GLI GLOBAL LEGAL INSIGHTS

Pricing & Reimbursement

2021

Fourth Edition

Contributing Editor: **Grant Castle**

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Published by Global Legal Group

GLOBAL LEGAL INSIGHTS – PRICING & REIMBURSEMENT

2021, FOURTH EDITION

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We are extremely grateful for all contributions to this edition.
Special thanks are reserved for Grant Castle of Covington & Burling LLP for all of his assistance.

Published by Global Legal Group Ltd.
59 Tanner Street, London SE1 3PL, United Kingdom
Tel: +44 207 367 0720 / URL: www.glgroup.co.uk

ISBN 978-1-83918-134-4
ISSN 2517-6463

Printed and bound by TJ Books Limited, Trecerus Industrial Estate, Padstow, Cornwall, PL28 8RW
July 2021

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PREFACE

Welcome to the 2021 edition of *Global Legal Insights – Pricing & Reimbursement*.

I hope this is a valuable resource for those seeking to navigate the ever-changing landscape for the pricing and reimbursement of medicines, with all the inherent complexity and challenges.

The *Guide* contains a summary of the rules and practices in 18 jurisdictions in a wide array of geographic locations and highlights the many and varied approaches the countries have developed to control the prices and reimbursement status of vital medicines. The authors have worked hard to offer their perspectives on the most recent developments in their own jurisdictions and to explain significant changes and key trends. The authors also discuss policy issues that affect pricing and reimbursement decisions. These include efforts to address 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 issues that affect every jurisdiction, including global budgets, competition, fraud, and domestic and international politics.

There are many challenges for both the companies that develop and market medicines and the payers that must allocate healthcare budgets and spend taxpayer money judiciously. Those budgets are becoming more and more limited, while populations are growing and becoming increasingly elderly. Many jurisdictions have faced years of austerity following the 2008 financial crisis and now face further challenges as a result of COVID-19.

From the innovative industry perspective, we have seen changes in the focus of research efforts and the nature of the medicines it develops. There has been a shift from drugs for large patient populations treated primarily by general practitioners in primary care to more specialist medicines, where treatment is either initiated or delivered in secondary hospital settings. There is a greater focus on diseases that are difficult to treat, such as cancers, neuro-degenerative, auto-immune and viral diseases. Oncology is a particular challenge, since treatment is often towards the end of a patient's life, where even a successful medicine may not save a patient, but could extend the time patients can spend with their families and loved ones. Pricing and reimbursement systems have struggled to value the precious but often poor quality life extension that these products offer.

The challenges are perhaps even greater for orphan or ultra-orphan medicines that treat small patient populations with what is often an unmet clinical need. Despite the regulatory market exclusivity protections that are used to incentivise the development of these medicines, companies will only recoup their development costs if healthcare systems can find ways of pricing and reimbursing products that are necessarily expensive. Meeting that challenge will ultimately determine whether companies continue to develop these vital products, and is often the difference between the failure or survival of the many small companies that operate in this space.

These challenges and the need for new pricing and reimbursement mechanisms to address them can only become more acute as companies move into the regenerative medicine space. Gene and cell therapy products often treat tiny patient populations but – particularly for gene therapies – may offer a cure for seriously debilitating or fatal diseases. If patients are treated young, a single treatment may promise a long, healthy and fulfilled life. Companies want a return on their investment, but the high prices of these treatments – often in the millions of the relevant currency – are often out of kilter with existing mechanisms for pricing and reimbursement of even orphan medicines.

The challenges are therefore many and varied and the actions payers and companies are taking to address them are equally as diverse. In many cases, there is no easy solution because of the challenges of dealing with finite healthcare budgets and the need to allocate carefully the hard-earned funds that taxpayers provide.

From a pricing perspective, fewer and fewer countries offer industry freedom of pricing. Many jurisdictions run pricing approval processes, where they seek to impose or agree a price, often on the basis of some form of health economic assessment or by reference pricing. The ways those reference pricing mechanisms work also vary. Some are external, focusing on costs of medicines in a selected number of other jurisdictions. Others run internal reference pricing systems, where prices are set

relative to other products for a particular condition. In the latter case, increased competition and the availability of generic medicines will often force prices down.

Once prices are set, the next question is whether or not a product will be reimbursed. In many cases, the agreement or setting of a price will necessarily mean that reimbursement follows, but that is not always the case. An increasing number of jurisdictions are relying on health technology assessment processes to determine whether reimbursement of a product at a price is a cost-effective use of health service resources. These often rely on complex health economic evaluations, in a pure sense, where the relevant body first assesses the effectiveness of a product and then seeks to determine whether that provides value for money. A good example is the process run by the UK's National Institute for Health and Care Excellence ("NICE"), which relies on the health economic concept of the quality-adjusted life year ("QALY") to assess the cost-effectiveness of a product relative to one or more comparators. Only if the incremental cost-effectiveness ratio ("ICER") falls below certain financial thresholds will the product be reimbursed.

Many other jurisdictions carry out similar processes, but also consider therapeutic benefit or try to factor in certain value judgments, including whether the product responds to an unmet need, whether the condition is seriously debilitating or whether the products are life-extending. Many now accept that the emergence of drugs for increasingly small patient populations and regenerative medicines now requires such value-based judgments. These are very difficult to apply in practice because these value-based judgments are inevitably subjective and many health economic assessment bodies find making them particularly challenging. They will therefore often tend to gravitate towards pure health economic assessments in situations where those assessments are simply not fit for purpose.

The same could be said for health technology assessment of drugs used in combination, a feature of the treatment of many conditions, including cancers and viral diseases. Inevitably, the cost associated with the use of multiple products in combination may not be reflected in incremental clinical benefits and this means that a conclusion that the combination is a cost-effective use of health service resources becomes increasingly unlikely.

Whatever the approach, these health economic assessments are often time-consuming, costly and burdensome and are typically seen in only a small number of developed countries, although there are moves towards joint health technology assessments by multiple jurisdictions. The result is an increased focus on steps that health services can take to manage healthcare expenditure after pricing and reimbursement procedures are completed. This has resulted in increased use of managed access agreements, whereby companies will seek to agree the terms upon which products may be purchased and used within a healthcare system. These can be – and often are – simple financial arrangements providing for either additional discounts or rebates. However, there is often tension between selling products at a discount and the potential impact on pricing in other jurisdictions that use external reference pricing. The confidentiality of discount or rebate arrangements can then become paramount. Payers are well aware of this tension and we see a focus on increased transparency of net or discounted prices. A WHO Resolution on Price Transparency (available at https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_ ACONF2Rev1-en.pdf) encourages states to "*take appropriate measures to publicly share information on the net prices of health products*", i.e., the "*amount received by manufacturers after subtraction of all rebates, discounts, and other incentives*". A number of jurisdictions, such as Italy, have responded by refusing to treat the financial arrangements that they agree with companies as being confidential.

In summary, pricing and reimbursement of medicines has become an increasing challenge for industry and payers, particularly in oncology, the orphan/ultra-orphan space and for innovative regenerative medicines. Payers are becoming more and more creative when seeking to achieve the right price. This publication does not claim to provide solutions to all these issues, but I hope that it would be a useful navigation tool during many products' journeys to the patients that need them.

Grant Castle

Covington & Burling LLP

Market access to medical innovations and relevance of international pricing

Dr. Lincoln Tsang, Margaux J. Hall & Hannah Kerr-Peterson
Ropes & Gray LLP

Introduction

Various key geographical markets have developed new pathways and policies to facilitate the earlier adoption of new medicines and medical technologies to stimulate research and development (R&D) and to promote regional competitiveness. These include break-through designations and, most recently, the 21st Century Cures Act in the US and PRIME designation in the EU. In December 2020, the European Commission published Pharmaceutical Strategy for Europe. It puts forward a patient-centric, EU-based approach to pharmaceutical policy that envisages enhancing quality and safety of medicines to build a stronger EU wide health policy framework. Following its departure from the EU, the UK has also enacted new primary legislation seeking to expedite product approval of, and improve market access to, transformative medicines and medical technologies with a view to stimulating R&D and improving patient outcomes.

But despite these scientific and regulatory endeavours, payers and policymakers are increasingly objecting to rising healthcare costs. Cost-containment measures have resulted in many innovative therapies, including advanced therapies and those intended to treat rare diseases, not being adopted for clinical applications or otherwise not being made available to patients – through their exclusion from coverage and reimbursement based on their perceived impact on affordability and/or based on the uncertainty of the clinical effectiveness in a real-world setting.

The new reality is that global spending on prescription medicines in 2020 was estimated in the region of $1.3 trillion. The United States alone spent in the region of $350 billion. It is projected that these spending rates will likely increase at a rate of 3%–6% annually worldwide through 2025, reaching in the region of $1.6 trillion in total market size in 2025. This excludes spending on COVID-19 vaccines, where total cumulative spending through 2025 is projected to be $157 billion.[1]

Thanks to more targeted therapies – as a result of the investment in gaining greater understanding the genomics to identify new molecular targets – cancer treatments account for a significant proportion of prescription medicine costs. It has been reported that in 2018, global spending on cancer treatments was approximately $150 billion, and has since increased by over 10% annually.

Moreover, in recent years, there is greater impetus among global organisations and NGOs such as the World Bank and the World Health Organization to promote universal health coverage. Various stakeholders have embraced universal health coverage, with the goal of ensuring that patients have equitable access to healthcare they need without suffering financial hardship. The push for universal health coverage is particularly strong in low and

middle income countries as part of the global health sustainability agenda. More broadly, to achieve the objective of equitable access, the NGOs and governmental organisations are more closely scrutinising drug pricing. Some are demanding greater transparency in drug pricing and/or are advocating for international price referencing (see below).

Governments in different jurisdictions are contemplating new approaches to government reimbursement of new therapies – whether by reforming government reimbursement structures or setting prices based on an assessment of "value". Yet, while governments aim to address drug prices, most governments simultaneously acknowledge the importance of preserving incentives for innovation. In this regard, present-day drug pricing debates come at an interesting moment in time as the COVID-19 pandemic has reinforced the significance and the urgency of rapid biopharmaceutical innovation. The pandemic has brought into stark light the need for deliberative drug pricing policy that balances the competing needs of (i) new financing approaches for novel therapies, with (ii) preserved – or even enhanced – incentives for biopharmaceutical innovation. No doubt the COVID-19 pandemic will continue to be an important backdrop to international drug pricing debates. As we reflect on the drug pricing legal and policy debates unfolding in various jurisdictions across the globe, the following converging themes emerge:

Strong, and growing, interest in value-based pricing

Value-based pricing has been a prominent feature of policy discussions. Specifically, governments have expressed an increased desire to achieve better value for money in healthcare spending while keeping incentives to innovate. Accordingly, "value-based pricing" has gained increasing momentum. Underlying the principle of "value-based pricing" is the notion that prices of new medicines and technologies reflect their "value" to the society, as assessed against a range of criteria for the purpose of reimbursement. One important aspect of the value-based approach is that pricing strategy involves more than just setting a price. The strategy seeks to capture the value that is generated in the product development to differentiate the new treatment modality from the existing therapy because the former will fulfil an unmet medical need. It necessitates an early understanding in product development of what constitutes value to guide product development decisions so that the relevant evidence is generated. Differential value assessment is influenced by clinical, health economic and societal considerations. The assessment may vary considerably according to disease area, treatment regimes and patient characteristics.

"Value" can be technically defined as "what consumers would be willing to pay or to give up for a good or service". Under this definition, the value proposition will depend upon the perspective from which the assessment is conducted. What a patient considers valuable may not be the same as what a physician considers valuable. Moreover, the interests and values of different stakeholders, such as payers, healthcare providers or producers of medicines and medical devices, may not be aligned. Moreover, value refers to the specific features attributed to a given drug in a particular context, such as its degree of innovation, availability or accessibility, or its importance in relation to public health. Therapeutic value has been defined as "the effect conveyed on a patient following administration of a pharmaceutical which either restores, corrects or modifies a physiological function(s) for that patient".

In jurisdictions like the U.S., value-based pricing is a novel concept when it comes to government payment for drugs. In the U.S., not only does the current legal framework for government reimbursement of drugs not expressly anticipate value-based pricing, there are multiple legal barriers to innovative financing and value-based arrangements that impede implementation of such arrangements even in commercial (i.e., non-governmental) markets.

Accordingly, a shift to value-based pricing models would necessitate certain legal reforms to allow for the types of multi-year, patient-tracking-based, value-based payment models that payers (and drug developers) might wish to pursue in the U.S.

At the same time, the implementation of value-based pricing models can lead to complex and contentious issues. While the rhetoric of policy makers and diverse stakeholders generally aligns in advocating for value-based pricing models, when it comes the time to execute value-based pricing, stakeholders must answer the thornier question of *how* to assess the value of a therapy and *who* should be tasked with doing so.

The UK's healthcare delivery is principally provided through the single payer system, the National Health Service. The NHS spends about $22 billion annually on pharmaceuticals, of which approximately $14 billion is spent on branded drugs – representing 13% and 10% of the allocated budgets by the Treasury. Growth in NHS funding is expected to slow, meaning that access to innovative technologies will depend on savings found elsewhere. The UK Department of Health and Social Care uses the pharmaceutical price regulation scheme to control expenditure on branded drugs. This is notwithstanding the fact that manufacturers enjoy freedom of pricing in the UK. However, there are several indirect controls which influence the price set by a manufacturer. The National Institute of Health and Care Excellence (NICE), a non-departmental body of the Department of Health and Social Care, is responsible for determining the "value" of branded drugs. Establishing the value of a drug requires an assessment of whether the additional health expected to be gained from its use exceeds the health forgone as other NHS treatments are displaced by its additional cost. This is achieved by comparing the incremental cost effectiveness ratio (ICER, the ratio of the additional health gained to the additional costs) with a threshold for cost effectiveness. NHS bodies are legally obliged to fund the treatments NICE has recommended.[2] In practice, the supplier of a drug with a high list price will often be prepared to negotiate a discount in order to obtain a positive NICE recommendation. Moreover, the UK policy is to control market access to innovative products by placing a limit on the total NHS spending on branded prescription medicines.

Certain key European countries consider "innovation" as a key determinant for assessing value. Innovative technologies or medicines could be considered in the context that they are either more effective, or cause fewer or milder adverse effects, or are easier to use than existing therapies used for the same condition, although not all commercial innovations have the same therapeutic value. Specifically, the degree to which a product improves health outcomes is considered a core criterion in many European countries coupling with the need to take into account cost-effectiveness or budget impact.

In the U.S., third-party entities such as the Institute for Clinical and Economic Review (ICER) are playing an increasingly prominent, and controversial, role in such discussions of value-based pricing. ICER has been active in assessing a "value" of new-to-market therapies, and in analysing drugs that have had substantial price increases that, in the judgment of ICER, are unsupported by adequate evidence.[3] Recently, ICER indicated that it intends to evaluate the coverage policies of drugs across the largest commercial plan formularies (evaluated based on covered lives) to determine whether the plans are offering "fair" access to treatments.[4] As the scope of ICER's work expands, ICER's role has been controversial. ICER has been criticised for having an "arbitrary, nontransparent, non-peer-reviewed" analysis that, nonetheless, can adversely impact patient access to therapies.[5] Furthermore, ICER's use of the QALY framework in connection with analyses has drawn concerns that less effective, but cheaper, treatments will be prioritised over more effective therapies.[6]

We expect that questions of who is qualified to evaluate value, and based on what metrics, will continue to feature prominently in drug pricing discussions globally. Furthermore, we expect that this trend towards "value" and cost-effectiveness will intensify with the increasing emphasis on personalised or precision medicine, including in connection with advanced therapies such as gene-, cell- and tissue-engineered products, as well as those intended for treating debilitating and life-threatening conditions. The methodological approaches used to assess therapeutic benefits and health economics, and in turn to justify market access, will continue to be a key area of focus for drug developers.

Governments' increasingly active role in scrutinising drug pricing

Second, governments are playing a more active role in questioning the drug pricing decisions of drug developers on anti-competitive and other grounds.

The European Commission and national competition authorities have shown a renewed interest in addressing excessive pricing issue in the last few years. Excessive prices refer to prices set significantly above competitive levels, which reflects the strong market power of a company. The Commission in 2017 opened an investigation into concerns that a pharmaceutical company engaged in excessive pricing in relation to life-saving cancer medicines and questions regarding whether the company abused a dominant market position in breach of EU competition law. In addition, a number of European countries have taken action nationally. In June 2018, the UK Competition Appeal Tribunal quashed the Competition and Markets Authority finding that an epilepsy drug was unfairly priced. The Tribunal judgment stresses that excessive pricing cases should remain rare and that the authorities should be wary of stepping in the shoes of price regulators, unless they do so on a sound basis, informed by proper evidence and analysis. The European Commission considers it necessary to review the system of incentives, improve the competition of generic and biosimilar medicines, and review the EU competition rules in the pharmaceutical sector as important factors to improve the access and affordability of medicines. Importantly, the European Commission notes that the lack of competition in the pharmaceutical market can hinder savings when innovative products lose their market exclusivity. The Commission will also continue to carefully review mergers between pharmaceutical companies to avoid distortion of competition.

In the U.S., political interest in addressing drug pricing and reimbursement has been high in the past few years, with bipartisan legislative and regulatory proposals accompanying Congressional inquiries into pricing practices. In 2014, several members of Congress sent letters to more than a dozen drug developers requesting information about the prices charged for generic drugs, with a particular emphasis on generic drugs subject to large price increases.[7] Over the past few years, several drug developers have been investigated by Congressional committees. Certain developers have been subject to subpoenas, requests for document productions, and Congressional hearings related to drug pricing and competitive practices.[8] Companies may confront financial, reputational, and other costs in responding to these government requests. It is worth noting that, historically, these were not costs that the industry had to bear. Beyond this, the U.S. Congress' increasingly active role in scrutinising drug pricing reflects another emerging trend – that of the government potentially moving away from a "free market" approach to drug pricing and, instead, seeking to more actively regulate drug pricing decisions. This appears to be a converging trend across multiple jurisdictions.

Movement towards a global view of drug pricing

Finally, certain jurisdictions that have traditionally approached drug pricing as a domestic-only matter are adopting a more international view of drug pricing. The issue of price

interdependency between different countries represents a particularly acute challenge for the industry. Proposals to have the price in one country influence the prices in other countries are principally implemented through cross-border price referencing. Cross-border, or geographic, price referencing is a price-control mechanism whereby the health authority in one country references prices in a select group of other countries when determining the maximum price that it will pay for a medicine. This price control mechanism has been applied in many European countries. For example, the UK is among those countries that are most widely referenced by other countries in relation to pharmaceutical prices. Therefore, although the UK pharmaceutical market accounts for just over 3% of global sales, pharmaceutical prices in the UK likely impact on prices in various countries that reference their prices to the UK.

Moreover, in 2019 at a global forum on fair pricing and access to medicines hosted by the World Health Organization, delegates from governments and civil society organisations called for greater transparency around the cost of research and development as well as the production of medicines to allow buyers to negotiate more affordable prices.

In the U.S., both political parties have now introduced drug pricing legal reforms that would establish drug reimbursement rates in government health programmes by reference to drug prices in select Organisation for Economic Co-operation and Development (OECD) countries. While no such proposal has yet been implemented – and attempts to implement such proposals have been met with fierce legal challenges[9] – it is increasingly common for U.S. policymakers to suggest that the U.S. should benchmark its own drug reimbursement rates off of prices in other countries – and OECD countries in particular. International reference pricing – which was anathema to many U.S. policymakers a matter of years ago – is now ever-present in political discourse and appears to be here-to-stay for the foreseeable future. This development reinforces the fact that approaches to drug pricing are important not only from a comparative and normative perspective, but also from a pragmatic perspective as foreign approaches to drug pricing may directly influence domestic drug reimbursement.

