally.
- The industry continues to face growing scrutiny from the UK Competition and Markets Authority ("CMA"). In particular, the CMA has investigated alleged anti-competitive agreements and conduct and suspected excessive and unfair pricing. Largely, this concerns allegations that manufacturers of generic products have inappropriately increased prices of products for which there is no meaningful competition.
- Anecdotally, there are signs that the uncertainties concerning Brexit have had an indirect effect on pricing and reimbursement. Potential stockpiling and market uncertainties have led to price volatility and stock-shortages. In the longer term, a no-deal Brexit could see controversial laws enabling pharmacy substitution coming into force. Clearly, these could have a knock-on effect on the UK's branded products market.

Successful market entry

Formulating a successful strategy for market entry will depend on the type of product in question and its place in the NHS' complex architecture. The following are some general points to consider:

- **NICE appraisal**. A company should investigate whether its product could be subject to a NICE appraisal and if so, whether it could meet NICE's cost-effectiveness criteria. The company could also explore qualifying for Highly Specialised Technology status or the Cancer Drugs Fund. For high-cost products, the company should consider the possibility of offering a Patient Access Scheme.
- **Specialised commissioning categories**. Falling within the scope of Specialised Services, Highly Specialised Services, the Cancer Drugs Fund or benefiting from Accelerated Access Collaborative Support would increase the likelihood of a high-cost product receiving NHS funding.
- **Commercial negotiations with the NHS customer base**. Companies should consider what their optimal pricing and discount strategy would be in the procurement space. This is particularly important if a product's main use is in secondary care.
- **Understanding NHS prescribing policies**. In the UK, market penetration is often a greater concern for companies than market entry. The NHS' prescribing policies (both local and national) have a significant impact on the uptake of a new product. Understanding these is therefore important.

* * *

Endnotes

1. Regulation 5 of the Human Medicines Regulations 2012.
2. See also Regulation 220 of the Human Medicines Regulations 2012.
3. "Conditions for which over the counter items should not routinely be prescribed in primary care: Guidance for CCGs" NHS England, 29 March 2018.
4. Schedule 1 to the NHS (General Medical Services Contracts) (Prescription of Drugs, etc.) Regulations 2004.
5. Schedule 2 to the NHS (General Medical Services Contracts) (Prescription of Drugs, etc.) Regulations 2004.
6. Pursuant to the Health and Social Care Act 2012.
7. Regulations 7(2)-(3) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 (SI 2013/259) and as set out in the NHS Constitution.

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Abstract

The cost of prescription drugs in the United States is substantially higher than in any other country in the developed world, but treatment outcomes and the quality of care lag behind those of other countries. Efforts to reform the system, to improve quality and reduce cost, face an uphill battle to build any consensus in the current highly divided social and political environment. However, despite this volatile context and the barriers to change that it creates, all stakeholders agree that continued growth in US healthcare spending is unsustainable.

The high cost of prescription drugs makes newspaper headlines every day. Although more than 80% of drugs are dispensed in lower-cost generic formulations, a small but growing number of new, highly effective specialty brands are driving an annual rate of growth in drug spending that exceeds the rate of inflation. In response, employers and health insurance plans are limiting coverage and/or shifting cost to their members in the form of higher deductibles or coinsurance that increase the individual's financial exposure.

Some reform efforts have survived the otherwise toxic social and political environment: An additional 8.7 million Americans have been able to purchase prescription drug coverage as a result of the implementation of the Affordable Care Act in 2010 ("Obamacare"). And, passage of the 21st Century Cures Act in 2016 has helped accelerate the FDA's regulatory review process, allowing new drugs to come to market more quickly, and at lower cost.

But challenges remain. Despite calls for transparency, pharmaceutical manufacturers' pricing strategies remain opaque, and list prices for prescription drugs do not reflect the prices that most people actually pay for these drugs. Manufacturers set higher list prices, and then offer rebates and other discounts to the pharmacy benefit managers ("PBMs"), but rebate amounts are customer-specific and highly confidential. In response, a growing number of states have passed pricing transparency laws that require drug companies to report drug price increases, making access to and the cost of specific drugs highly variable from one state to another. But while these new laws appear to be having some moderating influence on drug price increases, it remains unclear whether this is more than a temporary effect.

It is unlikely that the US Congress will be able to work together to advance any essential changes to prescription drug pricing policies in the foreseeable future, but the reform effort will continue at the federal regulatory, state, and local levels. Because of the apparently unresolvable policy differences among political parties, the healthcare reform debate has shifted from Congress to the courts. As of the date of this writing, the Fifth Circuit of the US Federal Appeals Court is evaluating the constitutionality of the Affordable Care Act in a case brought by 20 state attorneys general and endorsed by the Trump Administration.[1] If the court decides to strike down the ACA, the question of the constitutionality of healthcare

reform could advance to the US Supreme Court for the third time.

Despite ongoing healthcare policy and political upheaval, some important facts about the US market remain unchanged. In order to be successful, prescription drug manufacturers will continue to need to build robust clinical and economic evidence of the value of their products in order to persuade employers, PBMs, and health plans, which set drug reimbursement rates, to cover and pay for them. Successful access to the US market demands continuous evidence development, early and on-going communication with purchasing decision-makers, and development of new tools, including digital and mobile medical technologies, that customers can use to measure and report the impact of pharmaceutical product use on treatment outcomes, the cost of care, and their quality of life.

US market overview

The problem: The high cost of healthcare

Each year, the United States spends more on healthcare than any other country in the world,[2] yet access to care and the quality of services provided lag far behind other nations.[3] In 2016, the United States spent nearly twice as much as 10 other high-income countries on medical care but performed less well on important population health measures. A recent study found that the US had:[4]

- the highest percentage of adults who were overweight or obese (70% *vs.* 56%);
- the lowest life expectancy of the 11 countries studied (79 years *vs.* 82 years); and
- the highest rate of infant mortality (5.8 deaths per 1,000 live births in the US *vs.* 3.6 per 1,000).

The high cost of prescription drugs in the US is the single largest reason for differences in overall healthcare spending between the US and other high-income countries. On a *per capita* basis, Americans spent approximately $9,500 on their healthcare in 2016, compared

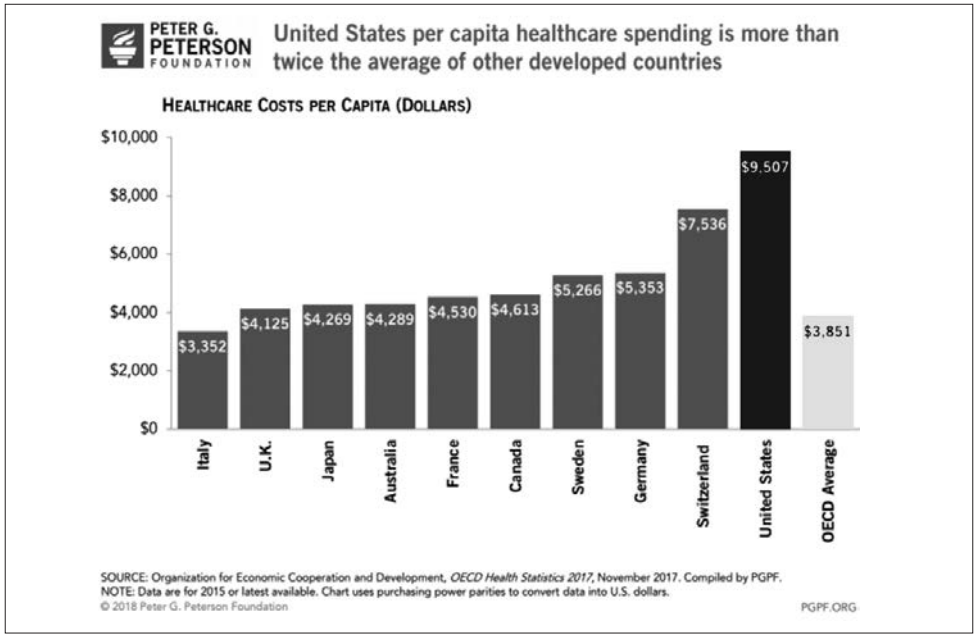

Fig. 1: *Per capita* healthcare spending in U.S. *vs* other nations

to an average of $5,400 in peer nations. Of that amount, $1,443 was spent on prescription drugs vs. a range of $466 to $939 in other countries. For several commonly used medications, the American price was more than double the price in the country with the next highest cost. Overall, spending on prescription drugs represented 15% of all healthcare spending, or approximately $329 billion.[5] This amount is expected to grow to between $370 billion and $400 billion by 2021.

Four billion prescriptions were filled at US outpatient pharmacies in 2011, representing on average more than 12 prescriptions per person each year. Nearly 70% of Americans routinely take at least one prescription drug, and more than half of Americans take two.

Half of those who take prescription drugs to help manage chronic diseases do not take their medications correctly,[6] exposing the broader healthcare system to the higher downstream costs of acute healthcare interventions that are needed when less expensive preventive care has not been consistent or successful.

Prescription drug costs drive healthcare spending

A recent report found that manufacturers have raised outpatient prescription drug prices in the US an average of 31% (median increase is 9%) during the second quarter of 2018 alone. Most of the recent price increases are well above the current US inflation rate of less than 3%. For many of the drugs, this is the second price hike in six months. For example, Pfizer raised the cost of Viagra (sildenafil citrate) by 9% in January and another 9% in July 2018. A 30-pill bottle of the drug is now listed at more than $2,200.[7]

Pfizer said that the list prices of its drugs do not reflect what most patients or insurance companies pay. Novartis has also raised prices on some products, but noted that the actual costs of its drugs have decreased in recent years when discounts and rebates are taken into account.

Between 2007 and 2013, annual increases in spending on prescription drugs in the US were flat, in part because a number of commonly used medications had come off-patent and began to be dispensed in generic form. Then, in 2014, spending spiked by 12% over 2013 levels because several extremely high-priced but effective drugs came to market. By 2014, Americans spent $11 billion on these specialty drugs for treatment of hepatitis C alone. This represents about one-third of the $32 billion in increased spending across all prescription drugs combined.[8] Spending on specialty drugs continued to increase another 15% to $121 billion in 2015.

Beyond the growth of the specialty drug market, entities across the supply chain are increasingly contracting and consolidating both horizontally and vertically. For example, each of the three largest Pharmacy Benefit Managers ("PBMs") maintains some form of common ownership with large retail chains and/or specialty pharmacies. Similarly, the three largest wholesale distributors own and operate specialty pharmacies and physician practices. Extensive consolidation has reduced transparency in the financial relationships among payers and other participants in the drug supply chain.

Spending on outpatient prescription drugs continues to grow, with more than 15% of the healthcare expenses for a family of four now going to drugs dispensed at the pharmacy. And, these figures do not include prescription drugs delivered in hospitals, outpatient infusion centers, or physician offices. When these other drugs are also included, the total drug spend is more than 20% of the average family's spending on healthcare each year.[9]

Cost-shifting

Health insurance plans (also called payers) are increasingly shifting financial responsibility for purchasing drugs to their beneficiaries. The average American's personal financial

responsibility for brand name prescription drugs dispensed at a pharmacy has increased more than 25% since 2010, reaching $44 per prescription on top of the payments made for that prescription by their health insurance plan. Overall, individuals' total out-of-pocket spending increased by 54% from 2006 to 2016, while health plan spending increased at a slower rate of just 48% during that same period.[10]

Continued growth in the cost of outpatient prescription drugs in the US is unsustainable. Healthcare reformers have developed three solutions: to lower drug costs; increase quality; and ultimately, reduce overall healthcare spending without limiting access to care.

Solution 1: Reform the US Healthcare System

The health insurance market in the US is highly fragmented with state and federal governments and private entities offering a variety of competing options from which Americans choose according to their age, employment status, income level, family size, and geographic location. Figure 2 arrays the primary types of payers that offer health insurance benefits in the US.

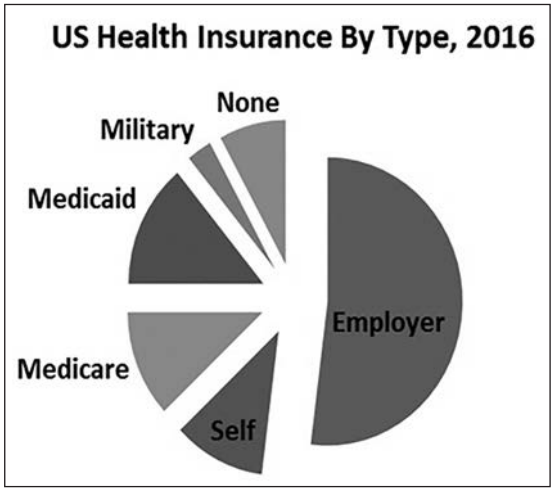

Fig.2: Primary sources of health insurance in the US, 2016

Health insurance for more Americans

Since passage of the Affordable Care Act of 2010 (also known as the "ACA" or "Obamacare"),[11] the number of Americans with some form of health insurance has grown to just over 90% of the population.[12] While this number is smaller than in other high-income countries with single-payer or government-sponsored healthcare systems, it represents a substantial increase over the number of Americans who had carried health insurance prior to implementation of the ACA, when many people did not have insurance, because they: (1) could not afford it; (2) did not qualify for health benefits because of their employment status; (3) had a pre-existing health condition that excluded them; or (4) decided that they did not need it.

"*Obamacare*"

Neither US political party has succeeded in previous attempts to expand access to health insurance or reduce the cost or care. But faced with the prospect of losing their majority in Congress, Democrats pushed through two separate health reform bills in 2010 without a single Republican vote. In March 2010, the President signed the bills into law, creating what is now called The Affordable Care Act ("ACA"). The legislation was written quickly, with plans to modify conflicting provisions later. But Democrats lost their majority in the next election, and subsequent Republican majorities have worked to "Repeal and Replace" the law. Key provisions have also been challenged in court.

The ACA was originally structured around two core provisions:

- **Individual mandate**: To create lower-cost options for purchasing health insurance, the ACA required everyone to purchase health insurance or pay a penalty. This was intended to create large "risk pools" of individuals with a broad range of health states

so that the higher costs of caring for sicker individuals could be spread over a larger pool of sick and healthy people whose healthcare expenses collectively were lower.

- **Expand Medicaid eligibility**: To qualify for Medicaid benefits, individuals and families must demonstrate household income below a threshold set by the state where they live. That threshold is calculated as a percentage of the Federal Poverty Level ("FPL") or Poverty Threshold,[13] an amount that is updated annually by the US Census Bureau. In 2018, the poverty threshold is $12,140 for an individual, and $25,100 for a family of four.

  The ACA required states to expand Medicaid eligibility to those with annual incomes of 138% of FPL (or $16,753 and $34,638 for an individual and family of four, respectively.) Thus, individuals and families whose income had previously been too high to qualify for Medicaid would be eligible for health insurance through the expanded Program. The federal government would withhold its financial contribution to any state that refused to expand its program.

The ACA has driven the most significant changes in the US healthcare system since the creation of the Medicare and Medicaid Programs in 1965. Many important provisions have been implemented. Among others, the ACA:

- **eliminated exclusions for pre-existing conditions**: The ACA made it illegal for health insurance plans to deny coverage on the basis of pre-existing health conditions, such as cancer or heart disease. These conditions had previously rendered some individuals essentially "uninsurable", and forced others to remain at one job, knowing that they or their dependants would not be covered by a new employer's health plan; and
- **mandated coverage of "Essential Health Benefits"**: The ACA required employers of a certain size to offer health insurance that covered a minimum number of broadly defined "Essential Health Benefits." These included, for example, pharmacy, women's preventive healthcare, hospitalisation, behavioural and mental healthcare and other services.

An additional 8.7 million Americans were able to purchase prescription drug coverage in 2014 as a result of the implementation of the ACA.[14] However, the number of newly insured individuals, multiplied by the higher cost of new specialty drugs, has added to the growth in drug costs and the volume of prescription drugs dispensed in retail settings in the US.

"*Repeal and replace*"

While some provisions of the ACA have been broadly popular, such as eliminating the pre-existing conditions exclusions, others have caused controversy. For example, some employers protested that they could not afford to provide health insurance for their employees; others refused to cover contraceptive services required under the women's preventive health benefit on religious grounds.

Ultimately, the dispute made its way to the US Supreme Court, which issued a split decision:[15]

- *Constitutional*: The "individual mandate" was really a tax,[16] and comprises a valid exercise of Congress' power to "lay and collect taxes."[17]
- *Unconstitutional*: Withholding federal funds from states that refused to expand their Medicaid Programs would violate the law.[18]

Then, in a second challenge to the constitutionality of ACA to reach the US Supreme Court, petitioners argued that the plain language of the statute provided tax credits only to those in states that had set up health insurance exchanges. The Court rejected that interpretation and upheld the ACA in 2015.[19]

Health system reform: a work in progress. . .

Other legal challenges were mounted, and Congressional Republicans launched an unsuccessful bid to repeal the ACA and replace it with the American Healthcare Act ("AHCA").[20] Ultimately, politics has overtaken health policy development.

- **Individual mandate rescinded**. A recent overhaul of the US tax system reduced the tax penalty that the ACA imposed on individuals who refused to purchase health insurance to $0, effectively eliminating the tax.[21]
- **Medicaid expansion incomplete**. Thirty-one states and the District of Columbia (Washington, DC) expanded their Medicaid programs; the 19 remaining states have not.
- **Essential Health Benefits no longer required**. The Trump Administration has issued new regulations permitting the formation of "Association Health Plans" that may not include all Essential Health Benefits.[22]
- **Executive authority stopped implementation**. President Trump has issued a series of Executive Orders to delay or prevent implementation of other provisions of the ACA.

This latest legal threat to Obamacare was filed by a group of 20 Republican states attorneys general in February 2018. That case argued that the 2017 changes to the US federal tax law effectively eliminated the ACA tax penalty because Congress lowered the penalty for not purchasing health coverage to $0, even though the mandate remains on the books. The lawsuit was once seen as a long-shot, but it has received serious consideration by Republican-appointed judges. As of the date of this writing, the case has advanced to the Fifth Circuit of the US Federal Appeals.[23]

Solution 2: Reform the regulatory review process for new drugs

The 21st Century Cures Act of 2016 ("Cures Act")[24] built on reforms that had been introduced through the ACA. The Cures Act endorsed advances in precision medicine, supported research at the National Institutes of Health ("NIH"), and invested in the formation of young, emerging scientists, among other important provisions.

Importantly, the Cures Act also authorised funding to accelerate new drug discovery, encouraged development of non-traditional clinical trial designs, promoted the use of "Real World Evidence," and required FDA to reform its regulatory review processes for innovative drugs and biologics.

The US Food and Drug Administration

The Food and Drug Administration ("FDA")[25] is responsible for the safety, effectiveness and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. It oversees the safety and security of the US food supply, cosmetics, dietary supplements, products that give off electronic radiation, and tobacco products. Headquartered outside of Washington, DC, it has local and regional offices around the country, and around the world. FDA was established in 1906 by the Food and Drugs Act,[26] and expanded by the Food Drug and Cosmetic Act[27] of 1938 ("FD&C" or often, simply "the Act").

Federal law requires that a drug be the subject of an approved marketing application before it can be legally transported or distributed across state lines.

FDA's Center for Drug Evaluation and Research ("CDER") is responsible for evaluating new prescription and non-prescription drugs before they enter the market to ensure that they work correctly, and that the health benefit of using the drug outweighs any known or potential risk.

Accelerating the regulatory review and approval process

Once pre-clinical testing has been completed on a new drug candidate, the manufacturer

initiates a series of interactions with FDA to secure approval to sell the product on the US market.

(a) **Request a "Pre-IND" consultation**

FDA encourages manufacturers to arrange a Pre-IND meeting before submitting an Investigational New Drug ("IND") application. This is a preliminary meeting with FDA reviewers to discuss the potential design, endpoints, experimental methods, etc. of clinical research intended to demonstrate the safety and effectiveness of the investigational new drug candidate in humans. Communication between the manufacturer and FDA generally takes the form of written comments that may be supplemented by teleconferences or meetings. FDA may recommend research strategies to accelerate the drug review process, including use of modelling and simulation, real-world evidence, and other tools for collecting and evaluating product safety information in real-time.

(b) **Submit an Investigational New Drug ("IND") application**[28]

The IND provides formal notice to FDA that a manufacturer intends to initiate human clinical studies of a potential new drug. Manufacturers must comply with certain safeguards of the IND process, including engaging an Institutional Review Board ("IRB"), securing informed consent from study subjects, distributing the drug through qualified channels, maintaining adequate manufacturing facilities, submitting safety reports, etc. The sponsor must wait 30 calendar days from the date it submitted the IND application before initiating clinical trials.

(c) **Register the study at ClinicalTrials.gov**[29]

ClinicalTrials.gov (https://clinicaltrials.gov/) is a searchable database of government and privately-funded clinical studies conducted in the US and around the world. For each listing, the database identifies the target disease/condition, describes the intervention, provides a summary of the clinical study protocol, the locations and contact information for study sites, and other information. As a condition of IND approval, manufacturers must register certain types of studies[30] and keep the registration current.[31] Civil monetary penalties of up to $10,000 a day may be levied for failing to register.

(d) **File the appropriate application for marketing approval**

FDA has created review processes for both innovator and follow-on products. Detailed information on each of these regulatory pathways may be found on the FDA website.

(i) New Drug Application ("NDA")

Manufacturers of novel, single-source drug candidates submit an NDA to provide information on the scientific and clinical testing conducted on the new drug candidate, a statistical and clinical analysis of study findings, proposed indication(s) for use, information about the manufacturer, and a survey of the relevant peer-reviewed literature. Manufacturers generally submit individual modules of the NDA electronically when they have been completed.

A complete index of guidance documents addressing the new drug application process may be found at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ Guidances/ucm121568.htm.

(ii) Abbreviated New Drug Application ("ANDA")

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act, more commonly known as the "Hatch-Waxman Act",[32] to open a shorter approval pathway for generic copies of already approved reference drugs. Under

Hatch-Waxman, manufacturers may file an Abbreviated New Drug Application ("ANDA") for a drug product that is identical, or bioequivalent to a brand/reference drug in dosage form, strength, route of administration, quality, performance characteristics, and intended use. Although generic drugs are chemically identical to their reference products, they are typically sold at substantial discounts from the branded price and often drive price reductions for the brand as well.

An overview of guidance documents addressing the abbreviated new drug application process for new generic drugs may be found at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm.

(iii) Therapeutic Biologic Application ("BLA")

Large molecule biologics are regulated by FDA through the Center for Biologics Evaluation and Research ("CBER"). These products include monoclonal antibodies, cytokines, growth factors, enzymes, immunomodulators, thrombolytics, proteins and other non-vaccine immunotherapies.

Information about the regulatory review process for innovator biologic products may be found at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm.

(iv) Abbreviated Biologic License Application ("ABLA")

The Affordable Care Act created a new abbreviated regulatory pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product through the Biologics Price Competition and Innovation Act ("BPCI"), part of the ACA.[33] Under BPCI, manufacturers submit an abbreviated Biologic License Application ("ABLA") to demonstrate that the follow-on product is biosimilar if data show that, among other things, the product is "highly similar to or interchangeable with an already-approved biological product."

More detailed information on the regulatory pathway for biosimilars may be found at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm.

(e) **Register and pay User Fees**

In the late 1980s, individual drug reviews often took years to complete because FDA lacked adequate funding to hire the staff needed to review drugs in a timely manner. In response, Congress authorised FDA to collect "User Fees" from manufacturers for each new NDA or ANDA submitted, to provide the agency the funding needed to hire review staff to review submissions more quickly. FDA committed to accelerate review times and provide annual reports on their performance.