Conclusion

Healthcare systems are undergoing significant transformation in the recent years. The practice of medicine has transitioned from largely empirical to more patient-specific treatment pathways. Recent scientific breakthroughs and technological advancements have improved our understanding of disease pathogenesis to enable differential diagnosis, leading to more precise, predictable and bespoke healthcare that is customised for the individual patient. Genetic, genomic, and epigenetic alterations appear to be contributing to different diseases. Thanks to these research efforts and increasing public-private collaborations, we now can enjoy more targeted and effective treatment and prevention of a wide range of conditions and diseases. These advances are important in modern healthcare, and equitable access to them has been considered by global coalition of NGOs and patient advocacy groups to be a fundamental human right. Fulfilling that right creates tremendous social value but demands a significant paradigm shift in health policy because of the inevitably high costs associated with providing more universal access to such healthcare innovations. This has become the new reality in managing limited resources in an increasingly cost-conscious healthcare ecosystem. As described above, global expenditure on pharmaceuticals has increased and will continue to do so.

Across the globe, legislators and regulators are signalling unprecedented interest in addressing pricing of medicines and medical technologies. Many have focused their attention on newly-launched products that are novel not only in terms of their clinical potential in challenging

therapeutic areas where there exists an unmet medical need, but also because of their price. There is a need to align the expectations of all those involved in R&D, public procurement, pricing and reimbursement, and health technology assessment to manage timely market access to innovations in a patient-centric manner. Ultimately, various stakeholders must seek to achieve a balanced approach that ensures that innovations are appropriately rewarded and also recognises that pricing needs to be calibrated according to local legal frameworks and healthcare environments – all in furtherance of the goal of offering equitable access to innovations.

* * *

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Dr. Lincoln Tsang
Tel: +44 20 3201 1565 / Email: Lincoln.Tsang@ropesgray.com

Dr. Lincoln Tsang is a partner and head of Ropes & Gray's European Life Sciences Practice. He is qualified as a lawyer and a pharmacist with post-graduate training in toxicology and cancer pharmacology, and concentrates his practice on UK, EU and cross-border regulatory compliance and enforcement, including litigation, internal investigations and public policy matters affecting the life sciences industry. Lincoln advises clients on research and development strategies relevant to product approval and market access, product life cycle management, product acquisition, and risk and crisis management. He also regularly represents clients before various regulatory bodies on a wide range of matters, including clinical trials, product approval, advertising and promotion, manufacturing, safety vigilance, and health technology appraisal relevant to pricing and reimbursement decision-making for medicines and medical devices. He has also appeared before various legislatures as an independent expert on product approval and market access of medical products.

Margaux J. Hall
Tel: +1 202 508 4811 / Email: Margaux.Hall@ropesgray.com

Margaux Hall is a partner in the Ropes & Gray's nationally recognised health care practice. Margaux is a leading lawyer in drug pricing, managed care and value-based payment arrangements. She brings to clients an understanding of the transformative legal and policy issues affecting pharmaceutical manufacturers, and the life sciences and health care sectors more broadly. Named a *Law360* "Rising Star" for health care in 2019, Margaux provides: sophisticated regulatory and strategic business counsel to clients on matters involving innovative contracting arrangements; drug price reporting obligations under the Medicaid, Medicare, and the Public Health Service programmes, as well as state drug price transparency laws; and vertical integrations and other transactions related to the pharmaceutical supply chain. She also provides sophisticated regulatory and business strategy advice to national and regional health insurers who manage prescription drug benefits in compliance with Medicare Advantage, Medicare Part D and Medicaid managed care programme requirements.

Hannah Kerr-Peterson
Tel: +44 20 3201 1612 / Email: Hannah.Kerr-Peterson@ropesgray.com

Hannah Kerr-Peterson, associate in Ropes & Gray's European Life Sciences Practice, concentrates her practice on the regulation of pharmaceutical, medical device and digital health technologies in the UK and at the EU level. Hannah advises clients in relation to product classification, clinical research, product approval, manufacturing, distribution, advertising and promotion, safety vigilance, and pricing and reimbursement, as well as product life cycle management, product acquisition, and risk and crisis management. She also regularly assists clients to resolve disputes with various regulatory bodies including NHS England, the Medicines and Healthcare products Regulatory Agency and the Prescription Medicines Code of Practice Authority.

Ropes & Gray LLP

2099 Pennsylvania Avenue, NW Washington, D.C. 20006-6807, USA
Tel: +1 202 508 4600 / URL: www.ropesgray.com

Australia

Greg Williams, Colin Loveday & Sheena McKie
Clayton Utz

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 25.7 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 2021, is approximately 38 years, compared to approximately 35 years in June 1999. The Australian population is also growing – the annual population growth rate as at September 2020 was 0.9% (down from 1.5% in the year ending 30 June 2019), in part due to a substantial decline in net overseas migration. Typically, roughly two-thirds of Australia's 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 reporting on Australia's Health for 2020:[2]

- the life expectancy of a person born in 2016–2018 is 80.7 years for a male and 84.9 years for a female (which has been rising steadily over time);
- in 2016–2018, the leading cause of death in Australia varied by age, with chronic diseases featuring more prominently for people aged 45 years and over, and external causes (e.g. accidents and suicides) being the leading causes for people aged 1–44. Coronary heart disease was Australia's leading single cause of death in 2018, with dementia being the second leading cause of death;
- chronic disease is becoming increasingly common. Based on 2017–18 estimates, almost half (47% or more than 11 million people) have at least one of 10 selected chronic conditions, with one in five having multiple chronic conditions (e.g. heart disease, cancer, stroke, diabetes, arthritis and asthma). Many chronic conditions share risk factors that

are modifiable, including tobacco smoking, high blood pressure, insufficient physical activity, poor diet and overweight and obesity. In 2017, Australia had the fifth highest obesity rate (out of 23 countries in the OECD) for people aged 15 and over. In 2017–18, 67% of Australian adults were estimated to be overweight or obese; and

- often, people living in rural and remote and/or lower socioeconomic areas of Australia, people with disability and Aboriginal and Torres Strait Islander people experience high rates of illness, hospitalisation and death than other Australians. Indigenous Australians also have a lower life expectancy at birth (around nine to 10 years).

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 receive 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; although prescription medicines that are not available on the PBS can also be supplied by private script (without Government subsidy); 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 the Department of Health for 2021–2022 aims to deliver AU$121.4 billion in 2021–2022 and AU$503 billion of overall investment over four years. Of particular note, the Government has invested over AU$25 billion as part of the emergency health response to the global COVID-19 pandemic since March 2020. The reported investment in this Budget includes AU$1.1 billion to extend the COVID-19 health response, AU$1.9 billion to drive the COVID-19 vaccine rollout, Medicare investment

including a AU$204.6 million telehealth extension and AU$43 billion to support the PBS over four years (including AU$878.7 million for new and amended listings).[3] 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. In 2018–2019, those rebates, which are discussed in greater detail in section "Policy issues that affect pricing and reimbursement" below, were 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 that 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. 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 15 medicines available to eligible patients for the treatment of 10 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]

A medicine must first be considered by the Pharmaceutical Benefits Advisory Committee (PBAC; see further below) for subsidisation on the PBS, before it can be considered for funding on the LSDP. 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 2021, is up to AU$41.30 or AU$6.60 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$4.42); and an additional fee for ready-prepared items (currently AU$1.29). 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 permit 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. The current Safety Net thresholds (as at 1 January 2021) are AU$316.80 for concession card holders and AU$1,497.20 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 2.0, December 2020),[20] which provides further detailed information about the processes, procedures, timelines and documents required. This procedure guidance also provides information about consideration of vaccines for the National Immunisation Program.

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 and are bioequivalent or biosimilar and which are listed on the PBS, or that 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 Seventh Community Pharmacy Agreement between the Commonwealth, the Pharmacy Guild of Australia

and the Pharmaceutical Society of Australia (commencing 1 July 2020) sets 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 that 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 fifth, 10th and 15th anniversary of listing for drugs on the F1 formulary (5%, 10% and 5%, respectively),[27] subject to exercise of a Ministerial discretion in appropriate cases;

- 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 exercise of Ministerial discretion, as well as certain exemptions for new pharmaceutical items that 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 as "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, particularly in certain therapeutic areas. This concern led to the Department's Biosimilar Awareness Initiative, directed at prescribers, pharmacists and consumers. That Initiative (introduced in 2015) aims to support awareness of and confidence in the use of biosimilar medicines. In certain therapeutic areas, this has also been supported by changing the administrative steps required to prescribe a particular medicine, to encourage biosimilar uptake.[32]

The Department continues to look for new ways to encourage biosimilar uptake. For example, when biosimilar versions of Adalimumab were listed on the PBS on 1 April 2021, the Department has specified that biosimilar brands of Adalimumab, but not the originator brand, are substitutable for ongoing treatment.

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 that are currently of 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 the 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.[33] The Memorandum of Understanding was generally thought to have been effective in achieving cost control on PBS expenditure,[34] 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 an initial five-year term,[35] an extension until 30 June 2020 and a further extension to 30 June 2022.[36] 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.[37] 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. Views on the effectiveness of these two Strategic Agreements (and the Health Technology Assessment system itself) in maintaining the balance required for a sustainable medicines policy differ substantially.

As at the time of writing, the Commonwealth and Medicines Australia are involved in negotiations for a new Strategic Agreement to replace the existing agreement when it expires on 30 June 2022.

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 15 years (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.

For sponsors, this creates a problem because the perceived cost of their products to the 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.[38]

The Department initially 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. The significant uncertainty relating to the legal and practical difficulties associated with such arrangements have seen this be

further delayed. There is still no agreement as to which of proposed models (if any) for a reformed payment system should be pursued and it seems unlikely that these changes will ever be brought into effect.

More recently, the Government took on the task of seeking amendments to all current Deeds of Agreement, which reflect the special pricing arrangements, to move to a monthly (rather than quarterly) rebating system (as well as other changes to the evidence supporting the monthly rebate invoices to streamline the process).[39]

The Government's approach to special pricing arrangements more generally appear to remain under consideration; however, reports of new criteria and, potentially, a substantial conceptual change to the circumstances in which the Government may agree to such an arrangement have not yet come to fruition. Any 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 criticism of the speed with which medicines are able to be listed on the PBAC.

In the Fifth Edition of its *Facts Book* (June 2021), Medicines Australia reported that for the period 2010–2019, most therapeutic areas took over seven months on average to achieve a successful listing on the PBS once a positive recommendation was received from the PBAC. The average number of days across therapeutic areas to gain PBS listing was 285 days (or 9.4 months). Having regard to the PBAC's recommendation, rejection and deferral rates from 2010 to 2020, Medicines Australia reported that the highest proportion of positive recommendations was in 2019 (75% of submissions), compared with a low of 61% in 2020. Annual recommendations and rejections show a decline over time and the deferral rate shows an increase over time.[40] The PBAC's rigid meeting schedule exacerbates the problem with timely access of reimbursed medicines because it means that if a submission is rejected or deferred 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.

In the interests of transparency of the PBS listing process, the Medicine Status Website was launched in February 2020 and aims to enable the public to track the process of a medicine from PBAC application to listing.[41] In addition, though not without controversy, the Department of Health published a "Procedure Guidance for standardised redactions to Public Summary Documents" in April 2020, which seeks to minimise negotiation between the Department and sponsors of the redactions to confidential or sensitive information set out in Public Summary Documents.[42]

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.

The Government has recently introduced a cost recovery approach to the fees associated with listing a medicine on the PBS, by reference to a detailed schedule of fees. That cost recovery scheme has resulted in a significant increase in those fees for sponsors. At the same time it has sought to decrease the times for PBS listing of priority medicines by introducing a system of the prioritisation of listing applications according to need. This system is in its early stages and it remains to be seen whether it will have any effect on time to reimbursement in Australia.

Finally, as with the rest of the world, we note that the COVID-19 pandemic has had a significant impact on sponsors of medicines, prescribers, dispensers and patients. The Government in Australia has acted promptly to address a range of matters in this space, including a shift to telehealth, introducing limits to discourage or prevent stockpiling, permitting remote dispensing of PBS medicines and relaxing restrictions which would otherwise require face-to-face attendance of vulnerable people at hospitals, health centres or pharmacies. We will be interested to see which of these initiatives will remain available in the future.

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 (https://www.abs.gov.au).
2. https://www.aihw.gov.au/reports-data/australias-health. "Australia's health 2020" is described on the AIHW website as the 17th biennial report on the health of Australians, presented as a set of data insights, health snapshots and a brief, visual report.
3. Budget 2021–22, Portfolio Budget Statements 2021–2022, Budget Related Paper No 1.7 – Health Portfolio, 2021; https://www.health.gov.au/sites/default/files/documents/2021/05/budget-2021-22-portfolio-budget-statements-budget-2021-22-health-portfolio-budget-statements.pdf. See also 'Guaranteeing the essential services', https://budget.gov.au/2021-22/content/essentials.htm#one.
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). This figure has not been updated in the 2019–2020 Medicines Australia Federal Budget Submission (https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2020/02/Medicines-Australia-Pre-Budget-Submission.pdf nor the Medicines Australia Pre-Budget Submission 2021-22 (https://www.medicinesaustralia.com.au/wp-content/uploads/2021/03/MA-Pre-Budget-Submission-2021-22.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. https://www.health.gov.au/initiatives-and-programs/life-saving-drugs-program.
9. https://www.health.gov.au/sites/default/files/documents/2020/10/ensuring-the-future-sustainability-of-the-life-saving-drugs-program.pdf.
10. https://www.health.gov.au/sites/default/files/documents/2020/10/procedure-guidance-for-medicines-funded-through-the-life-saving-drugs-program-lsdp.pdf (section 3 – "Funding criteria").
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 programme, Highly Specialised Drugs Program and IVF Program (https://www.pbs.gov.au/browse/section100).

18. https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf.
19. Page 4, PBAC Guidelines.
20. https://www.pbs.gov.au/industry/listing/procedure-guidance/files/Procedure-guidance-for-listing-medicines-on-the-Pharmaceutical-Benefits-Scheme-v2.0.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.pbs.gov.au/info/general/seventh-community-pharmacy-agreement.
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/general/biosimilars.
33. http://www.pbs.gov.au/info/industry/useful-resources/memorandum.
34. 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.
35. https://www.gbma.com.au/wp-content/uploads/2015/09/GMiA_StrategicAgreement_SignedCommonwealthandGMiA_-150524_FINAL.pdf.
36. https://www.gbma.com.au/wp-content/uploads/2016/01/GBMA-agreement.pdf.
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38. http://www.pbs.gov.au/info/industry/pricing/improving-access-to-medicines-improved-payment-administration.
39. The Government's Guidelines for Deeds of Agreement (version 1.5 dated 7 October 2020), including a template Deed, can be found here: https://www.pbs.gov.au/pbs/industry/listing/elements/deeds-agreement.
40. https://www.medicinesaustralia.com.au/wp-content/uploads/2021/06/Medicines-Australia-Facts-Book-2021.pdf.
41. https://www.pbs.gov.au/medicinestatus/home.html.
42. https://www.pbs.gov.au/info/news/2020/04/procedure-guidance-standardised-redactions-to-psds.

Greg Williams
Tel: +61 2 9353 4798 / Email: gwilliams@claytonutz.com

Greg Williams is a Partner in the Clayton Utz product liability group. Greg advises and conducts litigation for clients operating in the pharmaceutical and medical devices industries. Greg's experience ranges from acting in large-scale product liability class actions and commercial litigation, to advising on regulatory issues, advertising and labelling requirements, and product safety issues.

In the regulatory sphere, Greg advises numerous Australian and overseas pharmaceutical and medical device clients on all aspects of the product life cycle, including regulatory and contractual arrangements for clinical trials, privacy, product registration and reimbursement, advertising disputes, and product safety and recalls. Greg has a Master's Degree in Biochemistry.

Colin Loveday
Tel: +61 2 9353 4193 / Email: cloveday@claytonutz.com

Colin Loveday heads the Clayton Utz product liability and class actions groups. He is an experienced trial lawyer, with particular expertise in the defence of class actions, and has worked extensively with defence lawyers in other jurisdictions in the coordinated defence of multinational mass tort claims. Colin has been intimately involved in the development of Australia's product liability laws. His defence work includes a variety of prescription products and medical devices, infrastructure failures, financial products and other consumer products. Colin is internationally recognised for his work in the field of drug and device litigation.

Colin also has a special interest advising manufacturing, pharmaceutical and medical device clients on regulatory requirements, clinical trials, labelling and advertising issues, product recalls and hazard alerts and priorities management issues. He practised as a barrister in New South Wales between 1985 and 1990, before becoming a partner at Clayton Utz.

Sheena McKie
Tel: +61 2 9353 5732 / Email: smckie@claytonutz.com

Sheena McKie is a Special Counsel in Clayton Utz's commercial litigation practice group and is a member of the national product liability group. Sheena has more than 10 years of experience in high-profile, large-scale class actions, complex commercial and product liability litigation.

Sheena's advisory practice centres on work for clients in the consumer products, pharmaceutical and medical devices industries, including regulatory issues, advertising and labelling requirements, product safety issues and product recalls, clinical trials and pharmaceutical pricing and reimbursement.

Clayton Utz

Level 15, 1 Bligh Street, Sydney, NSW 2000, Australia
Tel: +61 2 9353 4000 / URL: www.claytonutz.com

Belgium

Pieter Wyckmans, Pauline Meskens & Michiel D'herde
Quinz

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 pharmaceutical specialties. 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 the COVID-19 pandemic has further accelerated health expenditure. Cost-containment measures are therefore essential to keep expenditures within bounds. These cost-containment efforts inevitably have an impact on the reimbursement system.

Market introduction/overview

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.[1]

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.[2]

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.[3]

Pharmaceutical pricing and reimbursement

Regulatory classification

The general framework on all medicinal products can be found in the Law of 25 March 1964 on medicines ("**Medicines Act**") and the Royal Decree of 14 December 2006 on medicines for human and veterinary use ("**Medicines RD**"). The national competent authority is the Federal Agency for Medicines and Health Products ("**FAMHP**"), who is responsible for ensuring, from development to use, the quality, safety and efficacy of medicinal products.

To market a medicinal product in Belgium, the pharmaceutical company must submit an application to obtain a marketing authorisation. There exist multiple procedures to obtain such authorisation, and the relevant competent authority depends on the procedure that has been selected by the applicant. The FAMHP is responsible for application proceedings under the national procedure, the decentralised and the mutual-recognition procedure, and the European Medicines Agency for the centralised procedure.

The requirements for each application differ depending on the type of medicinal product for which a marketing authorisation is requested.

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.[4] 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.[5] Similarly, for so-called "copied" medicinal products, the pharmaceutical company can rely

solely on a bibliographical dossier (meaning that references to published scientific literature suffice) if there is a well-established use of the active ingredient in medical practice for at least 10 years in the European Union and its efficacy and safety has been demonstrated.[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, needs 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" ("**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**").

The Belgian legislator has opted to work with a positive reimbursement list in accordance with Article 6 of the Transparency Directive.[14] 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.[15] The final reimbursement decision will be taken by the Minister of Social Affairs and Public Health on the advice of the CRM.[16] The reimbursement application must be submitted simultaneously with the separate pricing application.[17] 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 above under section "Pharmaceutical pricing and reimbursement" and below under "How are drug prices set? What is the relationship between 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).[18]

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.[19]

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):[20]

- 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 ("copies").

Depending on the (sub-)class in which a medicinal product is ranked, different reimbursement procedures and timelines apply.[21] 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.[22] As for medicinal products ranked in sub-classes 2C, 3B or 3C, the procedure may not take more than 90 calendar days.[23] For all other medicinal products, the standard period of 180 calendar days will apply.[24] It is to be noted that the RD Reimbursement includes specific procedures with respect to parallel imported medicinal products, orphan medicinal products and biosimilars.[25]

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.[26]

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),[27] the reimbursement basis (see 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.[28]

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 permitted to deviate from the CRM's proposal, but only for social and/or budgetary reasons.[29] 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.[30] Negative reimbursement decisions can be challenged by the applicant before the Belgian administrative court, 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.[31]

The COVID-19 "clock-stop", a measure pursuant to which the binding deadlines in relation to the reimbursement procedure had been suspended indefinitely in the beginning of the COVID-19 pandemic,[32] no longer applies as from 1 April 2021.

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-paid 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 under section "Who is/are the payors?", "Pharmaceutical pricing and reimbursement", the patient contribution is determined and limited by law.

Categories A and Fa include vital medicinal products, such as medicinal products for the treatment of cancer or diabetes. Medicinal products included in categories 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 categories 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 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 (or copied) 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, and subject to certain exceptions, the reimbursement basis of the original product will automatically be reduced by a certain percentage. In principle, a reduction of 43.64% will occur (as of 1 September 2021, the reduction will be deepened to 44.75%). 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. The opening of a reference cluster for an active ingredient might also trigger the application of the "combi cliff" for combinations which contain that particular active ingredient but for which a reference cluster was not yet opened. For those combination preparations, the reimbursement base (at ex-factory level) may not exceed the sum of the reimbursement bases (at ex-factory level) of the reference individual preparations with the highest reimbursement base per unit that still

belong to the group of the "least costly" medicinal products. Additionally, at the opening of a reference cluster, the "old drugs cliff" (a further price decrease in the event a medicinal product has been included on the list of reimbursed pharmaceutical specialties for 12 years, see below under "Policy issues that affect pricing and reimbursement", "Pharmaceutical pricing and reimbursement"), if not yet applied, will be applied as well.

A lower reimbursement basis entails a lower contribution by the health insurance, which means that the original medicinal product would 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) to the level of the new reimbursement basis; or
(ii) remove the medicinal product from the list.

If the applicant does not choose between these two options, option (i) will automatically be applied.[37]

The former "safety margin", allowing pharmaceutical companies to apply a margin of 25% of the new reimbursement basis, capped at €5 in setting the public price has been abolished effective as of 1 July 2020.[38]

Additionally, 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 price control by the Price Department of the Federal Public Service ("**FPS**") for Economic Affairs.[39] A pharmaceutical company can only effectively market a medicinal product if an official maximum price has been determined. 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.[40] 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).[41] The Minister of Economic Affairs determines the price on the basis of the scientific and economic information submitted by the applicant.

As of 1 July 2021, any such request must be made through the dedicated "Mediprices" portal set up by the FPS for Economic Affairs and paper applications will no longer be possible.[42]

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.[43] 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.[44] 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.[45] A specific procedure applies for increasing the ex-factory price; this procedure is similar to the procedure for obtaining the initial ex-factory price.[46]

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 be, on the request of the applicant, calculated by the Price Department and communicated to the applicant.[47] 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%).[48] The aforementioned pre-defined profit margins for wholesalers and pharmacists will always be maximum margins,[49] 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.[50] 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.[51]

One of the structural 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 (or a copied medicine) enters the market and is reimbursed, 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 too 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.

Another cost reducing measure, introduced since 2018, is the ceiling price measure, which implies that an innovative medicinal product shall no longer be reimbursed if that product continues to be more expensive compared to "the least costly"[52] 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.[53] If a medicinal product is no longer reimbursed on the basis of this measure, it can re-enter the list of reimbursable medicinal products without following the full reimbursement procedure before the CRM (see "What is the process for securing reimbursement for a new pharmaceutical product?"), if its price is reduced to such extent that it is again part of the group of least costly medicinal products, within a period of two years after it has been removed from the list of reimbursable medicinal products. This 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. This regime should also allow the health insurance to free up additional budget that can be invested in the reimbursement of innovative medicinal products.

In addition, at the level of the prescribing healthcare professional and pharmacist, there are other budget control measures in place which are based on the principle of "least costly" or "low cost" medicinal product(s): (i) in the event a healthcare professional provides an INN-prescription, the pharmacist is obliged to provide the patient with a medicinal product which is part of the category of the "least costly" medicinal products;[54] and (ii) since 2012, the government has introduced "low cost" prescription quota, requiring healthcare professionals to prescribe a certain percentage of medicinal products which are part of the category of the "least costly" medicinal products.[55] Also, over the course of 2019, a specific pilot programme was set up to financially incentivise physicians in prescribing certain biosimilars. The pilot project was introduced specifically for biosimilars as the uptake thereof is lagging behind in Belgium compared to its neighbouring countries.[56]

Furthermore, in addition to the patent cliff (see above under section "How is the reimbursement amount set? What methodology is used?", "Pharmaceutical pricing and reimbursement"), multiple other "cliffs" have been introduced with a view on decreasing public healthcare expenditure, such as the "old drugs cliff", and the "biocliff".

When an active substance (or a combination thereof) has been included on the list of reimbursable pharmaceutical specialties for a period of 12 years, a price decrease is mandated (both in relation to the ex-factory price and reimbursement basis), depending on the annual turnover of the pharmaceutical product in Belgium, which is referred to as the "old drugs cliff". The old drugs cliff comprises a base price decrease of 19.75%, and a turnover-based price decrease, the so-called "volume-cliff" (e.g. the old drugs cliff for active substances with a turnover of less than €1.5 million is equal to 19.75%, and for active substances with a turnover between €1.5 million and €10 million equal to 25.44%, etc.) The maximum mandated price decrease under the old drugs cliff (including the volume-cliff) for non-biological drug products is 33.97%.[57] We note that the old drugs cliff has been deepened in 2021, for example, prior to 1 April, 2021, the maximum price decrease under the old drugs cliff was capped at 29.42%. Pharmaceutical products that already have been subject to the old drugs cliff will need to regularise their prices and will be required to further decrease their price in order to align with the new old drugs cliff percentage.

For biological medicinal products, a similar old drug cliff applies. In addition, for biological medicinal products, a price decrease of 20% is mandated in the event a biosimilar of a biological medicinal product enters the market and the biological medicinal product meets the turnover threshold of €1.5 million (also referred to as the "price decrease 'biological medicinal products'").[58] Importantly, the entry to market of a biosimilar automatically causes the application of the old drugs cliff, even if the original biological medicinal product is not yet reimbursed for a period of 12 years ("biocliff"). *Vice versa*, the application of the old drugs cliff also causes the price decrease 'biological medicinal products' to take effect, even if no biosimilar has entered the market.

Pharmaceutical companies can request an exception to the mandatory price decreases under the old drugs cliff and the biocliff if they meet certain conditions.[59] For specific categories of medicinal products, for example, medicinal products included under sections III or IV-*bis* of the list of reimbursable pharmaceutical specialties, such exception applies automatically, without requiring an explicit request by the pharmaceutical company.

The abovementioned mandatory price decreases and the abolishment of the safety margin could lead to substantial price reductions for many "original" branded medicinal products, causing some pharmaceutical companies to withdraw such products from the Belgian market, out of precaution for the effects in other countries in the EU.

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 a minimum one and maximum three years, with the possibility of renewal.[60] 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.[61] 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.[62] 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.[63] 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. The KCE reiterated these concerns in its 2021 report on the benefits and costs of innovative cancer drugs (and their reimbursement) in Belgium.[64] This second issue has been recently addressed by the Belgian legislator, which has imposed broader transparency obligations (encompassing the confidential annexes) with regard to these agreements within the context of a management audit by the Belgian Court of Audit as mandated by the Chambers of Representatives.[65] However, in its 2021 report, the KCE still criticised the lack of transparency of managed entry agreements, pointing out that the new transparency rules only apply to agreements concluded after the entry into force of this new legislation, that the Court of Audit has no medical or methodological authority and that the select group of persons who have access to the managed entry agreement remain bound by secrecy, preventing independent investigators from conducting neutral economical evaluations of medicinal products.[66] It remains to be seen whether this latest report will again lead to further legislative initiatives regarding managed entry agreements, in particular in relation to their confidential nature.

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. Examples of such cross-border cooperation initiatives in which Belgium participates are the BeNeLuxA initiative and the recent International Horizon Scanning Initiative ("**IHSI**").[67]

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 that 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'*".[68] The success of these innovative, personalised healthcare solutions largely depends on the use of companion diagnostics, 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.

Recently, in 2019, the Belgian government took further action to facilitate access to personalised medicine by combining the procedures for reimbursement of medicinal products and their biomarker (companion diagnostic). For this purpose, a new article 33*ter* and Chapter VIII have been introduced in the RD Reimbursement, which 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. Previously, the lack of synchronisation between both caused issues with medicinal products being reimbursed earlier compared to their companion diagnostics. In this combined procedure, the assessment involves both the CRM and the Technical Medical Council ("**TMC**") (*Technische Geneeskundige Raad*/*Conseil Technique Médical*) in a joint "CDx Platform" and covers both the diagnostic test as well as the medicinal product in one health technology assessment. Consequently, the decision by the Minister determines the reimbursement of the package of the biomarker and medicinal product. If the Minister decides to reimburse the medicinal product in Chapter VIII, the linked biomarker will simultaneously be included to the list and reimbursed.

It is to be noted that currently the combined procedure only applies to medicinal products and molecular (biological) companion diagnostics. For other companion diagnostics (such as immunohistochemical tests), the separate procedures must still be followed.

Finally, driven by increasing public healthcare expenditure as well as heightened public awareness and scrutiny around drug prices, there is a clear tendency for lawmakers to force pharmaceutical companies in reducing the prices of their medicinal products, either by broadening the scope of existing measures, or introducing new measures. Such measures either directly impact the price or reimbursement basis of medicinal products (such as the patent cliff, biocliff, old drugs cliff, etc., see "Policy issues that affect pricing and reimbursement"), or indirectly incentivise pharmaceutical companies, e.g. by taxing sales on pharmaceutical products or penalising companies if the medicines budget is exceeded. Pursuant to this "claw-back tax", the pharmaceutical sector is held to pay a tax on turnover of pharmaceutical products in Belgium in the event the medicines budget in a given year is exceeded, with a maximum of 4% of the total medicines budget for that year.[69] It is to be noted that in 2020, generics and biosimilars were exempted from this clawback tax as part of a government effort to further boost generics and biosimilars in Belgium. It is not yet decided whether generics and biosimilars will be exempted again from the 2021 claw-back.

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.

* * *

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17. Article 10 of the RD Reimbursement.
18. Article 15, §1, third paragraph of the RD Reimbursement.

19. Article 35*bis*, §2 of the NIHDI Act; Article 4 of the RD Reimbursement.
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21. 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; and 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.
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25. Procedure parallel imported medicinal products: see Articles 43–49 of the RD Reimbursement; procedure orphan medicinal products: see Article 55 of the RD Reimbursement; and procedure biosimilars: see Articles 56–58 of the RD Reimbursement.
26. Article 6 of the RD Reimbursement.
27. 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.
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Acknowledgment

The authors would like to acknowledge Olivier Van Obberghen for his assistance in preparing this chapter. Olivier Van Obberghen works exclusively for clients in the Life Sciences and Innovative Technologies sectors. He co-heads the Life Sciences department of Quinz together with Pieter Wyckmans.

Olivier's transactional expertise covers the entire life cycle of a drug product (R&D, clinical trials, supply chain and technical operations, commercial distribution, and market access, (including pricing and reimbursement)), including M&A, product divestments and licensing deals (both early stage and established brands).

Tel: +32 2 255 73 92 / Email: olivier.vanobberghen@quinz.be

Pieter Wyckmans
Tel: +32 2 255 73 90 / Email: pieter.wyckmans@quinz.be

Pieter Wyckmans provides expert advice to companies and organisations active in the (bio-) pharmaceutical, biotech and smart devices sectors. Pieter co-heads the Life Sciences department of Quinz together with Olivier Van Obberghen.

Pieter's transactional expertise covers the entire life cycle of a drug product (R&D, clinical trials, supply chain and technical operations, commercial distribution), including M&A, product divestments and licensing deals (both early stage and established brands).

Over the last few years, Pieter has developed a particular regulatory expertise under EU and national laws. More specifically, Pieter provides his clients with expert advice on a broad array of legal and strategic issues regarding clinical trials and market access, including early access programmes, marketing authorisation procedures and pricing and reimbursement.

Pieter worked in-house for the legal department of UCB.

Pauline Meskens
Tel: +32 2 255 73 87 / Email: pauline.meskens@quinz.be

Pauline Meskens provides transactional and regulatory support to clients active in the life sciences sector. She has a background in intellectual property and ICT law and has gained experience in intellectual property disputes, including in the life sciences sector, and life sciences regulatory matters. Pauline currently provides regulatory and transactional assistance to pharmaceutical companies throughout the entire product life cycle – ranging from market access (including pricing and reimbursement) to healthcare compliance matters – and regularly advises on intellectual property matters.

Michiel D'herde
Tel: +32 2 235 72 71 / Email: michiel.dherde@quinz.be

Michiel D'herde provides transactional and regulatory support to clients active in the pharmaceutical and medical devices sector. His main areas of expertise comprise transactional and regulatory assistance throughout the entire product lifecycle, with particular experience in coordinating and supporting national and international R&D collaborations (H2020, IMI2) and advising on healthcare compliance matters, advertising and promotion, and market access (including pricing and reimbursement).

Quinz

Medialaan 28B, 1800 Vilvoorde, Belgium
Tel: +32 2 255 73 80 / Fax: +32 2 253 42 19 / URL: www.quinz.be

Brazil

Benny Spiewak, Gustavo Swenson Caetano & Daniela Guarita Jambor
SPLAW Advogados

Abstract

The legal framework of the Brazilian pharmaceutical market is complex and requires in-depth knowledge. In order to manufacture, import and sell drugs in Brazil, companies need to secure, in advance, certain licences and sanitary permits from the National Health Surveillance Agency ("ANVISA") and local/regional health agencies. Once a Marketing Authorization is received, companies must obtain approval of the price for certain categories of drugs before the Drug Market Regulation Chamber ("CMED"). The country's model for drug price controls consists of government-established price ceilings. No public system exists for reimbursing drug development expenses and/or drug prices. As the Brazilian health system is public, most people access drugs under the Brazilian Public Health System ("SUS") without charge. The Government acquires medicines through public bidding from companies that, in certain situations, must offer price discounts on products sold to the government. In the private system, health insurance companies remain subject to specific rules issued by the National Agency of Supplementary Health Care ("ANS"). Generally, health insurance companies must provide patients with treatments, products, including drugs, on a list of ANS-approved procedures.

Market introduction/overview

Despite its complexity, the Brazilian healthcare industry remains one of the most attractive in the world because of its innovative and new business dynamic. Brazil is the only Latin American country ranking among the top pharmaceutical markets worldwide, with a global market share of approximately 2.6%. Total revenue for the country's pharmaceutical industry reached almost US$32 billion.[1]

The foregoing is mainly the product of the country's universal public healthcare system, which offers local access to treatments and services within the SUS.

The Brazilian healthcare market is divided into public and private systems. On the one hand, the public system (particularly the SUS) provides increased pharmaceutical assistance by incorporating new drugs into its selection, a development that has gained the attention of companies, patient associations and patients. Approximately 75% of Brazilians depend on the SUS for treatments,[2] with a 31.4% increase in drugs purchased between 2015 and 2019.[3] On the other hand, access to treatments in the private system (consisting of health plans) rose by 96.9% during the same period.[4]

The pharmaceutical market plays an important role in the Brazil economy and continues to grow by double digits. In 2019, the pharmaceutical market expanded roughly 12% to R$112 billion.[5] As an institutional market, pharmaceutical retail accounts for most drug sales, and

grew 53% between 2015 and 2019.[6] End consumers (in this case, patients) made 75% of the corresponding purchases.[7] The growth of pharmaceutical retail has many contributing factors, including an ageing population and the possibility of new treatments.

At the same time, important issues such as repressed demand for drugs and insufficient investment in research are frequently discussed in Brazil. Despite the aforementioned growth, a repressed demand of up to 50% is estimated to exist for drugs.[8] Access to drugs in the country accounts for one reason for the repressed demand. The origin of the difficulty in accessing drugs stems from factors such as high and non-competitive drug pricing, questionable public policy strategies, a fragile regulatory agenda, low R&D investments, and a tax burden considered among the highest in the world. Unlike the global market, the growth of clinical research and the launch of new treatments has found little application in Brazil. One reason was the limited number of actions to stimulate innovation in the country, such as the promotion of research. While most research and development investment are undertaken by the public sector, recent governments have preferred to cut those budgets. Private sector investment in research is still nascent. For many researchers, Brazil remains an attractive country for research because of its heterogeneity, various climates, culture and socioeconomic conditions. For meaningful change, experts urge increased government incentives and support of scientific research, as well as simplified rules and regulations.

The COVID-19 pandemic promoted the emergence and growth of health startups and digital platforms in Brazil. Telemedicine regulations were quickly updated, and that type of visit reduced the need for physical contact between doctors and patients. Besides distance medical assistance, other branches expanded, such as e-commerce solutions for medical products and equipment, psychological and emotional help tools, home-based physical exercise solutions, service platforms for assistance with daily activities, protection and safety of the elderly, and systems for improving hospital management. According to estimates, approximately US$430m were invested in health techs in Brazil between 2014 and 2020.[9]

Pharmaceutical pricing and reimbursement

Pharmaceutical pricing

Companies interested in marketing drugs in Brazil must complete the following steps: (1) obtain Marketing Authorization ("MA") of the product from ANVISA (Article 7 of Decree 8,077/2013); and (2) receive approval of the drug capped price from the CMED (Article 7 of Law 10,742/2003).

Generally, the process of obtaining the MA at ANVISA requires the company to conduct prior clinical trials and, after confirming the product's safety, quality and efficacy, submit an application for granting the MA. Brazilian legislation determines specific requirements for evaluation and observation according to the category of drugs, such as brand-name, generic, similar, biological, psychotherapeutic, notified, dynamised and specific drugs. A drug's acceptance by foreign health authorities (such as the FDA and the EMA) does not guarantee its approval in Brazil. ANVISA performs a specific and detailed analysis of the product, which can involve asking the company to clarify and provide additional documents during the MA process, known as an "exigency". Rarely does ANVISA approve drugs without exigencies, and the evaluation time normally lasts two years.

After obtaining the MA from ANVISA, the company must receive the drug capped price from CMED. This process stems from the fact that the Brazilian government controls drug prices, including a price ceiling. While no legislation establishes a timeframe for requesting the drug capped price, regulatory authorities tend to consider two to three months a reasonable timeframe for doing so.