The first Prescription Drug User Fee Act ("PDUFA") was passed in 1992, authorising FDA to collect fees from companies that produce certain human drug and biological products. The law is reauthorised by Congress every five years. The sixth reauthorisation ("PDUFA VI")[34] was signed into law on August 18, 2017 to help fund FDA drug review through September 2022. Parallel user fee programs have been created for generic drugs ("GDUFA"), biosimilars ("BsUFA") and medical devices ("MDUFA").

(f) **Secure FDA approval for new drug**

FDA review staff look for "substantial evidence"[35] of efficacy before approving a new drug candidate to enter the US market.[36] Historically, FDA has interpreted this standard to mean that the manufacturer must submit data from at least two rigorous clinical trials (preferably randomised, double-blind, placebo-controlled) that independently show statistically significant and clinically meaningful benefit that outweighs any known or potential risks associated with the product.

In 1992, FDA responded to the AIDS epidemic by creating an accelerated review process to get certain potentially life-saving drugs to market more quickly when no alternative therapy was available. Congress codified the accelerated approval pathways through passage of the Food and Drug Administration Safety and Innovation Act in 2012.[37]

Drugs that qualify for accelerated approval include those that offer a significant benefit compared to available therapies for serious medical conditions where there is unmet medical need, based on preliminary evidence of efficacy. Manufacturers request accelerated review, and if FDA agrees, it will grant approval on condition that the manufacturer commit to conducting and completing confirmatory "postmarket" studies after the product is approved and in commercial use. There are currently three accelerated review designations:

- **Breakthrough therapy**: FDA may designate a new drug candidate a "breakthrough therapy" if preliminary clinical evidence suggests that the drug offers substantial improvement over existing therapies for serious and life-threatening diseases.
- **Fast track designation** facilitates development, and expedites review of drugs to treat serious conditions and fill an unmet medical need.
- With **Priority review**, FDA's goal is to take action within six months.

FDA approved 46 new drugs in 2017, the largest number of new drug approvals in more than 20 years. Of these, 37% were approved with "Breakthrough therapy" designation.

(g) **Fulfil postmarket obligations**

As FDA works to accelerate the review process to bring new drugs to market sooner, it has required manufacturers to conduct additional studies after approval to confirm the safety and effectiveness of their new drugs. While numerous manufacturers had previously failed to meet their post-market study commitments, viewing these studies as an unnecessary regulatory burden and expense, FDA has recently become stricter in enforcing compliance. Despite the additional expense, manufacturers often leverage postmarket data for use in reimbursement negotiations.

(h) **Promote product according to approved "label"**

The Food, Drug and Cosmetic Act requires manufacturers to promote their new drug products according to the approved label. The label is the primary tool that communicates information regarding safe and effective use of the product, and must include approved prescribing information, adequate directions for safe use and any applicable safety warnings.[38] Labelling is not simply the information contained on a drug container, but rather also includes:

Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, . . . reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published . . . for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the

manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor. . . [39]

FDA has generally prohibited so-called "off-label" promotion, except in specific situations, such as when clinicians present research or other information to peers at structured scientific meetings, or when clinicians contact a manufacturer to request additional product information. However, several companies have recently challenged FDA's prohibitions against off-label promotion. In one interesting case, a pharmaceutical company sued FDA, charging that the Agency had denied its right to free speech by not allowing it to present truthful and not misleading information to customers that was not included in the product's (Vascepa,® icosapent ethyl, Amarin) approved labelling. The company won the case against FDA.[40]

Recognizing the importance of this information to the payer community, in 1997 Congress created a safe-harbour to permit manufacturers to communicate "healthcare economic information" ("HCEI")[41] proactively to "a formulary committee, or other similar entity," provided the HCEI is based on "competent and reliable scientific evidence" ("CARSE") and "directly relates" to an approved indication.

Solution 3: Reform the reimbursement system for outpatient prescription drugs

An individual's health insurance typically reimburses some or all of the cost of prescription drugs.

Employer-sponsored plans

More than half of Americans purchase private (or "commercial") health insurance through their employers. The employer either contracts with a third party administrator to manage its own health plan (a "self-funded" plan), or purchases coverage from a private health insurance company ("fully insured"). In both cases, the employer pays half of the monthly cost of the benefit, and the employee uses pre-tax dollars to pay monthly premiums that make up the other half. The employee also pays any out-of-pocket costs at the point of sale.

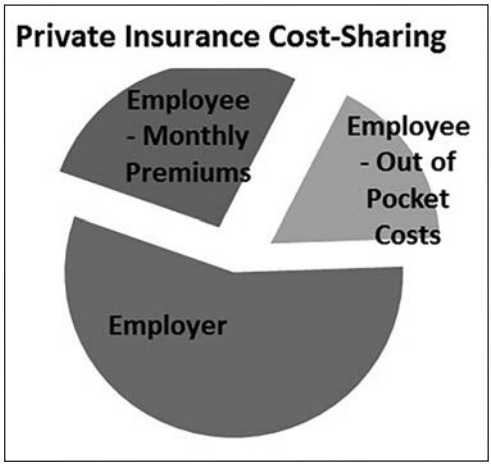

Fig. 3: Typical cost-sharing for employer-sponsored (private) health insurance plan

Employers are reluctant to change benefit-design or opt for health plans that might be perceived as limiting employees' choices, especially as employers are increasingly concerned with recruiting and retaining talent. Because employees are most sensitive to increases in the prescription drug co-payment amounts they pay at the pharmacy counter, a recent study found that deductibles and co-insurance increased from 2006 to 2016, but co-payment spending dropped by 38% in that period.[42] In an effort to make the benefit appear more affordable, actual cost increases were shifted to other, less visible expense categories.

Government-sponsored plans

Government-sponsored health insurance became available in the US after 1965, when Congress passed the Social Security Act,[43] authorising the creation of the Medicare and Medicaid programs. These programs are administered by the Centers for Medicare and Medicaid Services ("CMS").[44]

(a) **Medicare: Federal health insurance for the elderly and disabled**

Medicare is a federal health insurance plan for persons 65 years of age and older, for individuals who are younger than 65 with certain disabilities, and for persons with end-stage renal disease ("ESRD"). It was originally created as a hospital insurance plan ("**Part A**") with optional health insurance to cover physician services ("**Part B**"), but was later expanded. Under "Traditional Medicare", the beneficiary pays a monthly premium[45] adjusted for income. Once he or she has met an annual deductible,[46] Medicare pays 80% of charges and the beneficiary pays 20% up to a cap. The beneficiary can choose to see any doctor or visit any hospital. The vast majority of US providers accept Medicare payment, and in doing so, agree not to "balance bill" Medicare beneficiaries for covered services.[47]

Medicare Advantage ("**Part C**") was added to the Program in 1997.[48] Under Part C, private health insurance companies contract with the government to provide Medicare benefits. Today, more than 2,000 regional plans located around the country offer beneficiaries a range of different benefit structures, which may offer a greater number of options at a lower cost than traditional Medicare. Depending on where they live, most beneficiaries are eligible to join at least one of more than a dozen different plans, with one or more plans that offer a "Zero Premium" option.

A voluntary outpatient prescription drug plan ("**Part D**")[49] was added to the Medicare Program in 2003. Like Part C, Part D is also managed by private health insurers under contract with the federal government.[50] A beneficiary may enrol in traditional Medicare (Part A and B) and then purchase the prescription drug benefit (Part D). To do so, the beneficiary pays an additional monthly premium to participate in Part D, then, after meeting the annual deductible amount, pays a percentage of the cost of outpatient drugs until reaching the "catastrophic coverage" level where Medicare pays 100% of drug costs. Cost-sharing resets again to zero at the beginning of the following calendar year.[51]

Medicare pays for physician-administered outpatient drugs under Part B and for other prescription drugs under Part D. About 43 million (72%) of the 60 million people with Medicare have purchased outpatient prescription drug coverage under Part D. Beneficiaries who qualify for both Medicare and Medicaid (the "Dual Eligibles," generally low-income seniors) automatically receive prescription drug coverage through Part D.

Table 1: Medicare Part D Outpatient Prescription Drug Benefit: Benefit Structure and Cost-Sharing for CY 2019

Phases of Coverage	Cost-Sharing Obligations		Total Spending Out-of-Pocket	Total Spending
Deductible	Patient: 100% Up to deductible		$0-$415	$0-$415
Initial Coverage	Patient: 25% Up to $3,820		$415-$1,370 Deductible plus 25% of $3,820	$415-$3,820
Coverage Gap	*Brand Name* Patient: 25% Manufacturer: 70% Plan: 5%	*Generic* Patient: 37% Manufacturer: 63%	$1,370-$5,100 Patient pays up to Out-of-Pocket Cap	$3,820-$8,140
Catastrophic	*Brand Name* Patient: Greater of 5% or $8.50 copay	*Generic* Patient: Greater of 5% or $3.40 copay	$5,100 and Up	$8,140 and Up

Source: Minority Staff, Senate Finance Committee. June 2018

(b) **Medicaid: Joint federal/state health insurance for persons with low incomes, families, and for women and children**

Medicaid is a joint federal-state program that pays for healthcare services and long-term care for low-income individuals, including pregnant women, children, their parents, the elderly and disabled. The federal portion varies by state, but has historically averaged about 57%. Almost half of Medicaid enrollees are children in low-income families, and just under one-third are the parents of those children or low-income pregnant women. The elderly and disabled constitute the remaining quarter of enrollees.

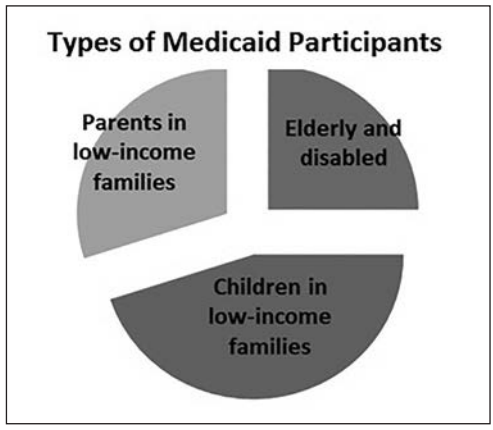

Fig.4: Medicaid program by beneficiary type

States administer their Medicaid programs according to federal guidelines that specify a minimum set of services that must be provided to certain categories of low-income individuals.

In order to sell their products to government-sponsored health insurance plans, drug manufacturers must enter into rebate agreements with the federal government to ensure that Medicaid receives a net price that is consistent with the lowest, or "Best Price"[52] for which the manufacturer has sold the product to any customer. In exchange for rebates, state Medicaid programs agree to cover that manufacturer's products with certain limitations.[53] States collect rebate payments on a quarterly basis.[54]

State governments spent 31% of their total annual budgets, or $929 billion, on healthcare and social services combined in 2015. By 2025, spending for these same services is expected to reach $1.6 trillion, or 38% of budget, assuming no significant policy action is taken in the meantime. Because 49 of 50 states are required by law to balance their annual budgets, (Vermont is the exception,) state legislatures will face increasing pressure to manage drug prices aggressively.

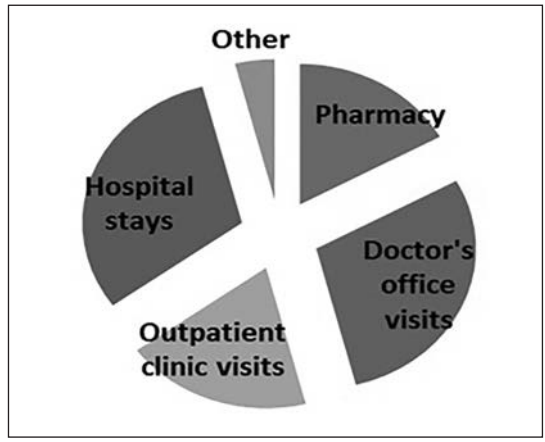

Fig. 5: Healthcare spending for a US family of four, 2018. See: http://www.milliman.com/mmi.

Structuring health plan benefits

Health insurance plans are typically structured into two parts: a medical benefit, which covers hospitalisations, doctor's office visits and other physician and professional services, and outpatient clinic admissions; and a pharmacy benefit which covers outpatient prescription drugs, and may also cover other services, such as distribution of durable medical equipment ("DME").