Currently, the pricing process is regulated by CMED Resolution 2/2004, which requires the company to present corresponding economic data and proposals for a price to CMED, in accordance with the Resolution's drug categories. To assign the drug capped price, Resolution 2/2004 divides drugs into six categories:

1. Category I covers a "*new product with a molecule patented in the country that brings gain to the treatment in relation to drugs already used for the same therapeutic indication, with confirmation of one of the following requirements: a) Greater efficacy in relation to the existing drugs for the same therapeutic indication; b) Same efficacy with a significant decrease in adverse effects; or c) Same efficacy with a significant reduction in the global cost of treatment*" (Article 2(I) of the Resolution).
2. Category II is for "*new products that do not fit the definition provided for in the last item*" (Article 2(II) of the Resolution).
3. Category III relates to the "*new pharmaceutical presentation of a drug already marketed by the company itself, in a same pharmaceutical form*" (Article 3(I) of the Resolution).
4. Category IV regards "*new drug presentation that fits one of the following situations: a) a drug considered new on the list of those marketed by the company, except as provided in Article 3(III); b) a drug already marketed by the company in a new pharmaceutical form*" (Article 3(II) of the Resolution).
5. Category V describes a "*drug fitting one of the following situations: a) new pharmaceutical form in the country; b) the new association of active ingredients already existing in the country*" (Article 3(III) of the Resolution).
6. Category VI is a generic drug (Article 3(IV) of the Resolution).

Each category has its own rules that the company must observe when proposing a drug price. Prices are adjusted annually and in accordance with inflation. For 2021, CMED approved the maximum readjustment of drug prices between 6.79% and 10.08%, depending on the drug's level and as set forth in Resolution 1/2021.

Recently, CMED published Resolution 2/2019, which lists drugs exempt from price controls, limited to OTC, psychotherapeutic (including traditional) drugs and injectable local anaesthetics for dental use.

Resolution 2/2019 created two large groups of drugs according to their nature, specifically, those released from "fixing/setting prices" and "price adjustments", either with or without a maximum sales price for the consumer, and those not released from any CMED price criteria. Communications 4/2019 and 5/2019 complement the regulation, specifying the general categories of drugs (for instance, psychotherapeutic and dynamised drugs) and their respective therapeutic classes.

According to Resolution 2/2004, the company is responsible for classifying the product into "fixing price" categories, while observing the legal definition for each category, as determined in Resolution 2/2004. The requirements and conditions for Category I are routinely challenged by industries and industry professionals.

To request a Category I drug capped price (known as an Informative Document), a company must present substantial information, including: (i) the drug's brand name in Brazil, as well as other brand names for the same drug, as used in specific countries (Australia, Canada, France, Greece, Italy, New Zealand, Portugal, Spain and the United States) and in the manufacturer's country of origin; (ii) the manufacturer's price, as sold in Australia, Canada, France, Greece, Italy, New Zealand, Portugal, Spain and the United States, and the manufacturer's price in the product's country of origin, excluding taxes (referred to as the "basket of prices"); (iii) the potential number of patients for treatment with the drug and a note on the corresponding

period; and (iv) a cost/efficacy comparative analysis between the drug and existing therapeutic alternatives, as established by Article 4, Paragraph 2, of Resolution 2/2004.

Resolution 2/2004 provides more guidance on the "basket of prices" in Category I: (i) the price proposed by the company shall not be higher than the lowest price traded for the same product in countries with the "basket of prices", including taxes added (Article 5, *caput*); and (ii) to confirm the authorised price, the drug should be marketed in at least three countries with the "basket of prices" (Article 5, Paragraph 1). If this condition is not met, the CMED's Technical/Executive Committee may act in the public interest by establishing a provisional price. It shall also ensure that the company commits: (a) submitting the approved provisional price for review every six months, until conditions are met; and (b) provide notice of the launch of the product, along with its respective price, in countries with the "basket of prices" (Article 5, Paragraph 2).

After a company requests a capped drug price (also known as an Informative Document), the CMED will assess the proposal and provide the approved price, based on technical and commercial aspects within the drug classification.

The decision provided by the Executive Secretariat of CMED is subject to two instances of appeal. First, a request for reconsideration directed to the Executive Secretariat on the original decision. If the Executive Secretariat upholds the decision, a company can appeal to the Executive Technical Committee ("ETC"). The ETC is a body composed of representatives of the Ministries of Health, Economy and Justice, as well as the Civil Office of the Cabinet of the Brazilian President and ANVISA. The ETC is the highest administrative authority to discuss decisions related to drug pricing. ETC decisions may take approximately six months to be issued. While not common, final decisions issued by CMED on price approval may be submitted for review by Brazilian federal courts if the decision is illegal or does not adhere to legal requirements.

Finally, CMED classifies drug prices into three categories: (i) Factory Price ("FP"), the maximum price permitted for companies to sell drugs to pharmacies, drugstores and the Brazilian government; (ii) Maximum Consumer Price ("MCP"), the maximum price that may be charged by pharmacies and drugstores; and (iii) Maximum Selling Price to the Government ("PMVG"), the price based on the application of the Price Adequacy Coefficient ("PAC") to FP. The PAC is a mandatory minimum discount applied on the sale of drugs to the SUS and listed in Communication 15/2017, or for compliance with a court order. Government-related mandatory discounts are readjusted on yearly basis.

Reimbursement of drug price *versus* drug access in Brazil

Public system

The public system offers no reimbursement of drug prices because the SUS offers its services, products and treatments without charge to citizens.

According to Law 8,080/1990, the Government should provide indispensable conditions for the full exercise of health, considered a fundamental human right. Therefore, the Government must develop public policies to reduce the risk of diseases and health problems and guarantee universal and equal access to actions and services for promoting, protecting and regaining health (Article 196 of the Brazilian Federal Constitution). The population must have adequate access to drugs through the SUS. The system must be analysed from a federal perspective, with all entities (federal, state and municipal governments) participating in acquiring, organising and distributing drugs to the population, based on their legal powers.

All sales of drugs to the Brazilian government are subject to public bidding, for which the public entity shall aim to acquire the drug at the lowest possible price. In specific situations,

the seller (manufacturer, importer and/or distributor) must apply the CAP, mainly for drugs sold to SUS and listed in Communication 15/2017 or to comply with a court order.

For technologies (including treatments, drugs and medical devices) to be made available to the population at the SUS, technology must be incorporated into public policies through a specific procedure at the National Committee for Health Technology Incorporation ("CONITEC").

CONITEC consists of two bodies: the Plenary; and the Executive Secretariat. The Plenary is primarily responsible for making recommendations on the incorporation, disinvestment or alteration of technologies for the SUS. The composition of the Plenary is quite heterogeneous, consisting of 13 members that include representatives from the Ministry of Health, ANVISA, ANS, the National Council of Health Secretaries ("CONASS") and the National Council of Municipal Health Secretaries ("CONASEMS"). Representatives from civil society, from the Federal Council for Medicine and from the National Council of Health ("CNS") also participate. Societal involvement in CONITEC decisions occurs not only through those two representatives, but also through consultations and public hearings.

When evaluating the inclusion of new technology into the public system, CONITEC considers scientific evidence regarding its efficacy, accuracy, effectiveness and safety. It also undertakes a comparative cost/benefit evaluation as compared to existing SUS-approved technologies (Article 19-Q of Law 8,080/1990).

The step-by-step process for incorporating technology is summarised as follows: (i) submission by the interested party of a request for incorporation; (ii) CONITEC's prior assessment of formal requirements, especially of studies presented, as well as any additional studies and research CONITEC may deem necessary; (iii) CONITEC's Plenary analyses the request, offers its recommendations and issues a final opinion; (iv) CONITEC submits the opinion for public comment and evaluates the responses; (v) CONITEC's Plenary ratifies/rectifies its recommendation; (vi) the need for a public hearing is determined and held, if needed; and (vii) the report is evaluated by the Secretary of Science, Technology and Strategic Inputs of the Ministry of Health, followed by a final decision on the SUS' approval or rejection of technology and publication of the decision in the Official Gazette.

Any natural person or legal entity may submit the request to incorporate technology which, at the very least, must include a description of the disease/health condition related to its use, a description of the technology, an evaluation in comparison to technology already available at the SUS, an economic evaluation study from the SUS perspective, and a budget impact analysis.

Public participation in the process of incorporating technologies for the SUS in encouraged through public consultations. A significant increase in participation was noted, particularly by patients, health professionals, companies interested in incorporating the technology and patient associations.

CONITEC has 180 days to assess the request for incorporation of technology into SUS. CONITEC reports are submitted for public consultation and, once public comments are added, the final report is submitted to the Ministry of Health's Secretary of Science, Technology and Strategic Inputs ("SCTIE"). That entity makes the final decision on incorporating technology into the SUS. Although CONITEC reports are not binding, experience shows that the Secretary normally follows the former's recommendations. If the Secretary decides on incorporating the technology, it must be made available for patient use within no later than 180 days. SCTIE Secretary decisions may be appealed to the Brazilian Minister of Heath.

Private system

In the private system, health insurance companies must supply patients who can afford health insurance with drugs included on the ANS List of Procedures.

The ANS regulates and oversees Brazilian supplementary healthcare with two main objectives: (i) regulation of supplementary health, consisting of policies and guidelines for defending the public interest and the supplementary healthcare market's sustainability; and (ii) qualification of supplementary health to establish a series of policies, guidelines and actions governing the sector, its operators, and institutions.

Among its functions, ANS must update and publish the List of Procedures, which is the minimum mandatory coverage of health-related procedures, products and services to be guaranteed by the health insurance company, based on the contracted health insurance plan.

Guidelines and requirements to be followed on the composition of the Minimum List of Procedures are those established under Law 9,656/1998.

Only drugs with MA granted by ANVISA may be included on the ANS List of Procedures.

That List of Procedures is updated every two years, as determined by the ANS Collegiate Board. The entity sets the schedule and deadline for receiving comments and proposals from individuals and companies.

"Judicialisation"

An exponential increase of lawsuits has arisen involving patient access to drugs, especially related to products not included on lists such as the SUS or ANS. This phenomenon is called "judicialisation" and is founded on guarantees of universal and free access to health in Brazil pursuant to Article 196 of the Brazilian Federal Constitution. Most judicial precedents favour patients. Drugs for treatment of rare diseases and cannabis products are among the categories of drugs/products that have become accessible through the Judiciary.

In a recent relevant decision (Special Appeal No. 657718), the Brazilian Supreme Court ("STF") established the requirements for government supply of drugs not on the SUS list: (1) the Government need not supply experimental medicines; (2) a product's lack of Anvisa approval generally prevents requiring its supply by court decision; and (3) as an exception, a drug pending approval with ANVISA may be supplied if the agency unreasonably delays its assessment of the application (a period longer than as established by Law 13,411/2016), provided that four requirements are met: (i) the existence of an application for registering the drug in Brazil, except for orphan drugs used to treat rare and ultra-rare diseases; (ii) approval of the drug by a well-known foreign regulatory agency; (iii) a lack of therapeutic alternatives or substitutes approved in Brazil; and (iv) corresponding lawsuits filed against the Federal Government.

Policy issues affecting pricing and reimbursement

Policy problems may affect drug prices in Brazil in two ways. First, the drug's initial price. As seen, the initial drug price considers prices of the same drug in countries with the "basket of prices". A global/local policy in a country with the "basket of prices" can influence the price of medicine in that country. And, to the extent that the price in the country sets drug prices in Brazil, the policy could affect the setting of the initial drug price in Brazil. It is worth noting that the political crisis must be verified at the time of the request for fixing the drug capped price before CMED. If there is a change in the price of the drug in any of the countries with the "basket of prices" after CMED sets the price, in theory the price variation would not influence the drug price in Brazil. Extraordinary situations may exist in which a

drug substantially and exponentially increases in price in Brazil. In those rare cases, its sale could be blocked, an unforeseeable result for the company that would allow for a revision of the drug price in Brazil.

Another scenario involves political interference during the annual readjustment of drug prices. During the COVID-19 pandemic, Provisional Measure 933/2020 was verified in Brazil, which temporarily suspended the annual price readjustment of medicines in 2020. While the issue is still debated before the Brazilian Senate (1,542/2020), it stands little chance of becoming law. For the first time since the creation of the CMED, we have witnessed purely political interference in drug prices. While we understand the urgency of such interference, we believe that it is best limited to exceptional cases.

Emerging trends

There is ongoing discussion in Brazil on the updated review of CMED regulation relating to the approval of drug prices, especially Resolution 2/2004, which establishes the requirements for approving drug prices in Brazil. Critics consider that outdated regulations, particularly in light of new categories of drugs such as biological products, as well as regulatory limitations on the type of evidence taken into account by CMED when assessing the superiority of new drugs. Expectations on newly overhauled regulation remain high after recent statements by CMED executives on the matter.

In recent years, alternative payment models have been more commonly discussed as the funding of high-cost drugs is addressed. In April 2019, the Ministry of Health published Ordinance 1297/19, which implemented a pilot agreement for accessing Biogen's Spinal Muscular Atrophy ("SMA") treatment Spinraza (nusinersen) through the SUS. While the Ordinance remains in effect, the project was suspended by the Ministry of Health for an indefinite period, pending CONITEC's final assessment of the drug.

Risk-sharing models are not common in Brazil, but are increasingly included on the agenda of public agencies and bodies. For instance, Bill No. 667/2021 remains under discussion in the House of Representatives in Brazil and seeks to amend Law 8080/90, which created the SUS and establishes the requirements for incorporating technologies into SUS. The proposed legislation would allow the Ministry of Health to adopt risk-sharing agreements for new technologies (https://www.camara.leg.br/proposicoesWeb/prop_mostrarintegra?codteor=1969805&filename=PL+667/2021).

Successful market access

Entering the pharmaceutical market in Brazil is complex and requires long-term planning. First, the company must determine which commercial strategy it will adopt in Brazil (import or manufacture of drugs). Then, it must establish itself in Brazil by acquiring and adapting to a location or establishing a partnership with a competent local company. The next step is to obtain sanitary licences prior to the activity and mandatory before ANVISA and Local Sanitary Surveillance, such as an Operating Permit, Local License and Certificates of Good Practice. In possession of these authorisations, the company may then apply for the MA of the drug. Once granted the MA of the drug by ANVISA, the company must then request the drug capped price before CMED. With the fixing of the price, the company may sell the product on the Brazilian market. Technical and legal assistance is recommended during the entire process of establishing the company in Brazil, in particular, to adapt physical facilities, prepare technical documents, and maintain a good relationship with the authorities, while always abiding by legislation and remaining helpful and proactive.

Endnotes

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Benny Spiewak
Tel: +55 11 2039 0130 / Email: benny.spiewak@splaw.com.br

Benny Spiewak, CCEP-I, CHC, is a partner at SPLAW and leads the Life Science practice. He is an experienced and certified Brazilian attorney (LL.B. from Mackenzie Presbyterian University in São Paulo in 2001). He earned a certificate in Intellectual Property Law from the Getúlio Vargas Foundation (Fundação Getúlio Vargas) in São Paulo in 2006 and a certificate in Intellectual Property Law and Technology Transfer from the University of New Hampshire's Franklin Pierce Law Center in Concord in 2006. He received a Master's Degree in Intellectual Property Law (LL.M.) from George Washington University in Washington, D.C. in 2009 and worked as a Foreign Associate at the Biotechnology Innovation Organization's International Intellectual Property Law and Policy Office in that same city in 2009. Since 2015, he has served as the Coordinator of Healthcare Compliance Academic and Certification Activities of LEC, in São Paulo. He teaches Health Law and Intellectual Property & Innovation at the certificate programmes of FIA and Oswaldo Cruz Foundation, both in São Paulo.

Gustavo Swenson Caetano
Tel: +55 11 2039 0130 / Email: gustavo.swenson@splaw.com.br

Gustavo Swenson Caetano is a partner at SPLAW and a co-chair of the Life Science practice. He is an experienced and certified Brazilian attorney (LL.B. from the Pontifical Catholic University of São Paulo in 2007). He earned a certificate in Intellectual Property Law from the Getúlio Vargas Foundation (Fundação Getúlio Vargas) in São Paulo in 2010 and a certificate in Administrative Tenders and Contracts from that same institution in São Paulo in 2013. He received a Master's in Intellectual Property Law (LL.M) from George Washington University in Washington, D.C. in 2016. He acted as a guest professor for Healthcare Compliance classes at L.E.C – Legal, Ethics & Compliance in São Paulo from 2015 to 2019.

Daniela Guarita Jambor
Tel: +55 11 2039 0130 / Email: daniela.jambor@splaw.com.br

Daniela Guarita Jambor is an experienced and certified Brazilian attorney (LL.B. from Mackenzie Presbyterian University in São Paulo in 2014 and Master's Degree in Civil Law from the University of São Paulo in 2021). She has represented clients in the Life Sciences sector since 2014, with particular emphasis on preventive, regulatory and administrative procedures in health law.

SPLAW Advogados

Alameda Campinas, 1077, 12º floor, Jardim Paulista, 01404-001, São Paulo/SP, Brazil
Tel: +55 11 2039 0130 / URL: www.splaw.com.br

China

Andrea Sorgato
Zunarelli Studio Legale Associato

Abstract

The complexity of pricing and reimbursement regulations is a key indicator of the evolution rate of a pharmaceutical law system. In recent years, China is facing the challenge to make its Healthcare system modern, inclusive, and able to cover the healthcare needs of Chinese citizens. The Pharmaceutical system – and the pharma pricing and reimbursement sub-system – is a key component of this process. The reform put in place by the Chinese Government involves deep changes in the Healthcare system, which have an impact on the whole life of drugs, from pre-clinical investigation activities to the commercial phase. Price setting and reimbursement procedures and areas of requirements are facing continuous reforms to conjugate huge healthcare coverage with sustainability of public insurance funds. Pharmaceutical companies must deeply know these changes. Being frequently updated is mandatory. The introduction of the revision of the National Drug Reimbursement List on a yearly basis, together with the VPB Volume-Based Procurement system to put in concurrence originators with generics (regardless of drugs domestic-made or imported) on a national-centralised scale, significantly infers drugs' life from its early stage, included price setting and market access strategies for negotiation of reimbursement.

Market introduction/overview

The Chinese pharmaceutical market is facing several reform processes to enhance the targets set forth by the national Plan *Healthy China 2030*. In 2016, the PRC Government launched the comprehensive reform of the national Healthcare system, to be completed according to the targets and methods explained in the Plan. Amongst them, the pharmaceutical system must be deeply reformed. China does not have an "universalistic" Healthcare system, and in the past Chinese citizens must bear the majority of their health cost by themselves. Recently, the importance of spreading the healthcare coverage as much as possible became one of the main targets for Chinese authorities. Although the NHS is still not an "universalistic" system, the wideness of coverage is notably increased, both on the number of citizens (to date, 95%) and on the reduction of *out-of-pocket* expenses. The reform of *Basic Medical Insurance* (BMI) funds, who manage the public expenditure of healthcare treatments, helped the implementation of this process by unifying the role of public insurance.

The Chinese pharmaceutical market is the second market in the world in terms of value of revenues, and the first market in terms of potential customers (according to the last Seventh Population Census, whose results have been made public last June 2021: People's Republic of China has now 1.4 billion resident citizens). Pharmaceutical public expenditure registered a remarkable increase, up to 268 billion USD (a 143% increase in the last 10

years). The bearing of pharmaceutical expenditure on the total healthcare public expenditure, however, dropped from 40.63% to 34.42%, which is the result of new policies on pricing and reimbursement, on one side, and on bidding and procurement tenders, on the other side, to limit the impact of pharma expenditure within affordable and reasonable costs.

The percentage of *out-of-pocket* expenses is still high if compared with the most developed countries. So far, in China patients must bear costs for therapies equal to 28.61% of the total amount. This impact (to be considered as a national average, according to the China Statistical Yearbook) is still remarkable.