Pharmacy benefit managers ("PBMs")

Pharmacy benefit managers ("PBMs") administer prescription drug benefits for health insurance plans and employers using a range of tools intended to increase clinical quality and appropriateness, provide decision support, and reduce cost. The PBM:

- negotiates contracts (rebates) with drug manufacturers and pharmacies;
- processes claims;
- develops and maintains drug formularies;
- performs drug utilisation reviews;
- manages clinical decision support programs targeted to specific disease states; and
- may operate pharmacies, including mail-order and specialty pharmacies.

Decisions on formulary design, cost-sharing for beneficiaries, and the size and scope of pharmacy networks are made on a contract-by-contract basis with the specific health plan or employer.

PBMs generate revenue by negotiating rebates with drug makers for preferred formulary placement for their drugs. This translates into broader market share for their products than for their competitors.[55]

PBMs receive fees for processing and dispensing drugs for plan sponsors, and operating their own mail-order and specialty pharmacies. PBMs also retain the margin, or "spread" between the amount they charge their customers (i.e., the health plan) to manage the benefit and the amount paid to pharmacies for dispensing prescriptions.

Pharmacies contract with PBMs to establish a payment rate for each prescription, plus a dispensing fee. Pharmacies collect patients' co-pays and send them to the PBM. Some independent pharmacies still negotiate directly with wholesalers to purchase prescription drugs, but the number of independent pharmacies is declining.

Patients remit co-pays (a fixed dollar amount) or co-insurance (a percentage of the cost of the drug) to the pharmacy, and make monthly premium payments to their health plan for their prescription drug benefit.

(a) **Prescription drug formularies: Employer-sponsored plans**

A formulary is a list of the prescription drugs that the PBM agrees to reimburse when they are prescribed for a member who meets specified criteria. A formulary system is a standard process used to develop, review, and update policies regarding the use of drugs, therapies, and drug-related products, and identifies those that are most medically appropriate and cost-effective for a given patient population.[56]

Formularies are structured into levels or "tiers." ***Covered generic drugs***, sometimes called preferred generics, are typically placed on Tier 1. These are the least expensive drugs for the PBM/health plan and require the lowest patient co-payment. ***Preferred brand drugs*** for which no generic equivalent is available are assigned to Tier 2. ***Non-preferred brands*** and ***specialty drugs*** may be assigned to Tier 3 or 4. To create incentives for beneficiaries to use generics and preferred brands, PBMs will often charge much higher co-pays for non-preferred products. ***High cost specialty drugs*** and ***biologics*** are typically assigned to the lowest tiers on the formulary (i.e., Tier 3, 4, or even 5) for which the plan pays only a small amount, thus shifting the financial responsibility for the high cost of these drugs from the employer or health plan to the members themselves.

Formulary structures are becoming more complex over time. While the three-tier flat-dollar co-pay structure was standard in the PBM industry in 2008, with a 68% use rate, today it is used by only 44% of plans (a 24% decrease over 8 years). Four-tier formulary designs are taking its place, typically placing higher-cost. specialty drugs on the fourth tier. Four-tier structures, with either flat co-pay (the same dollar amount is paid for any drug on that tier) or co-insurance (a percentage of the drug cost to the PBM), are currently used by 28% of plans, compared with just 8% of plans in 2008.[57] Many plans, including Medicare Part D plans, employ a five-tier formulary structure.

PBMs update their formularies on a routine basis to account for changes in the commercial availability of brand and generic drugs, and to recognize the value of rebates that they have negotiated with manufacturers (i.e., in recognition of a significant manufacturer rebate, a PBM could move the manufacturer's drug or biologic to a 'preferred tier' on the formulary, thus reducing the member's co-pay/co-insurance and making the drug more attractive to the member/consumer.)

(b) **Prescription drug formularies: Medicare Part D plans**

Commercial PBMs contract with the Medicare program to manage the Part D benefit using approved formularies that are required to provide appropriate access to covered drugs, biologics, insulin, certain medical supplies and vaccines included in broadly accepted treatment guidelines. To be approved by the Medicare Program, the formulary must be consistent with best practices in formulary design.[58]

Current rules require that an insurer's Medicare drug list cover at least two drugs (unless only one drug is available) for a particular category or class, as these are defined by USP or another body.[59] The two-drug minimum requirement must be met through providing two chemically distinct drugs, not two dosage forms of the same drug, or a brand and its generic. More than two drugs for particular categories or classes may be required if additional drugs present unique and important therapeutic advantages in terms of safety and efficacy, and if their absence from the sponsor's formulary would substantially discourage enrolment by beneficiaries with certain disease states.[60]

In addition, a separate provision also requires plans to cover "substantially all" drugs in six drug classes:

- anticonvulsants;
- antidepressants;
- antineoplastics;
- antipsychotics;
- antiretrovirals; and
- immunosuppressants for transplant rejection.

Part D sponsors must also cover treatment of opioid dependence when medically necessary.[61]

In an effort to address rising costs of prescription drugs paid under Part D, the Trump administration proposed to remove from the protected class status any drug for which the price increased at a rate higher than inflation, and/or any drug that was simply a reformulation of an older, cheaper drug. The Administration had intended to retain the protected class mandate, but, with these exceptions, force drug manufacturers to manage down drug price increases. It also proposed to allow Part D plans to impose step therapy and prior authorisation restrictions on access to these protected clases. However, in

response to significant pressure from the pharmaceutical industry, the administration ultimately withdrew these proposed changes.[62]

The Centers for Medicare and Medicaid Services ("CMS") reviews the specific drugs, and the tiering strategies employed in each formulary to identify any strategies that are significantly different from common practices for managing drug benefits so that these can be evaluated before being approved.

The PBM must limit the number of formulary changes made over the course of a plan year, provide notice of any such changes to beneficiaries and their physicians, limit changes in therapeutic classifications, and provide a transition process for new beneficiaries.[63]

46brooklyn Research, a non-profit corporation that studies US drug pricing data, recently published an analysis of changes to Medicare Part D drug prices[64] in which it found:

- Some generic drugs are priced fairly and consistently across the board, while others show substantial pricing variations across Part D plans.
- Brand drugs do not show much pricing variability, but some Part D plans could be pricing brand drugs well below list price.
- Many generic drugs covered under Part D formularies are significantly overpriced and "over-tiered" (placing the drugs on a higher formulary tier for which high out-of-pocket co-pays are charged.)
- Some Part D plans are inflating specialty generics drug prices when compared to true market-based cost.

(c) **Prescription drug formularies: Medicaid plans**

Coverage of prescription drugs is an optional benefit in state Medicaid programs, though all 50 states and the District of Columbia currently provide a drug benefit. If states provide drug coverage, they are required to cover all drugs of manufacturers that have entered into rebate agreements with CMS when prescribed for a medically accepted indication. They may only subject a covered outpatient drug to prior authorisation, or exclude or otherwise restrict coverage, if the prescribed use is "off label".

In 2012, when direct-acting antiviral drugs ("DAAs") were approved for treatment and cure of Hepatitis C ("HCV"), clinical efficacy was found to be extremely high, with cure rates of 95 to 100% being reported. Despite this, because the cost of a full course of treatment can range from $16,000-$94,000 per patient, some state Medicaid plans had begun to deny coverage on the basis of the drug's high cost. In response, Medicaid Drug Rebate Program officials and CMS sent a series of notices to states to remind them of their statutory responsibility to cover these drugs, especially because of their significant clinical efficacy and elimination of additional downstream costs associated with progression of untreated disease.[65]

No single solution?[66]

Ultimately, there is likely no single, best policy for reducing drug prices in the US. Outside of certain government programs like Medicaid that purchase prescription drugs at discounts set by federal statute, competition is often the most effective way to drive down drug prices. When many generic versions of the same branded drug enter the market, competition can push prices down by as much as 80%.

Congress has already taken action to increase generic competition. A 2012 law authorised FDA to charge manufacturers user fees for reviewing their generic drugs, and those funds

have enabled FDA to accelerate generic drug reviews and approvals. But this does not address barriers in the market that keep some prices high, even for drugs whose patents have expired.

For example, Humira (adalimumab, AbbVie), prescribed to treat severe rheumatoid and other forms of arthritis, plaque psoriasis and Crohn's disease, is the best-selling prescription drug in the world, costing nearly $40,000 per year in the US. Since its approval by FDA in 2002, Humira has been protected from direct competition by patents that drive market exclusivity.

Some of today's most expensive drugs, like Humira, are biologics, and by 2016, these large-molecule drugs accounted for half of all FDA drug approvals. To encourage investment in them, biologics are awarded 12 years of market exclusivity. As a result, some of today's drug-pricing proposals focus on biologics. For example, the Trump administration recently proposed changing how Medicare pays for certain physician-administered drugs by linking their prices to the lowest price paid for the same drug in other national markets, a so-called International Pricing Index ("IPI"). Another proposal has been to reduce prices automatically once their market exclusivity period has expired.[67]

Pharmaceutical pricing and reimbursement

Changes in the US healthcare market, driven by an accelerating pace of drug discovery and practice innovation, have produced new, highly effective treatments for complex medical conditions. However, the discovery process, together with the growing number of individuals with prescription drug coverage, have converged to drive dramatic growth in prescription drug costs.

CASE STUDY: When *Gleevec (imatinib mesylate, Novartis)*, a highly effective treatment for leukemia, first came to market in the US, its list price was about $26,000 a year. Today, there are several highly-effective drugs in the same family on the market with an annual list price of about $150,000 each. What happened is that each new entrant cost more than its predecessors, which then also increased their prices to meet the higher price point. When the first generic version entered the market in 2016, its list price was only slightly less, about $140,000. This phenomenon is sometimes called "sticky pricing".

The Pharmaceutical Research and Manufacturers of America ("PhRMA"), a trade association for makers of pharmaceutical products, released an August 2016 report intended to put the costs of developing innovative drug therapies into context.[68] Among other things, it identified the changing economies associated with drug development in the current market and observed that appropriate use of expensive drug therapy can reduce the total cost of medical care dramatically for some classes of patients.

Setting the list price for prescription drugs

Prescription drug pricing is complex, but at bottom, there is a list price set by the manufacturer called the "Wholesale Acquisition Cost" ("WAC"). Average Wholesale Price ("AWP") has become the *de facto* trade price with a 20-25% mark-up over WAC.[69]

Manufacturers set the list price, or WAC for their products. This is the amount on which rebates, service agreements and price concessions are calculated for negotiating purchase price and payment amounts throughout the supply chain. In theory, manufacturers have great flexibility in setting WAC at any price point they wish, but in reality, their options are constrained by global market dynamics and the competitive environment. Manufacturers take a number of factors into account in setting WAC for a new branded prescription drug, including:

- **Cost of research and development**: The US Government Accountability Office ("GAO") recently reported that worldwide spending on research and development for single-source, branded prescription drugs increased in real dollars from $82 billion in 2008 to $89 billion in 2014.[70] The Tufts Center for the Study of Drug Development estimated that total capitalised costs for a single new FDA-approved drug were approximately $2.6 billion in 2013.[71] Other estimates place the cost of new drug development at between $648 million and $2.6 billion.
- **Role of mergers and acquisitions in the research and development pipeline**: Rather than undertake drug development in-house, large companies increasingly rely on M&A to obtain access to new molecules and to fill their product pipelines quickly without assuming the cost of clinical labs, research personnel.
- **Marketing costs**: The cost of marketing and promotional activities over the life of the product can far exceed R&D costs, and are factored into calculating WAC.
- **Competitive position in market**: Manufacturers of new, single source products with patent protection have maximum flexibility in setting the initial WAC and changing price over time, though pricing of any other drugs in the same class that that have already been launched to the market often sets a ceiling for WAC for subsequent market entrants.

Novel pricing models

As manufacturers face increasing pressure to lower drug prices, traditional "price per dose" models are giving way to newer approaches to pricing that more closely link drug price to drug value.