To contribute to the reduction of the pharmaceutical expenditure, the Chinese Government issued several policies with the purpose to enhance, and at the same time, provide high-quality medical treatment, and control health public expenditure. The role of generic drugs has significantly changed. Drugs manufactured in China by Chinese manufacturers were generally considered non-high-quality products, with issues both in efficacy and safety. Since 2017, the Chinese Government have issued the new GQCE *Generic Quality Consistency Evaluation*, as a certification of quality for generics. To attend public procurement tenders, generics must have this certification in addition to relevant marketing authorisation issued by the *National Medical Product Administration* (NMPA). At the same time, the policy on procurement tenders has been changed into *Volume-Based Procurement* (VBP) tenders, held on a national scale, and managed by centralised institutions, to make concurrence, within the same procurement batch, between generics and their originators, whether they are "domestic" or "imported". However, the price difference between domestic and foreign products is still the main impact factor on the outcome of tenders.

To coordinate the general reform of pharmaceutical laws and regulation, the State Council issued the new *Drug Administration Law* (in force from January 1, 2019) and the implementing regulations named *Drug Registration Administrative Measures*, in force from July 1, 2020. According to these new regulations, there is no longer a difference between domestic and imported drugs. The classification is now only based on the categories of: (i) innovative drugs; (ii) improved new drugs; and (iii) generics/biosimilars. Thus, the key factor is to acknowledge innovation or not. A specific role has been granted to biotechnological drugs, and their biosimilars: for the first time, there are specific provisions for these products within the laws and regulation dedicated to the pharmaceutical sector. The therapeutic indications of these drugs, often used for chronic and degenerative diseases (with a relevant impact both on public expenditure and on society) urged Chinese lawmakers to regulate biosimilars with the same dignity as generics.

At the same time, the Chinese Government paid close attention to innovation and to the role of imported drugs. With the last revision of *Patent Law*, in force from June 2021, a specific regulation on *patent linkage* and *patent term extension* has been introduced. Innovation comes, traditionally, from foreign R&D: to achieve goals of *Healthy China 2030*, China needs to integrate domestic production with foreign investments on R&D, especially on innovative drugs. IPR related to these products must be protected to encourage investments in China. The reform is, however, not yet complete: the State Council will issue an implementing regulation, which is expected shortly.

Pharmaceutical pricing and reimbursement

Regulatory classification

Similar to many other countries, Chinese pharmaceutical laws regulate the classification in a different manner, related to the scope and purpose of classification.

With referral to the chemical structure of the drugs, the *Drug Registration Administrative Measures*, in force from July 1, 2020, now sets forth the classification in (i) *Traditional Chinese Medicine* (TCM), (ii) biological products, and (iii) chemical drugs. This classification has an impact on the possibility for foreign producers to register their drugs in China, given that foreign-invested manufacturers may not become holders of MA for TCMs. Moreover, the role of biological products now has the same repute of chemical drugs.

With referral to the possibility of purchasing drugs without prescription, drugs are classified as (i) prescription drugs, and (ii) non-prescription drugs. It must be noted, however, that the possibility to purchase a non-prescription drug out of the hospital network (where the prescription is, still, mandatory) is low, because the territorial pharmaceutical network is still marginal if compared with the hospital channel. This has an impact on the pricing and reimbursement outcome: to let physicians prescribe drugs, they must be listed in the drug catalogue managed by each hospital, which usually imposes further discounts to drug manufacturers to accept their product within the list. Furthermore, for those drugs with more dosages, usually hospitals list only one dosage, chosen by the manufacturer.

With referral to the existence or not of IPR, drugs are classified as (i) branded drugs (i.e. patented), (ii) originators (i.e. patent-expired) drugs, or (iii) generic drugs. With referral to biotechnological products, generics are classified as "biosimilars".

Moreover, regarding the grade of innovation of drugs, (i) innovative drugs, and (ii) improved-new drugs must be considered. The main feature of innovative drugs is the possibility to be considered as a new therapeutic class. While, instead, an improved new drug is a new version of an existing product, whose R&D allowed the manufacturer to apply for the registration of a different product.

The registration process of a new drug (to be considered as such if there is no bioequivalence compared with an "originator"), takes, on average, five to six years. The length of the registration process (beginning from investigational new drug activities, in preparation for Clinical Trials, to the release of Marketing Authorization by NMPA) is strongly affected by the performance of Clinical Trials. Clinical Trials usually must be performed in China, and they often take two-thirds of the total time for the registration process. On that, some reforms have been recently approved by the Chinese government, especially allowing foreign manufacturers to shorten the time of registration for those drugs already registered abroad, and to avoid the re-edition of the Trials for the same product (with the same dosage, formulation, indications, release form, etc.). It is possible now to use the report of the Trials performed abroad to apply for drug registration in China, with some limitations and conditions, to demonstrate the absence of differences of impact between Chinese and non-Chinese patients. On that, however, the Trial performed abroad must have involved Chinese patients within the volunteers enrolled in the Trial; the overseas Trial report must also follow other prescriptions and conditions set forth by NMPA to apply for Chinese drug registration.

Special channels are dedicated to innovative drugs to shorten administrative phase of the registration process (so-called green channel).

Who is/who are the payer(s)?

As outlined above, the Chinese Healthcare system is not universalistic. The cost of drugs is often included in the cost of medical treatment. To date, 95% of Chinese citizens have the health coverage through BMI funds. However, the out-of-pocket is still remarkable, with a 26% national average of the total cost of treatment. For those drugs not admitted to reimbursement, the cost of drugs is borne totally by patients.

In recent years, the role of private insurance has increased. To compensate the *out-of-pocket* component, or to expand their coverage to therapies or drugs not admitted to reimbursement, several Chinese citizens took out insurance policies with private healthcare insurance groups. The participation of private insurance to the achievement of targets of *Healthy China 2030* is encouraged by the Chinese Government, who consider private healthcare insurance an important factor to drop the burden of health costs on BMI funds.

BMI funds are organised on a Provincial basis. There is still a gap between first tier cities/provinces (especially the Yangtze River Delta (YRD) megaregion, which includes the municipality of Shanghai, and the two provinces of Zhejiang and Jiangsu) and other territories of China, especially in second or third tier cities (most of them are in the western part of the country). The coverage for health treatment is linked to the place of registered residence of each citizen (so-called HuKou). Foreigners, including those who are residents in China, are not included in the BMI system.

Drugs admitted to reimbursement are listed in the National Drug Reimbursement List (NDRL). Each Province/Municipality/Autonomous Region has its own DRL: usually local Governments, whose local BMI funds have different levels of funding available, and update their local DRL to further reduce the reimbursement price set out in NDRL.

To be admitted to negotiation for NDRL, listing in the National Drug Catalogue for Medical Insurance, Work-related Injury Insurance and Maternity Insurance is a pre-requisite. The National Health Security Administration (NHSA) updates the Catalogue by consultation with other Administration and Government organs, both central and local. Within the Catalogue, western drugs are classified according to ATC international classification.

On the occasion of the last revision of the Catalogue, NHSA stated that medicines eligible for reimbursement by BMI funds must be prescribed by licensed doctors (in out-patient) or ordered by doctors within an in-patient treatment. For those citizens who use their personal private insurance, BMI funds do not bear any costs related to drugs not falling within the described method of prescription.

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

For the time being, there is no standard procedure for entering the list, or for being admitted to reimbursement. In China, the revision of the NDRL must be consistent with the expenses affordable from year to year by BMI funds. NHSA is in charge to ensure the sustainability of the system by adapting the reimbursement of drugs to the expenditure capacity of BMI funds.

According to current regulations, NDRL is revised on a yearly basis. In the past, the List was revised infrequently. Since 2017, Chinese authorities sped up the process to comply with the duty of annual revision. The last revision was made in 2020, and it is in force from March 1, 2021. At that time, the NHSA focused on some therapeutic areas (with specific referral to oncologic drugs), to include these drugs for treatment at a reasonable cost for BMI funds.

Amongst them, several foreign manufacturers did not succeed the revision process, and their products have not been included in NDRL for the current year. While, instead, products of the same therapeutic area manufactured by Chinese pharmaceutical companies have been listed, being now reimbursed. Thus, securing reimbursement for a new pharmaceutical product is the result of different factors: NHSA often urges companies to make significant cut-offs of current prices according to epidemiologic data (with the cooperation of the Ministry of Health, who provide the data) to face those disease having more impact in the reference period. The targeted drugs change from time to time. In 2015, drugs for treatment of Hepatitis had an average reduction of 58% to 67%. In 2017, several drugs for cancer

treatment, cardiovascular diseases and haemophilia passed the negotiation upon a reduction of 44% to 70% of their initial price. In 2018, specific attention was paid to anti-cancer and leukaemia drugs, with a reduction of 56% to 71%. In 2019, several drugs for chronic diseases, cancer and rare disease were included in the negotiation. In 2020, the revision of the List aimed to include 119 new drugs to include all licensed Chinese PD-1 inhibitors (while, instead, all foreign drugs in the same therapeutic area did not pass the negotiation phase).

Currently, a new guideline for the 2021 revision has been already issued by NHSA. The incoming revision process set forth five different phases, namely (i) preparation, (ii) submission, (iii) experts' assessment, (iv) negotiation, and (v) publication of results. The process will be completed by November 2021 when the revised NDRL will be published.

According to the guideline, a specific focus will be dedicated now to identify drugs which have been included in the List for a long time, but with no records of purchase in the national procurement tender platform, in order to take these products out of the new revised List for the year 2021–2022. Moreover, NHSA stated to re-negotiate the payment criteria for those drugs whose price is significantly higher than other medicines in the same therapeutic area, to ease the burden on BMI funds.

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

In NDRL – and in the National Drug Catalogue for Medical Insurance, Work-related Injury Insurance and Maternity Insurance, as well – there are two different classes, respectively category A and B, according to the reimbursement rate and method. Class A drugs are fully reimbursed by BMI funds. However, reimbursement price for Class A is not negotiable. According to current provisions of the *Catalogue*, Class A pertains to commonly used drugs with lower prices. Class B drugs, unlike those in Class A, are not fully reimbursed, with a component of *out-of-pocket* percentage, to be borne by the patient. The reimbursement price of these drugs is negotiable within the revision process of the NDRL. Class B drugs are related to innovative drugs or other drugs for special purposes, with high costs.

Both NDRL and the *Catalogue* mention several drugs "negotiated under the contracted period", all classified in Class B. These drugs basically are related to cancer treatment, or cardiovascular diseases, diabetes, leukaemia, etc. For these drugs, the negotiation has been performed during the validity period of agreement between manufacturers and the Government. All these medicines are included in Class B.

Related to the co-payment method (referred only to Class B, while Class A drugs are fully reimbursed), BMI funds will participate to the payment only upon payment by the patient of the *out-of-pocket* component, which must be paid first.

The reimbursement amount is determined in various manners and methods. Excluding Class A drugs (who are fully reimbursed, with a low price), the last revision of NDRL (in force since March 1, 2021) registered different methods to negotiate and to urge manufacturers to accept significant reimbursement cuts. Several elements are considered. The main one is the IPR International Reference Price. China has a number of comparator Healthcare systems (mainly, western Countries) to refer to: this method, indeed, has a "chain reaction", because similar methods are used also in other Countries which use Chinese reimbursement price as its "reference price".

To negotiate reductions (since 2017, the NDRL has been updated yearly), the Government authorities usually manage the process into two steps. First, manufacturers must offer a price lower than 15% of an undisclosed price (or equal to it), determined by the Government authorities. Only if the offered price matches with the expectations set in the undisclosed price can the manufacturer be admitted to the second phase of negotiation.

The second phase is regulated according to the specific needs of each therapeutic class from time to time. To negotiate the price, authorities often refer to prices of tenders for procurement, and compare the auction prices with the affordability by BMI funds. However, criteria used by the Government to negotiate with companies are not transparent, and companies often must face the choice to either accept a given reduction (in several cases, with the same rate for a whole therapeutic class) or stay out of the NRDL.

Until 2017, due to the slowness in revision of NDRL, remaining out of the reimbursed drugs list meant losing significant market shares. Since 2017, the Government has revised the list on a yearly basis: now the yearly rhythm allows companies to make strategic evaluation on when get into the NDRL, if the reimbursement conditions offered by the Government are satisfactory for the manufacturers' expectations.

Finally, the centralisation of RDL must be considered. Until 2019, the RDL had two different levels, the national one and the Provincial one. Each Province had its own RDL (PRDL), with the power to add or cut up to 15% of the drugs included in NDRL. With the approval of the new National Drug Catalogue for Medical Insurance, Work-related Injury Insurance and Maternity Insurance (issued on August 2019), NHSA started to enforce the centralised level, with specific duties for all Chinese Provinces to strictly abide by the National List, especially with referral to those Class B drugs added by each Province. Within three years, all Class B drugs listed by Provinces in addition to the National Catalogue must be repealed by the Provincial list.

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

When a certain drug is marketed in China, the general rule is to grant the manufacturer to freely determine the price, except for some specific drugs (i.e., narcotics, psychotropic drugs) whose price is still fixed by the Government and cannot be determined by MA holders.

As in many countries, price setting is different according to the main features of each drug. With referral to the existence of a valid patent, or not, for those drugs registered for approval without being protected by IPRs, pricing strategy is strongly affected by the presence of generics in the market. In China, there is no "reference price" for drug purchasing by patients. However, with referral to imported drugs, for example, currently NMPA *National Medical Product Administration* classifies imported off-patent drugs as "generics" with no difference between originators and domestic-manufactured generics. This situation has a strong impact on the initial pricing strategy, given that in recent years foreign manufacturers no longer enjoy any premium or preferential treatment for their drugs either in procurement tenders or in bidding and listing procedures towards hospitals.

Besides that, the time lapse between launch into market and admission to reimbursement is the most critical period, considering that the out-of-pocket component is 100% of the drug price. With specific referral to new drugs and treatment, whose cost is extremely high (and, basically, not affordable with the only out-of-pocket component), price setting has an impact on further negotiations for inclusion in NDRL. Given that NDRL is now updated yearly, the time between the launch on the market and the negotiation for reimbursement is truly short. Thus, companies must pay attention on how to set prices when a new product is launched on the market. On that, several methods are currently available, although, recently, the role of Big Data is getting more important on price setting for new drugs in China. This is especially the case if referred to patients, epidemiologic trends, and to the capacity of expenditure of each BMI fund (citizens who are within Urban BMI get wider coverage than those citizens assisted by Rural BMI), where Big Data can play a key role in pricing. Companies must now set up a launch market price more consistent with the target of potential patients to have a solid basis to further negotiate with NHSA when the annual revision of NDRL is launched.

Finally, the Government has a role on price setting while a new procurement tender is launched. To date, the procurement phase is governed by VBP tenders where each procurement batch is identified by the active substance, and other features such as dosage, formulation, therapeutic indication, etc. The "reference" price is intended as the National Lowest Price: companies who want to attend the tender must offer at least 10% off. The "reference" price is often set in a non-formulaic manner. Companies, on their side, offer remarkable cutoffs, up to 80–90% of the initial price.

Issues that affect pricing

Several factors affect the final purchasing price.

The bidding and procurement tender system: in 2018, Chinese Government launched the so-called VBP Volume-Based Procurement, with the purpose to centralise on a national scale the procurement procedure for drugs. The VBP, initially implemented in four municipalities (Beijing, Shanghai, Tianjin, Chongqing) and seven Provinces, has been extended to the whole Country. For the time being, the VBP has been performed four times. As said, the outcome of each VBP tender shown remarkable cutoffs, up to 90% of initial offer price.

The marginal role covered by pharmacies in the territory force patients to pass through hospital channels basically for all kinds of treatment and therapies. Drug purchasing is a contractual relationship undertaken between patients and hospitals, where the latter purchase drugs by manufacturers through procurement tenders.

The invoicing system named "two-invoice" system: this policy is now valid and operative for the whole Country in the pharmaceutical industry. To prevent excessive increase of price paid by final users, the Chinese Government launched the "two-invoice" system to force manufacturers to have only one distributor between them and the final user, instead of a long distribution chain, which caused a remarkable increase of final prices to include distributors' margins.

Monopolistic practices: for example, by agreements between pharmaceutical companies and distributors to fix the price of products to be resold to third parties. This misconduct is punished by the Chinese Anti-monopoly law (art. 14) as a monopoly agreement. The State Administration of Market Regulation (SAMR) has the task to investigate and fine those companies who force their distributors to fix prices to final users according to manufacturers' needs to restrict concurrence. Recently (April 2021), a Chinese pharmaceutical giant company has been fined by SAMR for 3% of its consolidated income for having committed monopolistic practices by forcing price setting between distributors and final users.

Policy issues that affect pricing and reimbursement

Competition with generics: unlike the previous situation where "originators" enjoyed preferential treatment in procurement tenders, the huge implementation of VBP system forces now all producers to compete within the same procurement batch (being equal formulation, dosage, indication, release, etc.), with no differences between the originator (off-patent) and generics. Thanks to the role covered in API production, Chinese manufacturers have stronger power to discount, compared with foreign producers.

Yearly revision of NRDL: the implementation of revision on a yearly basis of NRDL makes the admission to reimbursement closer to the launch of the product on the market. Thus, pharmaceutical companies must now adjust their pricing strategies to consider that, after being marketed, the "freely fixed" price duration might not reach one year. On the other side, the admission to reimbursement has a positive impact in terms of volumes.

The bidding phase, especially the local one, is still a significant limitative factor for expansion on the market, considering that each hospital has its own drug list, which pharmaceutical companies must apply to enter, in order to let physicians prescribe the listed drugs. This bidding process is still challenging for producers, given that – despite several reforms having already been implemented to ease the reimbursement process – the bidding phase is still in the hands of each hospital.

IPR protection: until 2020, China did not have specific protection to pharmaceutical IPR – different than ordinary rules set out in *Patent Law* for all kind of patents. With the implementation of the China-US Phase One agreement, China approved a revision of the *Patent Law* to include specific rules both on the so-called Patent Linkage, and on the Patent Term Extension. To date, the revision of the *Patent Law* is in force, but the State Council has not yet released the implementing regulations. However, the provision now in force improves the protection for those drugs who enjoy a patent protection that is still valid, to apply for a (Patent Term Extension) prolongation of the Patent exclusivity and to compensate the time needed for completion of Clinical Trials and Registration process. The extension may not exceed five years (art. 42).

On Patent Linkage, the newly approved *Patent Law* (art. 76) grants the right of the patent's owner to file a case before the People's Court on the alleged infringement by the producer of generics, and, based on the pending case, to ask the NMPA to suspend the regulatory process for approval of generics until the final judgment by the People's Court on the existence of the infringement, or not. The implementation of the new rule will allow MA holders of patented new drugs to have a higher level of protection. Thus, the concurrence will be affected given that generics might be prevented from marketing if the Court states that there is an infringement of patent's rights.

Emerging trends

Quality of generics: in procurement tenders, VBP is becoming the only way to allow hospitals to buy drugs through the centralised system governed by online platforms and tenders. In 2015, the Chinese Government launched the "Quality Consistency Evaluation" Program for domestic-manufactured generics, with the purpose to solve critical issues on the lack of quality and efficacy of generic drugs manufactured in China. It was then stated that only those generics with GQCE *Generic Quality Consistency Evaluation* Certificate were admitted to procurement tenders. The VBP, until 2020, strictly abides by this rule. However, with *opinion* no. 2/2021, the State Council gave some new rules to "normalise" the VBP system as the ordinary procurement system for the whole country. On that, the *opinion* states that "those generics who passed the GQCE shall have priority in VBP tenders". It is expected that, perhaps, other generics with no GQCE certificate will be admitted to tenders, to spread concurrence out. However, it is common opinion that generics with a lack of quality or efficacy will not be admitted to tenders: thus, it is possible that the State Council will allow producers to certify the quality and the efficacy of their products on a case-by-case basis.

Patent protection: where the newly approved rules on patent linkage and PTE will be fully implemented, pricing policy of patented drugs will be positively affected thanks to the new regulation for protection of IPR. Generics must now challenge expressly patents to have the chance to register drugs deemed as "equivalent" to their originator. They must also prove that the reference drug shall be acknowledged as "off-patent" instead of "patented". Now NMPA has the power to interfere in the registration process of a generic based on a pending case before the People's Court. The impact on the marketing of "branded" drugs, on one side,

and of "generic" drugs, on the other side, will be remarkable: the level of competition will affect the pricing due to the presence (or the absence) of the generics of a certain originator on the market.

Successful market access

From the introduction of VBP on, the market access strategy has significantly changed, especially for foreign producers. The impact of the duration of Clinical Trials is still remarkable. This is the case especially for new patented drugs. To save as much time as possible for the duration of the patent protection, the best strategy is move up clinical trials, and to get priority in registration and in registration certificate issuance. Usually, clinical trials take four to five years. Without PTE protection, the negative impact on the possibility to enjoy of IPR protection is high. The new rules on PTE will mitigate this impact. However, the comprehensive duration of the protection must not exceed 14 years. For foreign producers, usually the Chinese market is secondary compared to the western market: thus, often the issuance of a registration certificate in China is remarkably close to the Patent-term expiration. For those companies who aim to enter the Chinese market, it is strongly recommended to move up the decision to perform Clinical Trials for China registration.

Furthermore, the price setting strategy must take into consideration the increasing role of Big Data. This is especially the case with referral to drugs who aim to be reimbursed by BMI funds, and it is extremely important to have a deep knowledge of several data, both to setting the market price and to prepare the negotiation with Authorities during the annual revision of the NDRL. The role of Big Data is getting strategic in China. On September 2018, NHC *National Health Commission* acknowledged Big Data as a strategic source to improve the quality of Healthcare system, and urged holders (basically, public institutions of Healthcare System) to share it.

Andrea Sorgato
Tel: +86 21 5150 1952 / Email: andrea.sorgato@studiozunarelli.com

Andrea Sorgato (born in 1977, admitted to the Italian Bar Association in 2004) is the coordinator for China of Zunarelli Studio Legale Associato, Healthcare Dpt. He has experience dealing with Healthcare Law by assisting companies in all issues on Healthcare industry: agreements with the NHS; and reimbursement of health services provided by private hospitals. Andrea assists pharmaceutical companies on all legal issues concerning the sector: market access; pricing and reimbursement; generics; data protection; counterfeiting; registration before Public Authorities; biosimilars; procurement tenders; and clinical trials. He also assists Healthcare Companies for market entry in China: company incorporation; partner scouting; joint-ventures; negotiation with Public Authorities; and commercial agreements with local distributors. Andrea is member of the editing board of "Magazine of Pharmaceutical and Healthcare Law", funded in 1969. He is author of several contributions on Chinese Health and Pharma Law for international magazines.

Zunarelli Studio Legale Associato

West Beijing Rd. no. 1701, Unit 1209, Jing'an China Tower, 200040 Shanghai, P.R. China
Tel: +86 21 5150 1951 / URL: www.studiozunarelli.com

Germany

Dr. Ulrich Reese & Carolin Kemmner
Clifford Chance Partnerschaft mbB

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/overview

Market overview

Statutory and private health insurance

Germany currently has 83.2 million residents, who have access to free healthcare services based on a statutorily funded system, currently operating around 103 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 reached €410 billion (approx. 12% of GDP) in 2019, 29% of which was spent on care-related and therapeutic treatment, 25% on treatment by physicians, 15% on pharmaceuticals, and the remaining 31% on additional services and/or administration. The annual average spent of SHIs between 2009 and 2019 was €252 billion.

As to pharmaceuticals, total spent in 2019 reached approx. €44 billion, €21 billion of which were spent on patent-protected products, which covered only 6.5% of the prescriptions. Approx. 9% of the total health expenditure was spent on generic products.

In 2020, 32 pharmaceuticals (excluding biosimilar) with new active substances were launched in Germany. Six of them are licensed for the treatment of cancer and five for orphan diseases. The launch of 32 pharmaceuticals with new active substances comes very close to the 10-year average of 35 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 (approx. 25%).

Taking into account the demographic change, health expenditures will significantly increase due to the ageing population and the 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 BMG, 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 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 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 1 August 2009.

Rebate agreements

While the aforementioned rebates are mandatory, SHIs and pharmaceutical companies may also enter into individually negotiated, additional rebate agreements on a voluntary basis. The contractual partners have a wide discretion when designing the scope and content of such rebate agreements. The statutory provisions only provide examples for rebates, such as staggered prices depending on the respective quantity or volume discounts and, besides, allow for (other) differentiated regulations on the design of discounts. The conclusion of rebate agreements with SHIs may help pharmaceutical companies to increase sales volumes as pharmacists are under a general obligation to substitute rebated products against non-rebated products. This mechanism can result in a position in which the pharmaceutical becomes a somehow exclusive supplier of the rebated product for the concerned SHI.

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 2018, 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 randomised controlled trials, 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.

Framework agreement on the supply of medicinal products

Dispensing of medicinal products by pharmacists at the expense of the SHI is particularly governed by a framework agreement concluded between the German Pharmacists'

Association ('**DAV**') and the GKV-SV. It contains detailed rules on selecting the right medicinal product, related documentation and invoicing SHIs, including also sanctions for pharmacists who fail to comply with their obligations set out in the framework agreement. Hence, adherence to the framework agreement is a prerequisite for the pharmacists to be permitted to provide services in the SHI system and thus to receive reimbursement. The latest version of the framework agreement entered into force in April 2020, with additional amendments and addendums which followed since.

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; and 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.

German HTA process

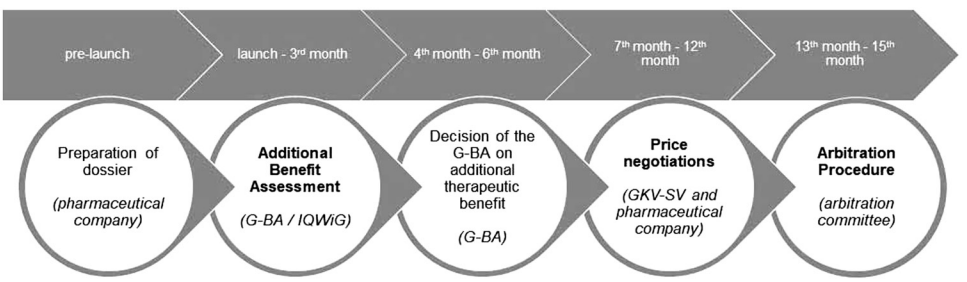
The AMNOG process does not change the general principle that pharmaceutical companies remain free to determine the launch price for innovative pharmaceuticals. Upon launch, however, they are obliged to submit a dossier to the G-BA in order to establish the cost-effectiveness of the new pharmaceutical. 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 the 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.

To ensure broad access to innovative products in all indications, it is a standard and well-established practice to agree on blended prices in such scenario. These blended prices reflect the fact of superiority in one indication and non-inferiority in the other indication.

This practice has been also confirmed by the Federal Social Court 2018, holding that blended pricing is 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. It should be noted, however, that SHIs continue to lobby for the possibility of an indication-specific pricing as an alternative model to the established mechanism of blended pricing.

A similar and to a certain extent related challenge, which can be frequently seen in price negotiations, relates to the question whether a "blended" pricing approach can also be followed in situations in which (i) no additional therapeutic benefit can be established, (ii) a reference group neither exists nor can be established, or (iii) several comparators across different indications with considerably different price levels exist. Such scenarios can create conflicts with the general principle that the negotiated reimbursement price must generally not exceed the annual costs of treatment of the cheapest comparator. However, if comparators relate to different therapeutic areas and indications (e.g. in the field of oncology), this strict principle does not appear to be a suitable basis for the determination of an appropriate price. Only a blended threshold combining annual costs of treatment for different comparators across different indications can ensure an adequate mapping of the different indications of the new pharmaceutical and its future prescription across these indications. While there is a strong tendency in price negotiations towards such blended pricing approach, it should be noted that this principle has not yet been confirmed by the Federal Social Court.

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 the 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 the initial product launch unless suspensive effect is exceptionally granted at the request of either party.

Policy issues that affect pricing and reimbursement

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. In fact, the AMNOG process has undergone a number of adjustment and changes during the last 10 years, but due to the high level of acceptance and flexibility of the AMNOG process rather fundamental reforms are currently not expected. 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; use and relevance of care-related data

The percentage of assessments in which no additional therapeutic benefit could be proven is considerably high (43% of overall 439 assessments by G-BA made between 2011 and 2019). With regard to sub-groups to stratified substances, this percentage increases to 62%, whereas 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, e.g., for respective sub-groups. In approx. 40% of all assessments the G-BA concluded the absence of suitable data. 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. It remains to be seen whether additional data (e.g. real world evidence or data

generated on the basis of the soon to come electronic patient records) will be accepted in the future and can provide a remedy in this respect. A first step was made in 2019 when a new law paved the way for consideration of data collections accompanying the use of the pharmaceutical in defined end exceptional constellations (e.g. orphan drugs). However, relevant institutions of the AMNOG process are still reluctant to recognise the relevance and usefulness of care-related data for benefit assessments.

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 right

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.

Free pricing in the 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 *Sovaldi* 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

EU harmonisation on HTA

The proposal for a European regulation on harmonised rules regarding HTAs by the European Commission published in 2018 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.

The initial proposal faced widespread resistance. *Inter alia*, the German Parliament considered the approach as non-compliant with subsidiarity the principle of and submitted a reasoned opinion to the European Commission in March 2018 on the following grounds: 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. In 2021, the legislative process is still ongoing. Meanwhile, the Council of the European Union published its partial mandate for the negotiations with the EU Parliament on the proposal. A number of additional changes to the draft regulation are in the process of being discussed between EU institutions (Parliament, Council and Commission, so-called trilogues). For example, the joint clinical assessment report at the EU level, which was an essential part of the initial proposal of the EU Commission and which aimed at standardising and unifying HTAs in the European market, is proposed to be ultimately downgraded to a non-binding assessment with a restricted scope. Since the proposal of the Council falls short of the objectives of the overall policy pursued in the field of HTA cooperation, criticism and further discussions are likely to follow. Although it remains currently unclear when an agreement between the relevant EU institutions can be expected, some stakeholders hope that the regulation might come into force during 2022, allowing application as of 2025.

Affordability of innovative pharmaceuticals

Not only in Germany, but also at an international level, a public debate on the affordability of new innovative (and very often expensive) products and therapeutic procedures has developed. This debate has been fuelled by the launch of true 'breakthrough' innovations in the field of gene therapy allowing the cure of chronical diseases but triggering costs in the range of EUR 2 million per patient. Petitions are discussed to introduce a more restrictive pricing regime for orphan drugs. Moreover, a stronger consideration of a cost-benefit ratio of a drug (or therapeutic procedure) is being advocated, so that expensive but less efficient measures could be excluded from reimbursement. Overall, however, it should be noted that these considerations have neither taken on any concrete form, nor are corresponding political developments to be observed. The majority of stakeholders are in favour of using alternative regulatory instruments and savings mechanisms (including more flexibility in pricing and contract models, pay-for-performance or risk-sharing approaches) before shifting the paradigm towards a full cost-benefit analysis comparable to the UK system (as so-called fourth hurdle). It therefore remains to be seen in what way the increasing cost pressure within the healthcare system will be mitigated after the pandemic has subsided.

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, as these pharmacies could then offer prescription pharmaceuticals ('**RX products**') at cheaper prices. National pharmacists are lobbying for a ban of distribution of RX products by mail order pharmacies.

In July 2019, the government eventually issued a draft bill for the Local Pharmacy Support Act ('**VOASG**') to, *inter alia*, respond to the ECJ judgment. According to the draft bill, the fixed price system for RX products would no longer be part of the regulatory regime as stipulated in the German Drug Act. Instead, the provisions governing the reimbursement system for the SHI as set forth in No. 5 Book of the German Social Code would require all pharmacies to comply with the general price regime set forth in the German Ordinance on Drug Prices (i.e. prohibiting the granting of benefits to patients when dispensing RX products) to the extent these products are remunerated by the SHIs. In fact, this proposal would lead to the same effect for foreign mail order pharmacies, at least for serving customers and patients covered by the SHI. In this light, the draft bill was subject to consultation with the European Commission. In October 2020, the EU Commission announced that there were no objections to the proposed legislation. Thus, the VOASG entered into force on 15 December 2020. That being said, it remains to be seen if the ECJ confirms the compatibility of the VOASG with EU law. There are ongoing complaints that the new law still does not fully comply with the principles laid down in the ECJ judgment.

Finally, against the background of the ECJ judgment, a verdict of the Federal Administrative Court issued in July 2020 referred to the question of whether the German pricing regime for RX 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 Constitution. The Federal Administrative Court deemed the pricing regime for RX products compatible with the German Constitution, stating that it pursues legitimate interests of public health.

Rebate agreements

Rebate agreements were criticised in many ways, especially with increased political discussions ongoing in 2019. First, some claim that they are responsible for the increased

supply shortages of pharmaceuticals. This goes back to the fact that sometimes the pharmaceutical company as a contracting party is not able to provide the agreed quantities of pharmaceuticals, while SHIs are expecting these quantities and while patients can generally only be supplied with rebated pharmaceuticals. In contrast, others see the reason for increased supply shortages in a growing number of pharmaceutical companies relocating their production sites and manufacturing capacities to low-wage countries, leading to the effect that only very few contract manufacturing companies are responsible for the (worldwide) production of a concerned API. As a consequence, individual failures in the supply chain have a major impact on the availability of pharmaceuticals. Furthermore, the rebate agreements were criticised due to the lack of transparent selection criteria with which pharmaceutical companies contract negotiations are initiated. As a result, some politicians are calling for the complete abolition of the system of rebate agreements.

To address some of these concerns, the Act on Fair Competition between Statutory Health Insurance Funds ('**GKV-FKG**'), in force since February 2020, particularly loosened the binding effect of the rebate contracts for the pharmacies. Generally, pharmaceuticals that are subject to a rebate agreement must be given preference when dispensed in pharmacies. With around 28,000 rebate contracts in force in Germany, this often means that pharmacies do not have the matching pharmaceutical in stock so that the patient could not be supplied with the 'right' pharmaceutical. To further combat supply shortages, since the GKV-FKG it is now possible to impose stockpiling for pharmaceutical companies as well as wholesalers. Besides, reporting of supply shortages is now mandatory rather than optional as it was the case prior to the new law.

The COVID-19 crisis once again encouraged criticism of rebate agreements, leading to further facilitations relating the rules of rebate agreements, as it was no longer possible to maintain the exclusive supply due to peaks in demand. Although supply shortages and mechanisms to prevent or at least proactively manage them was only recently addressed with the GKV-FKG, the political and also public discussion on the regime of rebate agreements, outsourcing of productions to low-wage-countries and the resulting effects for the supply of patients with pharmaceuticals continues, has been reignited.

Pricing for COVID-19 vaccination outside the usual regime

As in most countries, the costs related to coronavirus vaccination is borne by the German Federal Government, outside the usual and established regime of pricing and reimbursements of vaccines. Based on an ordinance enacted by the German Federal Ministry of Health, all insured (whether privately or publicly) and uninsured persons are granted the right to a free COVID-19 vaccination. The vaccines are procured by the German federal government (respectively the EU) at a central level. Pricing for the procured COVID-19 vaccines are negotiated and agreed between vaccine manufacturers and the German government (respectively the EU), outside the scope of the usual pricing regime for vaccines. With the end of the pandemic situation, COVID-19 vaccines are likely to become part of the usual set of vaccination required and indicated for all or certain groups of the German population. As such, it is expected that they will become subject of the usual pricing and reimbursement scheme applicable for all vaccines covered by the statutory health insurance (e.g. flu 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 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 process of designing clinical studies and the subsequent 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.

Dr. Ulrich Reese
Tel: +49 2 114 355 5491 / Email: Ulrich.Reese@CliffordChance.com

Ulrich Reese was admitted to the Düsseldorf Bar in 1995. He has been a Partner in the Düsseldorf office of Clifford Chance, and Office Managing Partner since September 2014, and co-heads the Global Healthcare & Life Science Sector Group. Ulrich advises a broad range of international corporations on the manufacturing, marketing, distribution and reimbursement of medicinal products and devices and is a private lecturer for pharmaceutical law at the University of Marburg and (co-)author of a number of legal publications such as Dieners/Reese, *Handbook of Pharmaceutical Law*, 2009. Furthermore, he is a regular advisor of the leading trade associations at a national and European level. Ulrich is chair of the expert committee 'Drug and Food Law' of the 'German Association of Intellectual Property Rights' ('**GRUR**') and a recognised leading industry expert by all national and international directories.

Carolin Kemmner
Tel: +49 2 114 355 5488 / Email: Carolin.Kemmner@CliffordChance.com

Carolin Kemmner is a Senior Associate with Clifford Chance and was admitted to the Düsseldorf Bar in 2015. She is a member of the core team of the firm's Healthcare & Life Science Sector Group and advises and represents pharmaceutical, medical devices and life sciences companies on regulatory, market access and healthcare compliance matters as well as on transactions. Carolin provides her clients with expert advice on all aspects relating to the development, advertising, marketing and distribution of various types of healthcare products, with particular focus on pricing and reimbursement. She has published various articles relating to the healthcare sector, in particular to pharmaceuticals and medical devices, and is a member of an expert committee of the German Medical Technology Association ('**BVMed**').

Clifford Chance Partnerschaft mbB

Königsallee 59, 40215 Duesseldorf, Germany
Tel: +49 2 114 355 0 / URL: www.cliffordchance.com

India

Archana Sahadeva
Sahadeva Law Chambers

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 reach USD 372 billion by the year 2022. The Indian Pharmaceutical Industry is the third largest in the world by volume.

Healthcare and pharmaceuticals are at an all-time boom 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.

Despite the exponential growth, India is increasingly combatting a multitude of issues such as: overdependence on imports for Active Pharmaceutical Ingredients ('APIs'); intermediates and key starting materials ('KSMs'); the need for skilled workers in the medical sector; home-based care services; access to medicines and healthcare in rural areas and affordability; and price control, etc.

To add to the list of issues, the country has been exposed to a crippling medical emergency in the form of COVID-19. This resulted in complete stoppage of import of APIs/KSMs from China. Although the same was resumed after a few months, the interregnum months where Indian pharma companies had to manage production with their existing stock, lay bare, highlighting the extent of import dependence of the country. Over the past year, the government has launched a series of schemes/guidelines, etc. to address some of the highlighted issues, which will be discussed in detail in the present chapter.