(a) **Indication-specific pricing**

Manufacturers may charge different prices for the same drug according to the indication for which it is used, so that the drug may be priced higher where treatment alternatives are fewer, or where treatment produces significantly better outcomes than existing alternative therapies.[72]

Sildenafil (Pfizer) received separate FDA approvals and unique drug codes for Viagra, sildenafil indicated for erectile dysfunction, and Revatio, sildenafil indicated for pulmonary arterial hypertension.

Manufacturer(s)	Payer(s)	Drug (Indication)
Amgen	Cigna CVS Health Harvard Pilgrim	Repatha (cholesterol)
Sanofi and Regeneron	Cigna	Praluent (cholesterol)
Amgen	Harvard Pilgrim	Enbrel (rheumatoid arthritis)
Eli Lilly	Harvard Pilgrim	Forteo (osteoporosis)
Eli Lilly	Harvard Pilgrim	Trulicity (diabetes)
Novartis	Aetna Cigna Harvard Pilgrim Humana	Entresto (cardiovascular)
Novartis	Humana	Gilenya (multiple sclerosis)
Merck	Aetna Cigna	Januvia and Janumet (oral diabetes drugs)
P&G and Sanofi	Health Alliance Medical Plans	Actonel (osteoporosis)
AstraZeneca	Harvard Pilgrim	Brilinta (acute coronary disease)
AstraZeneca	Harvard Pilgrim	Bydureon (diabetes)

Source: Sachs, Bagley 2018

However, manufacturers would only be able to negotiate reimbursement contracts for FDA-approved indications. Drugs that have significant off-label uses, even when supported by research, guidelines and compendia, are unlikely to be suitable candidates for indication-specific pricing, since a decision would have to be made regarding which price to be used for off-label uses. Manufacturers could not enter into contract negotiations that give the perception of promoting off-label use.

(b) **Outcomes-based pricing**

Manufacturers of high-cost specialty drugs may negotiate rebate agreements with customers according to the anticipated clinical outcomes associated with their drug(s) when taken as prescribed by individuals or subgroups of members. Such agreements can be very attractive to potential customers, but they may present financial and regulatory risks for both parties. To de-risk these types of agreements, the parties should exchange detailed information on drug performance, including data not on the label, and on the health status of the insured population. Manufacturers are cautioned to ensure that any data exchange is not viewed as off-label promotion. The number of outcomes-based pricing agreements has grown significantly in recent years. Table 2 (previous page) presents a list of select agreements that have been publicly announced.

(c) **Drug licences**

A drug licensing model offers the option of flat monthly or annual payment based on clinical appropriateness, similar to software licensing where the customer pays a fixed amount for a specified number of installations. A license-based model for antibiotics could reduce the financial disincentives associated with antibiotic development, such as low sales volume that occurs when providers try to use antibiotics sparingly to reduce the risk of drug resistance.

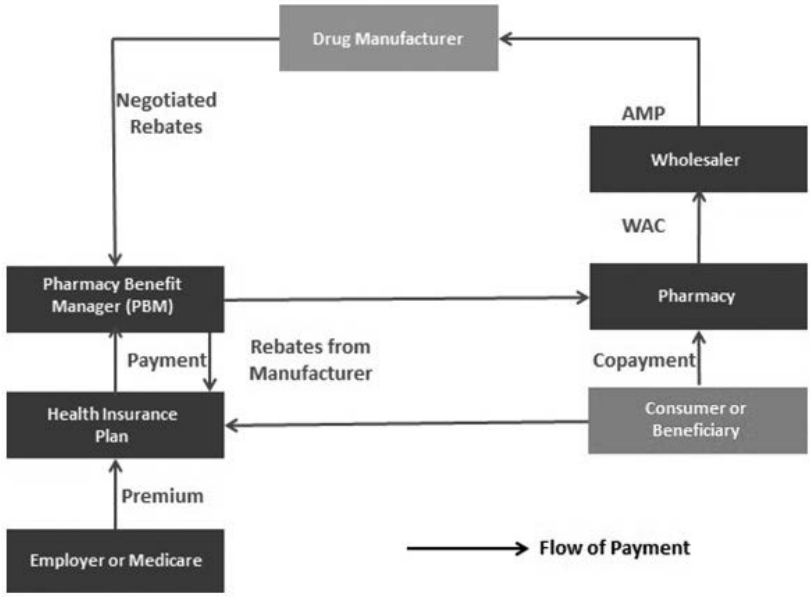

Fig. 6: Flow of money through US drug channels

Source: Congressional Budget Office

(d) **"Netflix" subscription model**

Similar to the drug licence model, the purchaser would pay a flat monthly or annual fee for unrestricted access to a specified drug. CMS has recently approved a number of state Medicaid plans' use of this model for purchasing hig- cost hepatitis C drugs.[73]

(e) **Drug mortgages**

Drug mortgages spread out payment over time. For example, direct-acting antivirals ("DAAs") can cure Hepatitis C with an eight-to-12-week course of treatment. But while the benefits of the cure accrue over a lifetime, under current models, the costs of the drugs ($16,000-$94,000) are recouped within a much shorter eight-to-12-week window of treatment, making the drugs unaffordable to some health plans.

(f) **"Buy-and-bill"**

For physician-administered drugs, healthcare providers use a "buy-and-bill" model in which a provider purchases the drug directly from a manufacturer or distributor, administers it to a patient, and then submits a claim to the health insurance plan for payment for the drug itself, plus a separate payment for administering the drug.

The flow of payment for outpatient prescription drugs

Generally, the manufacturer sells an outpatient prescription drug to a wholesale distributor at a list price set by the drug maker (WAC), minus discounts negotiated between the parties, typically 2 to 5. This discounted price is the Average Manufacturer Price ("AMP").[74] Additional discounts of 1 to 2% may be added to AMP for prompt payment, volume purchases, etc. The distributor then sells the product to a pharmacy at a price marked up to be roughly equivalent to WAC. A beneficiary buys the drug at the pharmacy after paying some form of cost-sharing (co-insurance or co-payment) set by his/her insurance plan. The insurance plan outsources management of its drug benefit to an intermediary, the PBM. The PBM negotiates with the pharmacy to set the co-payment and service fees that the pharmacy receives for dispensing the medication.

Manufacturer rebates to PBMs and health plans

Throughout the supply chain, participants exchange rebates, discounts, and other payments to encourage other entities to contract with them or to encourage purchasing a particular drug. For example, a manufacturer may offer a distributor volume discounts, prompt-pay discounts, or chargebacks if the manufacturer contracts directly with a pharmacy or health care provider. A manufacturer may also grant financial incentives or concessions to a PBM or pharmacy.

Manufacturers typically provide three types of rebates to PBMs:

- **Formulary rebates** are given in exchange for placing a manufacturer's product on the plan's formulary. They can be a substantial source of savings, anywhere from 0.5 to 0.75% of WAC. Manufacturers may offer even larger rebates if their products are placed on a preferred tier, or if their product is not subject to prior authorisation or other utilisation management. The rebate agreement may also require the plan to discourage use of competitor drugs by demanding that the plan impose a higher co-pay to purchase a competitor's product.
- **Market-share rebates** reward plans or PBMs for higher use of the rebated product than competing therapies.
- **Price protection rebates** are newer arrangements that compensate plan sponsors and PBMs if WAC rises beyond an agreed-upon percentage or dollar threshold. These rebates mitigate the risk of financial loses as drug prices go up.

Manufacturer discounts to distributors

The majority of outpatient prescription drugs are distributed through one of three companies; McKesson, AmerisourceBergen, or Cardinal Health. Sometimes referred to as the "Big Three", they collectively control between 85 to 90% of the US market.

Distributors have greater leverage in negotiations with manufacturers of multiple-source (generic) drugs because these manufacturers compete to gain a distributor's business. Thus, distributors often secure lower prices from manufacturers when purchasing generics, increasing the spread between the price at which distributors pay and sell a product. For this reason, distributors' profits are higher when handling generic drugs ($8 for every $100 spent on a drug at a retail pharmacy) than they are for brand-name drugs ($1 for every $100).

Another key financial arrangement between manufacturers and distributors is the "chargeback" used to compensate distributors after a drug maker negotiates directly with a third party in the supply chain (such as a pharmacy or health care provider), rather than going through the distributor. Under these arrangements, distributors may distribute drugs from a manufacturer to a pharmacy or provider and then "chargeback" the difference between a manufacturer's contracted price with a third party and the distributor's invoice price. Chargeback arrangements make up a substantial portion of distributors' net sales.

In the past two decades, distributors have reinvented their business models by charging manufacturers for additional services they provide, including packing and shipping drugs, data management, periodic retail demand information, current inventory levels, and reimbursement support services. In turn, manufacturers have developed performance-based incentives and discounts to encourage distributors to enter service contracts with them.

Manufacturer discounts to pharmacies

Manufacturers also negotiate directly with certain pharmacies and pharmacy chains. The market power of a pharmacy plays a key role in these financial relationships. Chain pharmacies that serve a greater number of consumers and hold higher market share are able to negotiate more favourable financial arrangements with manufacturers. These large chains stand in contrast to smaller pharmacies, which are less able to exert the necessary leverage to negotiate substantial price concessions. Pharmacies also exert greater leverage when negotiating for generic rather than brand-name drugs. This is mainly because, unlike plan sponsors and PBMs, pharmacies do not control or select the brand-name drug ultimately dispensed to the consumer. In contrast, for generic drugs, pharmacies select which product to stock from all available generic versions of a drug. As a result, generic manufacturers may offer discounts and rebates to pharmacies to encourage pharmacies to stock their product for consumers. Thus, while a drug's list price (WAC) may be a good indicator of the price pharmacies pay for brand-name products, pharmacies frequently pay below WAC for generic drugs.

Manufacturer rebates to Medicare

The Medicare program is the single largest purchaser of outpatient prescription drugs in the US. As such, if Medicare were to negotiate directly with manufacturers, it could exert significant pressure on them to demand deep discounts for purchasing their products, causing potentially major disruption to the global research-based biopharmaceutical industry ecosystem.

In fact, Medicare does not negotiate directly with pharmaceutical manufacturers. Rather, Medicare applies one of two different methods; one for drugs taken orally; the other for physician-administered drugs:

- **Medicare pays for orally administered outpatient prescription drugs under Part D**. Private health insurance plans and PBMs that have contracted with the federal government to administer the Medicare Part D benefit negotiate acquisition costs for outpatient prescription drugs independently. While they have sufficient size in their own right to negotiate attractive discounts with manufacturers, they do not negotiate as a block on behalf of the Medicare program.
- **Outpatient prescription drugs administered by a physician are paid under Part B**. Medicare pays for Part B drugs, that is, drugs administered by a physician or other healthcare professional, on the basis of a statutory formula: "ASP + 6." Each quarter, manufacturers report a weighted average of the sales prices offered to customers in each channel. This includes discounts applied. Medicare then takes the reported Average Sales Price ("ASP") and adds 6%. As product pricing and discounting varies from month to month, Medicare payment also varies.

Trump proposal to deliver rebates to beneficiaries at the point of sale

In January 2019, the Trump administration proposed to eliminate rebates currently paid by pharmaceutical manufacturers to PBMs,[75,76] to instead offer discounts directly to the beneficiary at the point of sale. The proposed rule aimed to change the incentives of the current pharmaceutical payment structure, primarily in Medicare Part D, where pharmaceutical companies are encouraged to set a high list price for their products, from which they negotiate with PBMs (acting on behalf of the insurance plans administering Part D) for a rebate on that list price, achieving a lower net price in the end. The difference between these two prices, which is now often referred to as the "gross-to-net bubble", has grown over time. But that rebate amount is often retained by the PBMs, not returned to the employer, health plan, or beneficiary. Trump's plan was strongly opposed by the pharmaceutical industry, and was ultimately withdrawn by the administration in July 2019.

Specialty drugs

Eighty-five per cent of health insurance plans in the US classify certain drugs as "specialty drugs" because they: (a) are very expensive (often more than $670 a month); (b) require special handling in the supply chain (e.g., temperature or shelf life); (c) must be administered by a healthcare provider; and/or (d) have significant side-effects that require counselling.

Specialty drugs make up only 1-2% of outpatient drugs prescribed, but represent 40-50% of drug spending, making them an important target for payers and policymakers. Current trends suggest that specialty drug spending will total $350 billion by 2020, or about 9% of US spending on all healthcare-related services.

Since the passage of Hatch Waxman in 1984, creating an abbreviated approval process for generic drugs, the practice of prescribing and/or dispensing lower-cost generics has grown to represent about 86% of all prescription drugs dispensed annually. However, any savings associated with generic substitution is being washed out by significant growth in both the number and the cost of new specialty drugs.

Orphan drugs

Orphan drugs are a class of products intended to treat rare diseases and disorders, defined as conditions that affect fewer than 200,000 people. Because of their more limited markets, the US Government created incentives to encourage manufacturers to develop these products, including tax credits for certain clinical testing, exemptions from certain user fees, and an extended period of market exclusivity totalling seven years.

Employer/PBM strategies to reduce drug spend

There are significant differences between drug prices set by a manufacturer, and the amount actually paid for its drugs in the US market. Manufacturer rebates to PBMs and pharmacies, government-mandated discounts that manufacturers must offer to Medicare and Medicaid, cost-sharing arrangements between employers or health plans and their employees/beneficiaries, all contribute to a complex web of confidential business agreements between and among players in the distribution channel for outpatient prescription drugs in the US. Employers and health plans actively participate in negotiating their purchase prices for individual drugs, but they have also developed strategies to manage the overall cost of the drug benefits that they provide to their members. Current strategies include:

1. **Substitute lower cost drugs**

   PBMs may recommend or require that lower-cost alternative drugs be dispensed in place of more expensive drugs when they are available and clinically appropriate.

(a) *Generic substitution*

Some PBMs encourage or require pharmacies to dispense the generic version of a brand name drug if a generic is available and both the prescriber and state law permit substitution.

Generic drugs have the same active ingredient, strength, dosage form, and route of administration as an NDA-approved brand name drug and share the safety and efficacy data of the reference drug. While they may be sold under different names than the reference brand, the FDA considers generic drugs to be "bioequivalent," or "therapeutically equivalent" to the reference product.[77]

Since the 1990s, use of generic drugs has grown dramatically, and while generic drug prices have themselves begun to increase over the last several years,[78] their use can still produce significant cost savings. In 2002, 40% of prescription drugs dispensed at retail pharmacies were generics. By 2015, that number had increased to about 78%. Today, nearly 85-90% of all prescription drugs sold in the US are generics, and the Association for Accessible Medicines, the trade association of generic pharmaceutical manufacturers, estimates that generics have saved consumers and the healthcare system $1.5 trillion in the past decade alone.[79,80]

(b) *Biosimilar substitution*

The Biologics Price Competition and Innovation Act of 2009 ("BPCI")[81] amended the Public Health Service Act,[82] to create a new regulatory approval pathway for follow-on biologic products similar to the abbreviated new drug application ("ANDA") process created by Hatch Waxman.

Biologics, such as human growth hormone, injectable treatments for arthritis, and stem cell therapy are much more complex than traditional, chemically synthesized drugs. Because they are manufactured from living organisms by programming cell lines, they are not identical, and thus are not technically "generic" biologics.[83] Rather, biosimilars are "***highly similar to or interchangeable with***" a reference product approved under a biologics licence application ("BLA").[84,85] A product is biosimilar if it is:

- highly similar to the reference product notwithstanding minor differences in clinically inactive components; and,
- there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product.

Some biosimilars are also considered to be "interchangeable" if they can be expected to produce the same clinical result as the reference product in any given patient, and the risk in terms of safety or diminished efficacy of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of using the reference product without such alternation or switch.[86]

The BPCI statute appears to allow PBMs to manage the cost of biological products by either excluding the more expensive reference biological product from the formulary, or implementing automatic edits requiring a beneficiary to use the less expensive biosimilar agent first, and only progress to use of the reference product if there were a lack of clinical efficacy or drug-related adverse event. It appears likely that PBMs would also implement rigid prior authorisation rules for beneficiaries to access branded biologics when a biosimilar is available.

2. **Apply a "pay-for-value" formula**

A number of independent organisations (i.e., with no ties to pharmaceutical manufacturers, employers or health insurance plans) have developed "value formulas" to provide systematic evaluation of the potential benefit of a new prescription drug or medical technology at various price points to a population of "covered lives". These formulas are intended to help employers, health insurers, and PBMs set the amounts they are willing to pay for the drugs they purchase.

One such organisation is the Institute for Clinical and Economic Review ("ICER"),[87] a non-partisan research organisation that evaluates the clinical and economic value of prescription drugs and other health care innovations objectively. ICER analyses clinical data and convenes key stakeholders at public meetings to translate this evidence of value into policy decisions that may help inform new product coverage and pricing determinations.

The ICER model includes steps such as:

- Objective evaluation of the clinical and economic evidence to account for potential benefit across a lifetime. This includes potential downstream cost offsets for new treatments that might take many years to be seen, and so that care options that might increase spending for one type of service (e.g. drugs) while reducing other spending (e.g. hospital costs) receive full credit for cost offsets and are not penalised in any way.
- Evaluation of the comparative clinical effectiveness of different treatment options through review of available evidence and judgment of the net health benefit of each.
- Acceptance of multiple forms of evidence, including high-quality randomised controlled trials ("RCTs"), but also observational analyses based on cohort studies, patient-reported data, and long-term registries, and the so-called "grey literature".[88]
- Consideration of other factors, including the ability to return to work, family and caregiver burden, impact on the public health, or on other aspects of the health system or society.
- Acknowledgment of the role of contextual considerations, such as severity of the condition, whether other treatments are available or other ethical, legal or societal priorities.

3. **Enter into risk-based contracts**[89,90,91]

Some payers negotiate risk-based contracts with pharmaceutical manufacturers under which the purchase price of certain high-cost drugs is tied to treatment outcomes, i.e.,

how well a drug works for specific segments of their member population. Such "value-based" deals are becoming more common, especially with very expensive specialty drugs. For example, when FDA approved Spark Therapeutics' Luxterna (voretigene neparvovec-rzyl) in 2017 for treatment of retinal dystrophy, the drug cost $850,000 a year. Spark offered employers and health insurance plans extended financing and rebates when no clinical improvement was observed.

(a) *Impact of risk-based contracting on "Best Price"*

Risk-based contracting presents potential challenges to compliance with complex Medicaid Best Price provisions. Manufacturers are reluctant to consider risk-based contracts because they fear that the variety of price concessions and services in a risk-based contract arrangement could lower a drug's best price, increase the manufacturer's Medicaid rebate obligations, and become a disincentive to pursuing such arrangements. (Note: this is not the average lowest price. A single rebate to a single customer could trigger Best Price.)

CASE STUDY: REIMBURSEMENT DENIED FOR HEPATITIS C CURE

A recent study found that government- and employer-sponsored health plans had denied reimbursement for more than 35 percent of prescriptions for Direct-Acting Antivirals ("DAAs") written for treatment of Hepatitis C between January 2016 and April 2017.
DAA therapy cures about 95% of people with chronic Hepatitis C, a viral liver disease that can cause liver failure or death, affecting about 3.5 million people. It kills 19,000 a year, according to the Centers for Disease Control and Prevention ("CDC"). However, one course of treatment with Harvoni is the same as the annual Medicaid cost for 29 people.
Examples of DAA drugs, which first became available in 2014, include:

Table 3: Estimated Price Range for Branded Direct-Acting Antivirals for HCV Treatment

Drug	Manufacturer	List price for course of therapy	Estimated price per pill
Harvoni (ledipasvir/sofosbuvir)	Gilead	$94,500	$1125
Sovaldi (glecaprevir/pibrentasvir)	Gilead	$84,000	$1,000
Epclusa (sofosbuvir/velpatasvir)	Gilead	$74,760	$890
Zepatier (elbasvir/grazoprevir)	Merck	$54,600	$650
Mavyret (glecaprevir/pibrentasvir)	Abbvie	$16,700	$200

Given the clinical benefits of curing chronic HCV infection, the cost-effectiveness of DAA treatment, and the importance of antiviral therapy to HCV elimination efforts, The high incidence of reimbursement denials adversely impacts strategies for HCV elimination.

Source: Gowda C, Lott S, Grigorian M, Carbonari DM, et al. Absolute insurer denial of direct-acting antiviral therapy for hepatitis C: A national specialty pharmacy cohort study. Open Forum Infectious Diseases. Volume 5, Issue 6, 1. June 2018, ofy076. https://doi.org/10.1093/ofid/ofy076

Regulators urge manufacturers to consult the regulations on determining Medicaid best price when negotiating value-based prices, and should "continue to document the calculation of best price, including any reasonable assumptions about the impact of their arrangements."[92]

4. **Deny reimbursement for expensive therapies**

   In order to manage the costs of providing health benefits, employers and health insurance plans may place restrictions on certain high-cost drugs, even when therapy can be highly effective in the near term and save significant downstream costs.

Manufacturer strategies to maintain drug prices: Financial assistance to consumers

Because the Wholesale Acquisition Cost ("WAC") or list price for a drug is the primary input to formulas used to calculate the purchase price of outpatient prescription drugs and the size of rebates offered to both private and government customers, higher WAC can be an important component of a manufacturer's global market strategy, despite the near-term barriers to access that it may create for individual consumers.

To help overcome these barriers, manufacturers commonly sponsor a number of programs to provide financial assistance directly to the individuals who purchase their products.

1. **Reimbursement support services**

   Many companies sponsor reimbursement support programs for prescribers and their patients who have health insurance. These programs are typically outsourced to third-party vendors who staff call centres from which they provide technical assistance, including insurance benefits verification, prior authorisation, and appeals support. Reimbursement support programs are generally offered as a service provided at "arm's length",[93] and at no cost to the prescriber.

   Manufacturers benefit from offering these programs to their customers because, in addition to facilitating access to reimbursement for their products and lowering price-related barriers to access, they are also educating current and future prescribers, patients and health insurance plans, introducing them to the brand and advising them on its clinical and economic value.

   US regulators monitor reimbursement support programs to ensure that the services offered are clearly delineated and that the offering does not grow into delivering free goods or services in exchange for prescribing or purchasing the drug, which could be viewed as a kickback.[94]

2. **Coupon programs**

   In recent years, PBMs and health plans have tried to guide patients toward less expensive drugs by making them pay a higher portion of a drug's costs when it is "non-preferred" on the formulary, or when a generic is available. Manufacturers have responded by raising the amount of temporary financial assistance they offer to customers through "co-pay assistance" cards – similar to a debit card – that reduce what consumers pay at the pharmacy. Coupons provide a form of direct financial support to customers regardless of financial means. They can be used to help build brand awareness and can create brand loyalty.

   Customers present drug coupons at the point of sale to receive an immediate discount. Figure 7 (following page) presents an example of one coupon.

   Individuals with government-sponsored health insurance (i.e., Medicare or Medicaid) are not eligible to use coupons because their use could be viewed as creating an illegal

inducement to purchase. In addition, some states, including Massachusetts, ban their use when a generic equivalent is available.

Payers and policymakers often criticise coupon programs for keeping individuals on brand when generics or other, less expensive alternatives are available. A recent study found that prescription drug coupon programs actually increase healthcare spending by billions of dollars a year.[95]

The researchers estimate that for brand-name drugs facing generic competition, coupons boost retail sales by 60% or more and increase spending by $30 million to $120 million per drug.

Fig. 7: Example of co-pay coupon presented at pharmacy.

Source: https://www.mavyret.com/copay-savings-card

To counter manufacturers' use of coupons, a number of PBMs have recently introduced new "co-pay accumulator" programs that segregate funds received from manufacturer coupons so that these amounts do not count toward meeting a member's deductible that must be paid before the pharmacy benefit begins to pay. Using coupons, the manufacturer covers most, or all, of the member's costs for the drug and these payments count towards meeting the deductible. But if the plan is using an accumulator, the member could still have to pay the deductible amount out-of-pocket once the co-pay card expires or runs out of money.