Market introduction/overview

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. Exports from India satisfy 40% of the generic demand in the US, 25% of all medicines in the UK and 40% of the world's vaccine requirements.[1]

India's domestic pharmaceutical market is estimated at US$ 42 billion in 2021 and is likely to reach US$ 65 billion by 2024 and further expand to reach US$ 120–130 billion by 2030. India's biotechnology industry comprises biopharmaceuticals, bio-services, bio-agriculture, bio-industry, and bioinformatics. The Indian biotechnology industry was valued at US$ 64 billion in 2019 and is expected to reach US$ 150 billion by 2025. India's drugs and pharmaceuticals exports stood at US$ 17.57 billion in FY21 (from December 2020 to April 2021).[2]

For the financial year 2021–22, the Ministry of Health has received an allocation of INR 73,932 crore. Under the Ministry, the Department of Health and Family Welfare accounts

for 96% of the Ministry's allocation at Rs 71,269 crore whereas the Department of Health Research has been allocated Rs 2,663 crore (4% of the allocation).[3]

In the last 16 years, the allocation to the Department of Health and Family Welfare has increased from Rs 11,366 crore in 2006–07 (revised estimate) to Rs 71,269 crore in 2021–22 (budget estimate). Over the period 2006–22, the Compound Annual Growth Rate ('CAGR') has been 13%. CAGR is the annual growth rate over a certain period of time.[4]

Major Segments of Pharmaceutical Industry are Generic drugs, OTC Medicines and API/ Bulk Drugs, Vaccines, Contract Research & Manufacturing, Biosimilars & Biologics.

Regulatory classification

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

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. 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 approval of Drugs, Conduct of Clinical Trials, laying down the standards for Drugs, control over the quality of imported Drugs in the country and coordination of the activities of State Drug Control Organizations by providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act, 1940 ('D&C Act'), the Drugs & Cosmetics Rules, 1945 ('D&C Rules') and other Rules framed under the Act. 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 to give greater focus and thrust on the development of the pharmaceutical sector in the country and to regulate issues related to 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 and is an independent Regulator for prices of drugs ensuring 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/Orders framed under the said Acts in order to further the aforesaid objectives of the Government:

1. **Drugs (Price Control) Order, 2013 ('DPCO 2013')**[5] – Issued in exercise of Section 3 of the Essential Commodities Act, this Order envisages the regulation of prices of essential drugs, including notified medical devices, in the country and monitoring of prices of non-essential drugs.
2. **Medical Devices Rules, 2017**[6] – 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.
   It is pertinent to mention that the applicability of the Medical Device Rules 2017 is to substances as identified in the Rules and also such devices which are notified as drugs from time to time under the D&C Act, 1940. In furtherance to this, the Government of India, on February 11, 2020[7] issued a gazette notification, *inter alia*, declaring essentially all medical devices in the country as Drugs. This notification has been in effect since April 1, 2020. By doing so, with effect from April 1, 2020, all medical devices in the country are regulated as per the provision of the Medical Device Rules, 2017. That apart, the prices of Medical Devices are now regulated and monitored in accordance with the provisions of the DPCO 2013.
3. **New Drugs and Clinical Trials Rules, 2019**[8] – 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 the intention to regulate clinical trials in the country. 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 included Indian patients.
   In fact, the provisions of these Rules were invoked by the Drugs Controller General of India ('DCGI') to grant Emergency Approval to two COVID-19 Vaccines *viz*. Covishield and Covaxin, on January 3, 2021.
4. **The National Medical Commission Act, 2019 (NMC Act)**[9] – This Act was passed to replace the Medical Council of India, with the intent to: (a) provide for a medical education system that improves access to quality and affordable medical education; (b) ensures availability of adequate and high quality medical professionals in all parts of the country; (c) promotes equitable and universal healthcare that encourages community health perspective and makes services of medical professionals accessible to all the citizens; (d) promotes national health goals; (e) encourages medical professionals to adopt the latest medical research in their work and to contribute to research; (f) has an objective periodic and transparent assessment of medical institutions and facilitates maintenance of a medical register for India and enforces high ethical standards in all aspects of medical services; and (g) is flexible to adapt to changing needs and has an effective grievance redressal mechanism and for matters connected therewith or incidental thereto.
5. **Drugs and Cosmetics (Amendment) Rules, 2020**[10] – The D&C Rules were amended, with effect from March 1, 2021, to include added responsibility on a 'marketer' in relation to the quality of drugs and other regulatory compliances, along with a manufacturer. A 'marketer' has been defined as a person who as an agent or in any other capacity adopts any drug manufactured by another manufacturer under an agreement for marketing of such drug by labelling or affixing his name on the label of the drug with a view for its sale and distribution.

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. The prices of drugs are left to market forces. 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 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 certain drugs.

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

The 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 and an annual increase in the MRP up to 10% is permitted for such drugs. 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, or else they risk facing recovery of the overcharged amount along with interest, and in some cases, a penalty.

As of May 2021, the NPPA has fixed the ceiling prices of 884 drugs and retail prices of 1,533 drugs.[11]

As detailed above, price control now extends to medical devices as well. Of these, only four – coronary stents, drug-eluting stents, condoms and intra-uterine devices – are included in the DPCO 2013 and are, therefore, subject to notified price caps. For the remaining medical devices, which has not been included in the NLEM, the NPPA is entitled to monitor their MRPs and impose sanctions on manufacturers if the prices of the devices exceeds 10% of prices prevalent in the preceding 12 months. As of February 16, 2021,[12] the NPPA has identified 24 categories of non-scheduled medical devices and called for price related information from all manufactures/importers of such devices.

While pricing of drugs is extremely essential, especially in a developing country such as India, often there are instances when manufacturing of price-controlled drugs is not economically viable for companies. The law as it stands to date, mandates that any company which wishes to stop production of price-controlled drugs, must issue a public notice and also intimate the Government in this regard at least six months prior to the intended date of discontinuation and the Government may, in public interest, direct the manufacturer of the price-controlled drug to continue with the required level of production or import for a period not exceeding one year, from the intended date of such discontinuation within a period of 60 days of receipt of such intimation.

As recently as August 14, 2020,[13] the price regulator has implemented guidelines for dealing with cases of discontinuation of price-controlled drugs. One of the proposals is to refer cases to a Standing Committee where (a) concerns regarding shortage is apprehended or the formulation is found to be critical for public health, (b) companies are intending to discontinue production/import and sale of scheduled formulations and has already launched or intends to launch new drugs to evade price control, and (c) cases requiring continuance of production/import and sale beyond 12 months. The recommendations of the Committee would then be put up to the NPPA.

Factors affecting pricing of drugs

Trade margins

One of the biggest contributors to prices of pharmaceutical products in the country is trade margins or the margins which pharmaceutical companies allow their distribution chain, including but not limited to wholesalers/distributors/retailers. For formulations whose prices are fixed and controlled by the NPPA, the DPCO 2013 provides for a trade margin of 16%. However, a trade margin is a powerful tool for a manufacturer to incentivise the trader/retailer to dispense a particular manufacturer's product. Thus, irrespective of whether a drug is under price control or not, there is a tendency to offer higher trade margins, which in turn affect the pricing of drugs. While the legislation, as it stands today, does not provide a mechanism for the price regulator to control the trade margins of drugs, of late, the NPPA has taken steps to cap the trade margins[14] in respect of 42 anti-cancer drugs and it proposed that capping of trade margins of other drugs/medical devices would follow suit.

More recently,[15] in the wake of the devastating second wave of COVID-19 that impacted the country in 2021, the NPPA adopted a similar approach to cap the trade margins of oxygen concentrators.

Patented drugs

In January 2019,[16] as a result of an amendment to the DPCO 2013, the Central Government has 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. Thus, patented drugs also fall out of the scope of price control, albeit for a period of five years.

Branded generics

Worldwide and even in India, generic drugs are considered as key competitors to drugs whose patent term has expired and which have fallen within public domain. However, in India generics are made available under multiple brands by different companies. Affixing brands on generic drugs, not only acts as a source originator of the particular drug, but is also indicative of the quality of the product to the prescribing doctor. That being said, branding generics also tend to introduce artificial product differentiation in the market, with no corresponding difference in the therapeutic efficacy of branded and non-branded generics.

Online pharmacies[17]

Of late, the country has seen a growth spurt in online pharmacies, which while on the one hand is viewed as increasing healthy competition in the market, on the other hand, at the time of writing this chapter, it is also seen as unregulated. The Government, on August 28, 2018 published a draft of a proposed amendment to the D&C Act, to include a Chapter on the sale of drugs by an e-pharmacy, the same having been embroiled in legal tussle, with established trade organisations staunchly opposing the amendments.

In fact, in October 2018,[18] the Competition Commission of India published a policy note, focusing on issues which pose a hindrance to affordable healthcare in the country.

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 ambitions healthcare plans in the country. Dubbed as 'Modicare' by the media, the plan has been launched with an intent to provide 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. The State Governments are expected to similarly set up State Health Agencies ('SHA') to implement PM-JAY.

The NHA will provide the 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 INR 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 the 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 under:

1. there is no cap on the size of the family and age of the members;
2. cashless and paperless treatment is available to beneficiaries in 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. the eligible beneficiaries can avail services across India, offering benefit of national portability.

The Economic Survey 2020–21 notes that PMJAY enhanced health insurance coverage. The proportion of health insured households increased by 54% in states that implemented PMJAY. In 2021–22, INR 6,400 crore has been allocated to the PMJAY Scheme, which is double the actual spend two years ago (Rs 3,200 crore in 2019–20).[19] So far, 21,583 hospitals have been empanelled under the Scheme and 12.46 Crore Scheme Cards have been issued to the beneficiaries.[20]

Other policies & emerging trends

The Government of India funds and operates several other healthcare schemes and policies, of which the following may be noteworthy:

- **The Draft Pharmaceutical Policy 2017**[21] – The key objectives of the Policy are:
  - making essential drugs accessible at affordable prices to the common masses;
  - providing a long-term stable policy environment for the pharmaceutical sector;
  - making India sufficiently self-reliant in end-to-end indigenous drug manufacturing;
  - ensuring world class quality of drugs for domestic consumption and exports; and
  - creating an environment for R&D to produce innovator drugs.

  This policy is, however, yet to see the light of day.

- **Telemedicine Practice Guidelines**[22] – With a singular motive to provide equal access to quality healthcare to all, using technology platforms, the government, on March 25, 2020 published the Telemedicine Practice Guideline. The purpose of these guidelines is to give practical advice to doctors so that all services and models of care used by doctors and healthcare workers are encouraged to consider the use of telemedicine as a part of normal practice. The guidelines are intended to assist medical practitioners in pursuing a sound course of action to provide effective and safe medical care founded on current information, available resources, and patient needs to ensure patient and provider safety.
- **Proposed amendment to the New Drugs and Clinical Trials Rules, 2019**[23] – The government of India has on, June 5, 2020, proposed certain amendments to the New Drugs & Clinical Trail Rules, 2019. By the proposed amendments, the government intends to put in place a mechanism to allow the importation/manufacturing of unapproved new drugs into the country, on compassionate grounds, for treatment of patients by hospitals/medical institutions. The amendments, if passed, could prove extremely beneficial to India, especially in medical emergencies such as COVID-19. The amendment is still at the draft stage at the time of writing this chapter.

  Production Linked Incentive ('PLI') Scheme for promotion of domestic manufacturing of critical Key Starting Materials ('KSMs')/ Drug Intermediates and Active Pharmaceutical Ingredients ('APIs') In India.
- **Production linked incentive scheme for promotion of domestic manufacturing of critical key starting materials ('KSMs')/Drug Intermediates and Active Pharmaceutical Ingredients ('APIs') in India**[24] – With an intent to make India self-sufficient and to promote pharmaceutical industry and to ensure availability at affordable prices, the Government notified this Scheme on March 3, 2021. The Scheme intends to boost domestic manufacturing of KSMs/APIs/Drug Intermediates and reduce India's import dependence. It is proposed that a total outlay of INR 6940 crore will be provided as an incentive during the tenure of the Scheme, which is a period of eight years from 2020–21 to 2027–28 subsequent to the base year.
- **Scheme for promotion of Bulk Drug Parks**[25] – The object of this Scheme is to set up Bulk Drug Parks to ensure drug security and to reduce import dependence of APIs. The incentive outlay is INR 3,000 crore for providing financial assistance for construction of Common Infrastructure Facilities in 3 Bulk Drug Parks. The tenure of the Scheme is for the years 2020–21 to 2024–25.
- **Production Linked Incentive Scheme for Promoting Domestic Manufacturing of Medical Devices**[26] – The object of the Scheme is to provide a financial incentive to boost domestic manufacturing and attract large investments in the Medical Device Sector. The tenure of the Scheme is proposed to be from 2020–21 to 2025–26.
- **Scheme for Promotion of Medical Device Parks**[27] – The object of the Scheme is to, *inter alia*, add strength to the existing infrastructure facilities in order to make Indian Medical Device industry a global leader. The tenure of the Scheme is proposed to be from 2020–21 to 2025–26.
- **PM AtmaNirbhar Swasth Bharat Yojana** – A new central scheme PM AtmaNirbhar Swasth Bharat Yojana, announced that the Union Budget 2021–22 is set to be launched with an outlay of Rs 64,180 crore over six years. The scheme will focus on: (i) developing primary, secondary, and tertiary healthcare systems; (ii) strengthening existing national institutions; and (iii) creating new institutions for the detection and cure of new diseases.
- **National Health Policy, 2017**[28] – 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 and at all ages, through a preventive and promotive 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.

- **National Health Mission ('NHM')** – This mission encompasses its two Sub-Missions, The National Rural Health Mission ('NRHM') and The National Urban Health Mission ('NUHM'). The main programmatic components include Health System Strengthening, Reproductive-Maternal- Neonatal-Child and Adolescent Health ('RMNCH+A'), and Communicable and Non-Communicable Diseases. The NHM envisages achievement of universal access to equitable, affordable and quality healthcare services that are accountable and responsive to people's needs. Continuation of the National Health Mission – with effect from April 1, 2017 to March 31, 2020 has been approved by the Cabinet in its meeting dated March 21, 2018. The allocation for NHM in 2021–22 (Rs 36,576 crore) is 4% higher than the revised estimates of 2020–21. Under the NHM, the rural component, i.e., the National Rural Health Mission has been allocated Rs 30,100 crore, (0.2% annual increase over 2019–20). The allocation for National Urban Health Mission is Rs 1,000 crore in 2021–22 (8% annual increase over 2019–20).[29]
- **The Uniform Code of Pharmaceutical Marketing Practices ('UCPMP')**[30] – 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 violating the Code.
- **Central Government Health Scheme**[31] – 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 can procure free/subsidised treatment from empanelled hospitals and obtain medicines from the CGHS dispensaries only. Reimbursements are valid only in the 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, it is aimed at expanding immunisation against seven vaccine-prevented diseases in children by 2020. To boost the routine immunisation coverage in the country, the Government of India has introduced Intensified Mission Indradhanush 2.0 to ensure reaching the unreached with all available vaccines and accelerate the coverage of children and pregnant women in the identified districts and blocks from December 2019–March 2020. Recently, the **Intensified Mission Indradhanush ('IMI') 3.0** scheme has been rolled out to cover children and pregnant women who missed routine immunisation during the COVID-19 pandemic.
- **Pradhan Mantri Bhartiya Janaushadhi Pariyojana** – Launched initially in the year 2008, the object of the Scheme is to provide quality generic medicines of all therapeutic categories to citizens at affordable prices by setting up stores or *kendras* across the length and breadth of the country. The Scheme has been approved for continuation with the financial outlay of Rs. 490 crore for the period from 2020–2021 to 2024–2025. The target is to open 10,500 PMBJP *Kendras* all over the country and to enhance the product basket up to 2,000 medicines and 300 surgical by March 2025.[32]

- **SUGAM** – An online licensing system introduced by CDSCO enables online submission of applications requesting for permissions related to drugs, clinical trials, ethics committees, medical devices, vaccines and cosmetics. The system also builds up the database of approved drugs, manufacturers and formulations, retailers and 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 site and drug formulations. Manufacturers can view their consolidated data about permissions issued to them from State FDA.

Successful market access

Given the exponential rate of growth of the Indian Healthcare sector, any new entrants are designed to succeed. However, with any super-competitive market, a few factors must be considered before entering:

1. 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.
2. Cost of production: While costs of manufacturing may be one of the lowest, expenses of setting up a new manufacturing unit, or for outsourcing to a pre-existing unit must be borne.
3. 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.
4. Distribution network: India already has an extensive manufacture and supply chain in this sector. While, little or no investment would have be made in this area, ensuring that your product is given preference over the other generics for the same composition, may prove to be the main task.
5. Innovation *vs.* generic/biosimilar: A huge factor regarding entry is whether the entity is an innovator or generic manufacturer. Innovator companies can face additional burdens of competing with debatably non-infringing generic companies that are offering their products at sometimes one-tenth of the innovator's selling price. India as a consumer market does not differentiate between generics and innovators. However, as with every consumer set, accessibility and affordability play the key role. It is pertinent to note that the revenue share of generics in the market in 70%, while that of patented drugs is 21%.
6. Return on investment: This factor needs to considered before entering a market where there may be several other companies offering the same medicine. In case of an innovator company, the cost of conducting research in India may be significantly cheaper as compared to other companies. At the same time, the innovated drug may be subject to fierce competition from generics and/or biosimilars even before its launch in the market. At the same time, the price of the innovated drug *vis-à-vis* the actual cost of production may provide an exorbitant price margin to the innovator.
7. Foreign Direct Investment: India allows 100% FDI through an automatic route; 100% is permitted for greenfield pharmaceuticals; 100% is permitted for brownfield pharmaceuticals; 74% through automatic route; and the remaining (up to 100%) through Government approval.

8. 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 under a granted patent is only imported, 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.
9. Patent system: The patent regime in India prescribes a stricter test for patentability in 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 case 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.
10. Drug licence: Any new drug will have to undergo the entire procedure of obtaining an approval 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 granting of a drug licence.
11. Advertising & Marketing: With the D&C Rules imposing a ban on advertising of drugs, marketing of drugs is challenging, especially for new entrants who also require to penetrate the existing trade channels. The Essential Commodities (Control of Unethical Practices in Marketing of Drugs) Order, 2017 proposes further restrictive incentives to medical practitioners and bars unethical marketing of drugs.
12. Research Opportunities: As mentioned above, India offers an exceptional platform for contract-based research and development. With a massive human resource and scientist pool, conducting research in India is a promising endeavour for new entrants.

With all its pros and cons, India still 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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Archana Sahadeva
Tel: +91 981 875 8576 / Email: archana@sahadevalawchambers.com

Ms. Sahadeva is a graduate of the Osmania University and holds a Master's in Business Law ('MBL') from the National Law School of India University ('NLSIU'), Bangalore. She holds a Bachelor's Degree in Electronics (Hons.) from the University of Delhi. She is also an Advocate-on-Record before the Supreme Court of India. She was admitted to the Bar in 2007. Her areas of expertise, in brief, include handling trade mark and copyright related litigation before various courts, including the Supreme Court of India. She has extensive experience in disputes pertaining to Pharma Regulatory and Policy issues. Pertinently, she handles issues arising out of the Drugs & Cosmetics Act, 1094, Drugs & Cosmetics Rules, 1945, Medical Device Rules, 2017, New Drugs and Clinical Trails Rules, 2019, Drugs (Price Control) Orders of 1995 & 2013, The Food Safety and Standards Act, 2006 etc., including but not limited to litigations and proceedings before the High Court, the Supreme Court, the Department of Pharmaceuticals ('DoP') and the National Pharmaceutical Pricing Authority ('NPPA'). She is actively involved in policy issues as well. She has been a regular Speaker at various Seminars and workshops and is a member of Intellectual Property Attorneys Association ('IPAA').