3. **Patient assistance programs ("PAPs")**

Patient assistance programs ("PAPs") provide a vehicle through which manufacturers can offer indirect financial assistance to individuals who use their products. These programs are generally administered through independent charitable organisations or by foundations established by the manufacturers.

Manufacturers make financial contributions to fund a charity or foundation which disburses funds on the basis of availability and individual need, determined according to a set of pre-established criteria.

Individuals apply directly to the PAP to request financial assistance. The program independently verifies financial need and may provide assistance if the requestor meets pre-specified criteria. The manufacturer cannot direct funds to any individual or group and cannot have access to detailed information about how or to whom their contributions are disbursed.

The U.S. Department of Health and Human Services ("HHS") Office of the Inspector General ("OIG") has continually acknowledged that properly structured PAPs can provide important "safety net assistance" to patients with limited financial means who cannot afford necessary drugs. However, these programs face increasing enforcement scrutiny from regulators and legislators on a state and federal level.

4. **Legal risks associated with financial assistance programs**

The federal Anti-Kickback Statute ("AKS") prohibits anyone from soliciting, receiving, offering, or paying any remuneration in return for a referral for an item or service that

may be paid for by a federal healthcare program.[96] Nonetheless, the OIG has approved certain independent charitable programs to help financially needy beneficiaries pay healthcare expenses when the programs are sufficiently independent from drug manufacturers, and do not violate fraud and abuse laws.

However, the OIG has noted that the AKS could be violated if a donation is made to a PAP to induce it to recommend or arrange for the purchase of the manufacturer's federally reimbursable items, and if a PAP's financial assistance to a patient is made to influence the patient to purchase (or induce the patient's physician to prescribe) certain items."[97]

In one case, United Therapeutics ("UT"), a Maryland-based biotech company, agreed to pay $210 million to settle allegations that it violated the AKS and False Claims Act by working through a foundation to pay the Medicare co-pays of patients taking its drugs. UT had allegedly made numerous donations to a charity, which in turn used the funds to pay the Medicare copays associated with UT's drug products for thousands of Medicare beneficiaries. The DOJ alleged that the charity routinely gave UT access to data which detailed how much the charity had spent to cover co-pays for UT drugs. The DOJ also alleged that UT maintained a program which offered free drugs to financially needy patients, but did not permit Medicare patients to participate, instead referring them to the foundation, thereby funneling claims to the Medicare program.

As a part of its settlement, UT entered into a five-year Corporate Integrity Agreement ("CIA") under which it established an Independent Charity Group, agreed to comply with rigorous requirements to ensure that the charity was independent from UT's commercial enterprise, and allowed government oversight and audits of its donations to PAPs.[98]

Policy issues that affect drug pricing and reimbursement

The Trump Administration has broadly endorsed changes to US policy on outpatient prescription drugs to require greater transparency in price setting, increased competition to drive quality and lower costs, and reduced regulatory burden to shorten time to market.[99]

Transparency in setting drug prices

Federal health policy makers have expressed grave concerns about the rising costs of prescription drugs in the US, but have taken little substantive action because the issue is so politically charged. The President has "tweeted" about reducing drug prices, and there was early concern that the Administration's Blueprint for lowering drug prices would include proposals to require drug makers to cut prices or limit their ability to increase them, but it did not.[100] Given deep division in the current political environment, it is unlikely that federal policy makers would be able to reach consensus on these issues in the foreseeable future.

However, a number of states have moved forward to implement new laws to contain prescription drug costs in their states.

For example, in June 2016, Vermont enacted a new law authorising the state attorney general to require manufacturers that had increased drug prices by more than 50% over a five-year period to provide justification for the cost increases. The state then posts this information for public review on an annual basis.[101] A new law in California requires manufacturers to provide 60 days' notice of significant price increases.[102] By March 2018, Oregon became the ninth state to enact similar legislation.[103]

A total of 16 states have introduced legislation requiring drug manufacturers to report the

rationale for drug price increases exceeding 10% over a 12-month period. Seven states also cap beneficiary cost-sharing for prescription drugs in employer-sponsored health plans.

At the national level, the Trump Administration tried to shed more light on the healthcare industry's opaque pricing practices by requiring Big Pharma to include drug prices in direct-to-consumer advertising, but a federal judge blocked that order in July 2019.

Increased competition

Medicare currently pays for outpatient prescription drugs taken by mouth under Part D, where it uses private PBMs to negotiate rebates with manufacturers, but pays for physician-administered drugs under Part B of the program. Because Part B payments are calculated on the basis of Average Sales Price ("ASP") plus some percent across all manufacturers of the drug, there is less competitive pricing pressure. To help drive down Part B drug costs, administration officials have talked about moving physician-administered drugs from Part B to Part D, where PBMs could secure more competitive pricing by negotiating manufacturer rebates. This is not a new idea, but would likely draw opposition from manufacturers that would be required to offer rebates on a broader range of their products.

The Secretary of the Department of Health and Human Services ("HHS") has also suggested that Medicare could use its administrative authority to eliminate negotiated rebates altogether, and transition to fixed-price discounting of prescription drugs for Medicare beneficiaries. This would be a significant change that could effectively give Medicare greater leverage to force price reductions.

Emerging trends

Three important trends are reshaping the US prescription drug market:

- Regulators appear willing to consider a broader range of evidence to support marketing approval and reimbursement for new drugs. If this trend continues, it could shorten the time to market for some products.
- Healthcare providers report that cost-containment has become their most important business priority. If this trend continues, purchasing agreements for expensive new drug therapies may be more difficult to execute, despite evidence of superior clinical efficacy. However, new products that offer tools to help providers contain growing healthcare costs will become more attractive to customers.
- A wave of vertical integration is changing the profile of the overall market. If this continues, it could make it more difficult to identify purchasing decision makers and give them greater leverage in negotiating drug prices. This trend could create new hurdles to successful commercialisation.

"Real World Evidence"

Before approving commercial use of a new drug candidate, FDA has traditionally required manufacturers to provide "substantial evidence" of efficacy from rigorous, well-controlled research on a study population that meets stringent inclusion criteria. While this methodology can provide clear answers to narrowly framed research questions, it also begs questions about product performance in the real clinical practice setting.

Through the 21st Century Cures Act, Congress directed FDA to accelerate the regulatory review process by considering the "totality of evidence"[104] on certain new drug candidates, ranging from rigorous clinical trial data to so-called "Real World Evidence" ("RWE"),[105] taken from claims data, longitudinal registries, and records on patients' satisfaction and social

determinants of health. Reviewing different types of data for approval could help drive more rapid adoption of clinical best practices and provide new tools for monitoring safe use.[106]

For example, FDA recently allowed researchers to create a "virtual control group" from a cohort identified through consulting a longitudinal population health registry in Finland for a study of treatment-refractory gastroesophageal cancer patients.[107] Using the virtual cohort allowed the study to be completed more quickly, and at lower cost, than if researchers were required to accumulate a randomised control group prospectively.

Cost containment

A recent survey of 146 US-based health system executives conducted by the Advisory Board Company[108] found that, while annual revenue growth continues to be an important business objective, cost containment has now become their primary strategic focus. With annual expense growth of 7% but revenue gains of only 6%, nearly two-thirds of respondents reported that preparing the organisation for sustainable cost control was their top aim, followed by adopting innovative approaches to expense reduction and diversifying revenue streams.

Health system CEOs recognize that with changes to reimbursement, the consolidation of traditional players in the drug channel, and the entry of non-traditional players like Amazon, sustainable cost containment becomes all the more urgent. These priorities will apply across the organisation and affect drug-pricing negotiations and purchasing decision-making. Manufacturers should evaluate novel pricing and contracting models discussed elsewhere in this chapter to help differentiate them from competitors.

Market consolidation through vertical integration

The PBM market is highly concentrated, with three PBMs (CVS Health, Express Scripts, and OptumRx) accounting for 85% of the total market, giving them significant leverage to negotiate deep rebates with manufacturers. In the current system, the size of specific manufacturer rebates, and the percentage of the rebate passed on to the employer or health plan, is confidential. This encourages manufacturers to set artificially high list prices, which they reduce through rebates to specific customers.[109]

To gain access to this information, large commercial health insurance companies, have recently turned to vertical integration. By moving PBMs in-house, they gain better control over rebate negotiations, and the opportunity to manage the total cost of care across medical and pharmacy services.[110]

This trend may create hurdles for new product adoption because:

- purchasing decision making is centralised at the corporate level;
- evidence thresholds for coverage and reimbursement are higher; and
- larger, vertically integrated entities have greater market share and, therefore, more leverage in rebate negotiations.

Successful market access

The US is the largest pharmaceutical market in the world. Arguably, it is also the most fragmented, and among the most difficult to enter and compete in successfully. Manufacturers should always take a global view when planning to enter specific markets to leverage investments made and assets developed in one market to help accelerate successful entry into subsequent markets. Presented below are 10 principles for successful market access.

Know the customer

Someone once observed that "When you've seen one market, you've seen one market. . ." Indeed, every healthcare and pharmaceutical market is unique.

The US healthcare market may be better described as "markets," because practice patterns, incidence and prevalence of disease, access to healthcare services, rates of health insurance coverage, and benefit design vary widely from one region of the US to another, suggesting that the profile of a typical customer will vary just as widely. For that reason, successful entry requires intensive listening, not just market research. Understanding how customers articulate the issues they face and the vocabulary they use to describe their unmet need should influence product design and evidence planning.

For example, a physician-administered drug that requires two intramuscular injections over a 48-hour period may face adoption hurdles if health insurers will only reimburse one office visit during that time period. Similarly, an economic model demonstrating the long-term cost-effectiveness of using an expensive new drug is unlikely to persuade a hospital operating room purchasing manager who is focused on reducing near-term product acquisition costs.

Successful products fit within clinical best practices and reimbursement policies. Evidence of treatment outcomes will be more persuasive if it demonstrates product value using the same language and the same measures that the customer used to articulate unmet need.

Engage stakeholders sooner, and frequently

Manufacturers should identify and engage stakeholders across the product lifecycle as early and as frequently as possible, keeping applicable regulatory restrictions on product promotional activities in mind. Thus, peer-reviewed journal articles, scientific poster presentations and discussions with patient advocacy groups on new research to address unmet medical needs all present opportunities for appropriate engagement with these stakeholders to build their interest and educate them about new products. In fact, manufacturers should proactively develop and refine an "end-to-end" evidence strategy to provide opportunities for ongoing engagement with key stakeholder groups about new product value.

FDA has recognized the importance of this type of customer engagement, and has recently released guidelines on the types of communication with stakeholders that are permitted because they comply with FDA regulations on promotional activities for prescription drugs. For example:

- In its guidance on medical product communications, FDA indicated that manufacturers are permitted to provide information to PBMs and health plans about unapproved products and unapproved uses of approved drug products if that information is "truthful and not misleading." The Agency commented further that this type of communication could eventually help accelerate coverage and payment decision-making after the products have been approved.[111]
- Similarly, in its guidance on communicating with payers, formulary committees and other entities,[112] FDA noted that providing healthcare economic information that pertains to the economic consequences of treating, preventing, or diagnosing a disease to PBMs and health plans before approval is also permitted. Early discussion with potential customers about the anticipated economic benefits of using a new product may improve customer "readiness" to make the purchase by giving them time to develop internal financial models they need to be able to purchase the product, thus shortening the overall sell cycle.
- Finally, through the Cures Act,[113] Congress directed FDA to provide guidance on the types of healthcare economic information that can be provided to customers through

distribution of evidence dossiers, reprints from peer-reviewed journals, software packages comprising a model with user manual, budget-impact models, slide presentations, payer brochures, etc.

In general, FDA anticipates that PBMs, health plans and other entities will review this information through deliberation as part of their process of clinical and financial oversight of selecting appropriate drugs for coverage and reimbursement.

FDA also advises manufacturers that present such information to identify and clearly acknowledge any weaknesses or limitations of the data. While drug companies may prefer not to do so, these frank observations about data quality demonstrate the company's understanding of the importance of robust evidence, and often lead to the PBM/health plan being more willing to take subsequent meetings with the company.

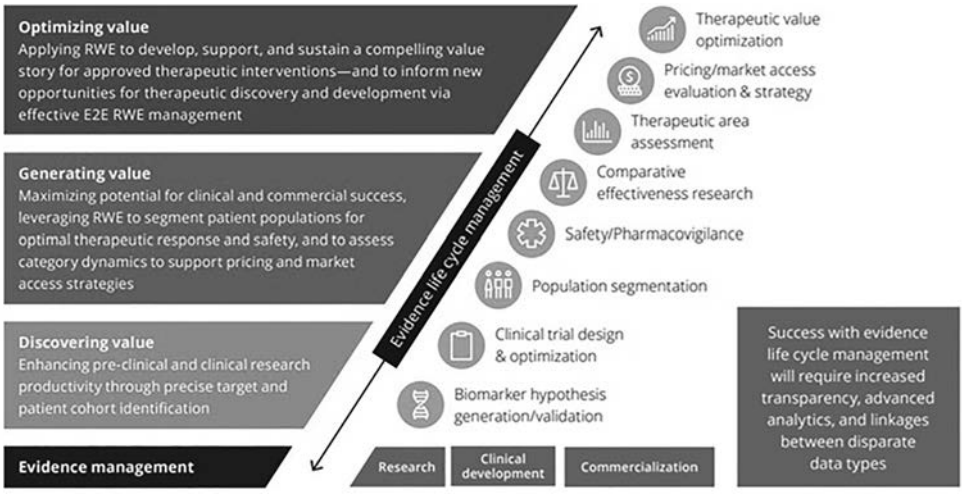

Figure 8: "End-to-End" Management of Evidence Across the Product Lifecycle

Source: https://www2.deloitte.com/content/dam/insights/us/articles/4354_Real-World-Evidence/DI_Real-World-Evidence.pdf?elqTrackId=cba898115de54fb5a9dc04206f4de617&elqaid=453&elqat=2

Build an evidence plan

Successful market entry demands continuous, "end-to-end" evidence development and strategic communication across the product lifecycle. As the drug company listens deeply to customers' needs and responds with effective solutions, it should develop and communicate new, robust evidence of clinical effectiveness appropriate to each stage of product commercialisation. Deloitte's life sciences and healthcare consulting practice, ConvergeHEALTH, recently developed a useful graphic to help demonstrate the importance of continuous evidence development, presented opposite as Figure 8.

Conduct a thorough legal and regulatory assessment, including an analysis of the risk of regulatory non-compliance and trends in enforcement

Drug companies should conduct an in-depth assessment of the legal and regulatory landscape in the markets they target for new product entry. In the US, a complex web of federal and state laws, licensing requirements, mandatory coverage regulations, inconsistent coverage and formulary placement by PBMs and health plans, etc., will all be relevant factors to consider.

Companies already familiar with US market dynamics through their experience with other commercial products should nonetheless confirm their understanding of specific requirements applicable to the new product class and intended use. If competitors have already entered the market with similar products, analysis of publicly available information on their product and any legal or regulatory hurdles that they may have faced would be instructive.

For example, if the government were to change the way Medicare pays for physician-administered drugs by moving them into Part D, how would that affect pricing for a product that is currently reimbursed at an appropriate rate under Part B? Drug companies should conduct these types of risk analyses early in the product commercialisation cycle.

Understand changing market dynamics

Continued focus on improving treatment outcomes while also reducing cost, is forcing stakeholders throughout the drug channel to bring innovative solutions to their customers; innovation that eventually sparks both new competition and new regulation. Drug makers that proactively monitor these market dynamics will be well-positioned to set the standard for future innovation by introducing new products and services that meet the changing needs of customers within a changing regulatory environment.

For example, renal dialysis has become a major area of growth in the US because the prevalence of diabetes and other kidney diseases has exploded. Now the seventh-leading cause of death in the country, diabetes affects 30 million Americans, or more than 9% of the population. Another 84 million Americans have pre-diabetes, a condition that can lead to Type 2 diabetes within five years. More than 1.5 million new cases of diabetes are diagnosed each year.[114]

Trends suggest that an increasing number of people require kidney dialysis earlier in their lives and for a longer period of time. Because the Medicare program has reduced payment for dialysis in the hospital, fewer and fewer hospitals are offering these services.

Renal dialysis is treatment-intensive, requiring about four hours a day, three times a week.

By monitoring market dynamics, dialysis providers Fresenius and DaVita anticipated the need to deliver affordable, intensive services at convenient times and locations for a rapidly growing population, and have opened smaller facilities located in the community, in shopping centres and strip malls that are more convenient for patients to get to, relatively inexpensive to build, and profitable to operate.

Develop a network of advocates among thought leaders and patients; engage them as "partners", not "customers"

Increasingly, drug companies need strong support from clinical thought leaders and from the patient community to advocate for accelerated approval and broad commercial availability of expensive new drugs.

The following is one remarkable example. In 2016, Sarepta Therapeutics submitted a new drug application ("NDA") for Exondys 51 injection (eteplirsen) for the treatment of progressive muscle wasting associated with Duchenne muscular dystrophy.

As part of its routine drug review and approval process, FDA convened a clinical advisory panel to study the data submitted in the NDA and recommend whether it should be approved for commercial use. Panel meetings are open to the public. At the Exondys meeting, the panel recommended that the drug not be approved because the available evidence was insufficient to demonstrate the drug's effectiveness. While not required to do so, FDA generally follows the recommendations of their advisory panels.

Members of the Duchenne patient advocacy community were furious and engaged in heated debate with the panel both at the meeting and in the press.

Despite the panel's recommendation, and at least in part because advocates from the Duchenne patient community had objected so strongly, FDA ultimately approved the drug for commercial use, with the caveat that the company collect additional postmarket data.

Sarepta priced the product at $300,000 for a one-year supply. Even though the number of patients is very small, health plans refused to pay such a high price for the drug, creating a situation where the drug was available, but not affordable. In response, clinical thought leaders and patients and their families met with health plans repeatedly to appeal the decision to refuse payment. Because of this intensive advocacy work, an increasing number of health plans will now pay for the drug.

Provide tools to measure and report product-related treatment outcomes

Drug manufacturers should develop tools to help their customers measure and report the clinical and economic impact of product use. Was the product clinically effective? Did its use reduce downstream treatment costs? Despite its high price, was the product cost-effective?

If the manufacturer can provide an easy-to-use tool to capture and analyse this data in a manner that customers can use, they can report it to formulary committees, health plans and other stakeholders. In addition, the manufacturer can use this real-world evidence to support price-setting decisions and to strengthen its position in rebate negotiations with PBMs.

Consider new models for pricing and contracting

Increasingly, PBMs and health plans ask drug companies to assume some or all of the financial risk associated with ineffective treatment. Especially in cases of ultra-high-cost specialty drugs, PBMs and health plans have demanded these arrangements as a condition of purchase. In these cases, manufacturers sell the product at full cost and then rebate the agreed amounts for the number of cases where specific treatment outcomes were not achieved.

Proposing new pricing and contracting models can help differentiate products from their competitors, but there can be risk associated with their use. For example, how is an episode of care defined? What is the appropriate performance metric? Is the treatment population comparable to the population(s) that the drug company has studied? Will the treatment effect be comparable?

Manufacturers should examine new pricing and contracting models and may be forced into accepting these types of agreements in order to access the market, but successful risk-based contracting demands careful analysis of multiple factors and sharing a considerable amount of data between the parties.

Take the long view, then take the short view

Successful market access strategies require commitment to and investment in developing assets that the company can leverage to adapt to new market dynamics and shorten the time to reach peak sales. By understanding or anticipating the clinical and economic evidence, the level of experience with product use in real world medical practice, and the clinical and patient advocates needed to be successful, companies can work backwards from the ultimate goal to plan a process to develop such assets in efficient, priority order.

For example, a company may intend to enter the US market (the "long view"), but find that, despite the ability to commit significant time and money, the regulatory and competitive hurdles are too high to overcome. Rather than waste these resources, the company might

target smaller markets with lower barriers to enter first (the "short view") where it can build the assets (data, experience, customer relationships) necessary to enter US market later. This type of process can significantly shorten the time that the company would otherwise have needed to achieve market share.

Do not underinvest

As a corollary to the principle above, the company that chooses to enter smaller, less complex markets first must nonetheless invest sufficient resources to be successful in those markets, and to generate an early revenue stream that builds the confidence needed to leverage the assets developed there in subsequent complex markets.

* * *

Glossary

Actual acquisition cost (AAC). Defined in federal regulations (42 CFR 447.502) as a state Medicaid agency's determination of the pharmacy providers' actual prices paid to acquire drug products marketed or sold by specific manufacturers.

Average manufacturer price (AMP). The average price paid to the manufacturer for the drug in the United States by wholesalers for drugs distributed to retail community pharmacies and retail community pharmacies that purchase drugs directly from the manufacturer. The calculation of AMP excludes the prices paid by certain payers (e.g., Department of Veterans' Affairs, Department of Defense, or Federal Supply Schedule) and providers (e.g., hospitals, long-term care facilities, mail order pharmacies, or managed care organisations) and certain discounts to wholesalers (e.g., prompt pay or bona fide service fees). In the February 2016 final Medicaid drug rule [CMS-2345-FC], CMS provides detailed technical guidance related to the calculation of AMP.

Average wholesale price (AWP). List price from a wholesaler to a pharmacy. AWPs for drugs are reported by pharmaceutical manufacturers and published in commercial clearinghouses such as Redbook, MediSpan, First DataBank, and Elsevier Gold Standard.

Best price. The lowest price available to any wholesaler, retailer, provider, or paying entity excluding certain governmental payers such as the Indian Health Service, Department of Veterans' Affairs, Department of Defense, Public Health Service (including 340B), Federal Supply Schedule and Medicare Part D plans.

List price. Most often the wholesaler acquisition cost (see below) is reported as the list price of a medicine. Typically, this price influences the final price paid at the pharmacy, but is often not the exact price. Intermediary markups and the design of the individual's health insurance plan influence the actual price paid by the individual and the insurance plan.

Outpatient prescription drug. Drug obtained with a prescription and typically dispensed from a retail or other outpatient pharmacy. Outpatient prescription drugs do not include drugs provided as part of or incident to, and in the same setting as, inpatient and outpatient hospital services, hospice services, dental services, nursing facility and intermediate care facility services, and physician services (e.g., physician-administered drugs).

Wholesaler acquisition cost (WAC). Price paid by a wholesaler for a drug purchased from the wholesaler's supplier, typically the manufacturer of the drug. WAC amounts may not reflect all available discounts, such as prompt-pay (cash) discounts.

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38. 21 CFR § 201.100(d).

39. 21 CFR § 202.1.
40. See: *Amarin Pharma Inc. v. FDA*, 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015).
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42. *Id*.
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44. Detailed information on both the Medicare and Medicaid Programs, including regulations, operating manuals, coverage, coding and payment information for healthcare products and services can be found at the CMS website: https://www.cms.gov. CMS is headquartered in Baltimore, MD.
45. An amount paid on a monthly basis to qualify for Medicare and other health insurance plans.
46. An amount paid by the beneficiary out of pocket before the health insurance plan begins to cover healthcare expenses.
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allow it to determine which drugs it would cover in its Medicaid program. The state had filed a waiver request to establish its own drug formulary similar to private insurance companies. Medicaid drug programs have historically covered all medications albeit with some prior authorisation requirements. Massachusetts has seen its Medicaid population jump more than 30% since it expanded Medicaid under the Affordable Care Act. In total, Medicaid covers 2 million Massachusetts residents, or one-third of the state's population. Massachusetts said it needed the option to more closely control Medicaid drug costs, which have risen 13% every year since 2010.

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