Sahadeva Law Chambers

C-65, First Floor, Jungpura Extension, New Delhi – 110 014, India
Tel: +91 981 875 8576 / +91 11 4213 3603

Ireland

Marie Doyle-Rossi & Maree Gallagher
Covington & Burling LLP

Abstract

In Ireland, State expenditure on medicines is approximately €2.7 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. Except for cancer drugs, there is a uniform application procedure to have a product added to this 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, and especially medicines for chronic diseases, is increasing. Population grew by an estimated 3.8% from the last census in 2016 to 2019, with the most significant growth in those over age 65.

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 costeffectiveness of their products. Despite these reforms, suppliers face significant challenges in securing reimbursement of new medicinal products in Ireland, especially hi-tech medicines and medicines for rare, 'orphan' diseases.

Market introduction/overview

Ireland has a two-tier healthcare system, 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. While Ireland spends around one-fifth more on health *per capita* than the EU average, public expenditure is below the EU average. Private health insurance spending explains this difference.

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 (the 'List of Reimbursable Items') and HSE expenditure on medicines is approximately €2.7 billion *per annum*.

Over the past decade, the population of Ireland has increased by nearly 7% to approximately 4.98 million. The demographic ageing of the population means that demand for medicines, especially medicines 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. This framework agreement has been extended to 31 July 2021, and at the time of writing (July 2021), further negotiations are underway. Despite the savings provided by these measures, there has been relatively 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 are typically deemed cost-ineffective when assessed on standard pharmacoeconomic criteria. However, even those products that are deemed to be costeffective are facing reimbursement delays due to the lack of overall affordability for the Irish healthcare system. It remains to be seen what effect the COVID-19 pandemic will have on healthcare expenditure for innovative medicines. 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 nonprescription 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 nonprescription 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) (commonly known as the 'medical card' scheme)*: a patient receives their medicines after paying a €1.50 per item prescription charge (up to a maximum charge of €15.00 per family per month) or for a patient aged over 70, the prescription charge is €1.00 per item (up to a maximum charge of €10.00 per person or family per month). The pharmacist receives a dispensing fee. The GMS scheme applies to those who do not have sufficient means to pay for their medicine.

- *Drug Payment Scheme (DPS)*: a patient pays a maximum of €114 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 a dispensing fee. The DPS is not means-tested, and therefore does not depend on a patient's income or other circumstances. Anyone who is ordinarily resident in Ireland can apply.
- *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 like the DPS, the pharmacist receives a dispensing fee.
- *Hi-Tech Scheme*: a patient receives expensive medicines required for long-term care either pays the first €114 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 under the GMS 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 the Public Services Pay and Pensions Act 2017 (Payments to Community Pharmacy Contractors) Regulations 2019 (SI 639/2019).

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 Items' (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. Except 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, after two extensions, until 31 July 2021 (2016 Agreement). IPHA and the State entered into negotiations on a new framework agreement on 25 June 2021.

The 2013 Act, together with the 2016 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 CostEffectiveness 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. A summary of each report is published on the NCPE website.
- 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 Agreement, where the HSE recommends a drug for reimbursement, but is unable to fund the product from 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 2016 Agreement. In practice, however, 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 exfactory price (price to wholesaler) in the UK and 13 EU Member States (namely, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Luxembourg, Portugal, the Netherlands, Spain and Sweden). Medicinal products are subject to an annual price realignment to the average ex-factory price of these 14 reference countries and only downwards price realignments are permitted. Suppliers must pay the HSE a rebate of 5.5% (1 August 2018–31 July 2020) of the ex-factory price. IPHA has said its member companies would continue to pay the HSE a rebate of 5.5% on medicines for supply to community and hospital services.

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 that require refrigeration.

The 2013 Act also introduced a system of reference pricing for generic and brand-named medicines that are deemed interchangeable. The 2013 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 IPHA. 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. However, 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 countries. If the product is not available in all 14 countries 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 countries in which the medicine is available. Where the medicinal product is not available in any of the reference countries, 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 to be not 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 was approximately €2.2 billion in 2020. It 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 (which increased over 70% from 2011–2017).

Similar to other developed countries, Ireland is experiencing demographic change. In 2019, the percentage of the population who were over 65 was over 14% (up from 12% in 2013). 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 often 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. In 2020, no specific funding was allocated for new medicinal products and new indications of existing products. Instead, the HSE was obliged to consider funding each newly recommended medicine in the context of its limited available resources. 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. Such patient opposition has led to the HSE funding specific medicines in a number of cases. 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 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. Recently, government allocated an additional €50 million to new medicines in the 2021 State budget.

The State needs to adopt a pricing and reimbursement policy that strikes a balance between affordable access to medicines and fostering innovation. However, it remains to be seen what impact the COVID-19 pandemic will have on healthcare expenditure.

Emerging trends

COVID-19: 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. The 2016 Agreement has been extended to 31 July 2021 and the new agreement currently under negotiation between the Government and industry is likely to focus on access for new innovative products on the one hand, and on cost and efficacy on the other hand. The pressure on the HSE's resources and expenditure is only likely to be increased by the COVID-19 pandemic.

Biosimilars: Despite the mandatory price cuts in innovative biologics following the entry of a biosimilar onto the Irish market, the uptake of biosimilars in Ireland remains low. In 2019, the HSE's Medicines Management Program reviewed the use of TNF-α inhibitors and recommended the use of certain biosimilar versions of Humira® (INN: Adalimumab) and Enbrel® (INN: Etanercept) as the best-value biological (BVB) medicines. In 2020, two additional TNF-α inhibitor biosimilars were designated BVB medicines. From 1 February 2020, the HSE's policy is that all adult patients commencing treatment with Adalimumab or Etanercept should be prescribed a BVB medicine and physicians should also consider switching existing patients to a BVB medicine. The HSE has indicated it intends to expand the BVB scheme to other therapeutic areas, such as colony-stimulating factors and erythropoietins.

Hi-tech drug reimbursement: The Drugs Group of the HSE continue to recommend additional drugs for reimbursement under the Hi-Tech Scheme. Between July 2020 – March 2021, the Drugs Group recommended the following drugs:

- Tagrisso for 1L EGFR mutation positive non-small cell lung cancer;
- Lynparza for 1L maintenance in BRCAm positive advanced ovarian cancer;
- Prevymis for prophylaxis of CMV infection;
- Rinvoq for rheumatoid arthritis;

- Zejula for ovarian cancer;
- Dupixent for atopic dermatitis in adults;
- Dupixent for atopic dermatitis in adolescent;
- Lenvatinib for hepatocellular carcinoma; and
- Fremanezumab for migraine prophylaxis.

Reimbursement delays: Over recent years, there has been a growing trend in reimbursement delays. For example, for 13 new innovative medicines recently reviewed by the HSE, the average waiting time for a reimbursement decision was 1,000 days from the product being granted a marketing authorisation. Generally, delays occur when price negotiations are required between the HSE and pharmaceutical companies, but can also occur after a new medicinal product has received a positive HSE decision that it will be added to the Reimbursement List for affordability reasons. Funding arrangements for new drugs in 2021 may assist with this. Nonetheless, for the time being, there are considerable delays in market access for innovative medicinal products in Ireland compared to the 14 reference countries.

Another recent survey of 34 countries (24 EU, and 10 non-EU) ranked Ireland 34th for time to availability of medicines. 'Availability' was defined as 'inclusion of a centrally approved medicine on the public reimbursement list in a country'. Ireland showed an average delay of 477 days from central EU marketing authorisation to local reimbursement; a rate that is four times slower than Germany's.[1] That pace is significantly slower than the standard of 180 days from request to decision that the HSE is obliged to adhere to. The survey also found that only 54 of the 152 drugs surveyed were approved in Ireland.

These delays are leading to increasing frustration and lobbying from the Irish innovative industry and from patient groups. IPHA reported in February 2021 that €30m was released for the reimbursement of 'backlogged' medicines at same time as the industry agreed an extension to the 2016 Framework Agreement.

Orphan products: 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 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. Proposed legislation, the Health (Pricing and Supply of Medical Goods) (Amendment) Bill 2018, sought to establish a unique process for assessing orphan drugs for reimbursement in Ireland but the Bill lapsed when the Government was dissolved in January 2020 for a general election. 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 coordination 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. Negotiations were underway at the time of writing (July 2021) on a replacement agreement to the 2016 Agreement, though there was no indication that the established criteria would change.

It remains to be seen what effect COVID-19 will have on healthcare expenditure, but any new pricing and supply framework agreement negotiated between the Irish Government and industry is still likely to focus on access for new innovative products and, in turn, cost and efficacy.

* * *

Endnote

1. EFPIA Patients W.A.I.T. Indicator 2020. Available at: https://www.efpia.eu/media/602652/efpia-patient-wait-indicator-final-250521.pdf.

Marie Doyle-Rossi
Tel: +353 1 531 4479 / Email: mdoyle-rossi@cov.com

Marie Doyle-Rossi is an associate in the Life Sciences practice of Covington & Burling LLP and is both an English and Irish qualified solicitor. Her practice focuses on life sciences regulatory, commercial and administrative law matters under EU, UK and Irish law.

Ms. Doyle-Rossi counsels medical device, biotechnology, pharmaceutical and consumer product manufacturers and trade associations on a broad range of issues, both contentious and non-contentious. This includes strategic legal and regulatory advice on biologics, orphans, market and data exclusivity, clinical trials, pricing and reimbursement, product life-cycle management, data privacy and compliance issues. She has particular expertise in GxP matters.

Ms. Doyle-Rossi also advises on corporate and commercial transactions, particularly regulatory due diligence.

Maree Gallagher
Tel: +353 1 531 4457 / Email: mgallagher@cov.com

Maree Gallagher is an Irish qualified solicitor who advises clients on EU food and life sciences law and policy.

Ms. Gallagher has over 20 years of experience working with companies to bring their products to market. She is regarded as one of Europe's leading crisis management experts and has extensive experience advising FMCG companies on product recall and reputation management across the EU.

Ms. Gallagher's expertise covers drugs and devices with a particular emphasis on biologics and GxP, food and beverages, AGRI, and consumer products. Her practice covers a very wide spectrum from product licensing to composition, labelling, and marketing. Her clients include large public companies as well as multinationals operating in the Life Sciences and FMCG sector across Ireland and the EU.

Ms. Gallagher also represents businesses facing regulatory enforcement action, and she acts as a strategic and public affairs adviser in her specialist areas.

Covington & Burling LLP

13 Merrion Square, Dublin, D02 HW89, Ireland
Tel: +353 1 531 4457 / URL: www.cov.com

Italy

Sonia Selletti, Mauro Putignano & Francesco Tiboni
Astolfi e Associati, Studio Legale

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, and within 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); and automatic switches from originator to equivalent drug, 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 seven to eight 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 have secured for Italy a strong position in the international ranking (*Bloomberg Global Health Index*, 2020).

Nevertheless, the value of rankings is often relative, since they vary depending on the valuation criteria used. Recent studies (*Gimbe*, 2019) 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, Italy witnessed a severe reduction in its capital spending in health: levels have been on a negative trajectory between 2010 and 2016 with only a small uptick in 2017 (OCSE, *Health at a Glance: Europe 2020*).

The 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 2018, total public and private pharmaceutical spending amounted to €29.1 billion, of which 77% was funded by the SSN. In the media, for each Italian citizen, the expenditure amounts to about €482. Spending paid by patients recorded an increase of +3.8% compared to 2017. In 2019, total pharmaceutical spending amounted to €30.8 billion, of which 76.4% was paid by the National Health Service (*Report OsMed*, 2020).

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. The incidence of healthcare expenditure on PIL increased by one point, from 5.5% in 2000 to 6.5% in 2018. Further increases of up to €120 billion were expected until 2021, even before the recent decisions relating to the COVID-19 crisis.

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 2020) 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 (+26%).

The sector is therefore an important national economic growth driver, in terms of both employment and investment.

The National Health System

Italy currently has 59.25 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 drugs, the State, through the *Agenzia Italiana del Farmaco* (AIFA – https://www.aifa.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 a 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"; and 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%.

Pursuant to art. 11, co. 1 *bis*, d.l. 158/2012, 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, and 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.

With Determination no. 166 of 10.02.2021, AIFA established the criteria for the inclusion of drugs in the Transparency List. In addition to drugs 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, are included in the Transparency List:

- drugs with the same dossier and authorised on the same legislative basis, with different names, and the same or different marketing authorisation holders;
- fixed combination application as provided by art. 12 d.lgs. 219/2006; and
- drugs that have not been registered as generic drugs but are deemed equivalent medicines from a clinical and/or therapeutic viewpoint by the AIFA Technical Scientific Committee on the basis of, *inter alia*, *in vivo* and/or *in vitro* comparative studies or the possibility of exemption from such studies.

The cases of removal from the Transparency List are also specified.

Determination no. 166/2021 pursues simplification and transparency, but has introduced some profiles of uncertainty. For this reason, it has been the subject of judicial appeals, not yet defined.

Biosimilars are expressly excluded from the Transparency List so that there is no automatic replacement.

How patients obtain 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 programmes. 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.

Recently AIFA required that a prior request for compassionate use is unsuccessfully undergone before asking for funding. It is debatable whether a drug listed in C-nn class can have access to the fund.

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 Ministry Decree issued on 1 August 2019, published in the Official Gazette on 24 July 2020, which repealed the deliberation no. 3/2001 of the inter-ministerial economic planning committee (CIPE).

With respect to the CIPE deliberation, the new Decree applies not only to authorised drugs, but also covers the inclusion of drugs in the list of law 648/1996 (*off-label*) and the purchase,

for public healthcare requirements, of specific categories of class C and class C-nn drugs by SSN entities.

A new departure is the emphasis placed on the additional therapeutic value that the drug must deliver in relation to the main therapies with which it is compared. If an additional therapeutic value is not proven, the company will have to provide further elements of interest, in terms of economic benefit for the SSN.

The Decree goes on to specify the elements to be set out in the scientific documentation presented by the company in its negotiation application.

Specifically, the company must provide information on the marketing, consumption and reimbursement of the medicine in other countries, on its production capacity and ability to manage contingencies, the details about the drug's patent status and also quantify any public-sector contributions and incentives the company receives for its R&D programmes.

It is also necessary to provide an estimated market share it expects to acquire in Italy in the 36 subsequent months, indicate the forecast expenditure and spending variations for the SSN arising from the proposed prices and quantify the economic and financial impact of marketing, for the additional purpose of the possible inclusion of the drug in the Early Access programs (law 648/1996).

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.

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; and
- 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 60 days before the natural expiry of the contract.

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 Decree 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"; and/or
- should new evidence emerge on the effectiveness and safety of the medicine suggesting that its therapeutic positioning has changed or substantially reducing the clinical benefits estimated at the time of the negotiation, or should a shortage arise.

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.

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 2020).

The negotiation procedure

The negotiation procedure is regulated by law. The standard procedure, for general application, has a duration of 180 days 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 MA is issued, 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.

During the negotiation, the drug 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 in relation with the comparators, 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.

The deadline for the conclusion of the procedure is 180 days. Only one interruption is permitted, which may be at the request of either the AIFA or the company. Should the maximum suspension period of 90 days elapse without any outcome, the negotiation procedure ends without an agreement and the drug is place in the class C.

In case of a 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.

It should be noted that although the decree recitals cite Resolution WHA 72/2019 on the transparency of drug prices, it does not include explicit indications intended to guarantee advertising of the net prices.

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.

For 2021 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 7.85% of the healthcare fund; and direct procurement spending for drugs purchased directly by the local health authorities, accounting for 7% of the fund.

Following the recent Reform introduced in December 2018, the Italian system sets out different rules for the two types of spending as of 1 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.

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 programmes; 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.

A recent sentence of Council of State has established that in the case that two drugs share all the levels of the ATC, including the fifth, concerning the active substance, they can be automatically considered "therapeutically equivalent", at least until scientific evidence to the contrary.

Prescription guidelines for biosimilars

Prescription guidelines adopted by the Regions to encourage prescription of lower-cost biosimilars affect market access policies. Biosimilars contribute to reduce spending: consumption of biosimilars, i.e. biological drugs similar to branded originators, but with an expired patent, grew by 80% in the 2019. Automatic replacement with biosimilars (and among biosimilars) is not permitted; 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; and
(ii) the physician's decision-making independence is guaranteed with regard to therapeutic suitability.

The physician also must justify the therapeutic reason for which he intends to prescribe a more expensive drug to his patient. According the Second Position Paper on biosimilars, the general rule is to prefer the biosimilar, since it has the same level of efficacy and safety as the more expensive *originator*.

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:

- a periodic review of the National Pharmaceutical Handbook and the adoption of initiatives to attenuate or eliminate price differences between therapeutically equivalent drugs;
- a 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);
- an update of the criteria for recognition of the innovative status of applicable drugs (also for price negotiation purposes);
- a 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

- A 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.
- 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. PSPs have played a central role in the current COVID-19 pandemic: home delivery for drugs, home administration of therapies, tools to manage from remote the assistance to patience.

COVID-19 urgent and interim measures on "early access" therapies

In order to face the emergency from COVID-19, in the absence of a treatment, physicians were forced to act in an emergency environment and have often applied off-label drugs and

drugs still under trial obtaining encouraging results. To foster and speed up the safe use of such products to save patients, the Italian Legislator introduced some extraordinary and temporary provisions such as article 40 of Law-Decree issued on 8 April 2020, providing that for the therapeutic use programme, presented by the pharmaceutical companies for the use of drugs, in the context of compassionate use in multiple patients and on the basis of a predetermined and identical clinical protocol for all the patients, the requests must be sent, together with a brief synopsis and protocol, to AIFA and to the Ethics Committee of the National Institute for Infectious Diseases (INMI) Lazzaro Spallanzani of Rome (who has assumed the role of National Ethical Committee). The approval of a therapeutic use programme by the INMI Spallanzani Ethics Committee, limited to the period of emergency, has immediate effect on the whole Italian territory. Instead, the nominal therapeutic use (i.e. named patient) based on scientific evidence and not within a defined clinical protocol, must be submitted to the local ethics committees (such as already established by the Ministerial Decree of 7 September 2017). Moreover, Article 27, paragraph 1, of the aforesaid Decree-Law also introduced a facilitated tax treatment with reference to the provision, by the pharmaceutical companies, of the drug free of charge for compassionate use for patients with COVID-19.

Aside to these efficient measures, a Task Force has been set up in AIFA and extraordinary meetings of CTS and CPR have been planned to ensure fast evaluation of products supporting the treatment of COVID-19 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, was drafted but not yet published. 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.

Sonia Selletti
Tel: +39 02 885 561 / Email: sonia.selletti@studiolegaleastolfi.it

- Sonia Selletti (born 1967) graduated in law, University of Pavia, 1991.
- Admitted 1994, Milan. Supreme Court Barrister.

After practising in international law and a period as head of the internal legal office of an Italian pharmaceutical company, in 1995 Sonia joined Astolfi e Associati where she is Partner Head of the Life Science Group. She has 25 years of expertise in the pharmaceutical and health legislation for medicinal products, cosmetics, medical devices and health supplements.

Sonia is a member of Supervisory Bodies in sanitary and pharmaceutical companies pursuant to Legislative Decree 231/2001 aimed at preventing criminal liabilities of corporate entities.

She is the director responsible for the specialist legal journal, *Rassegna di diritto farmaceutico e della Salute*. She has authored various publications on legal topics concerning Life Sciences and is co-author of "e-patient e social media", *Il Pensiero Scientifico Editore*, 2016.

Sonia collaborates with the University of Pavia. She also provides training courses in the healthcare and pharmaceutical field at CME events for health professionals.

Mauro Putignano
Tel: +39 02 885 561 / Email: mauro.putignano@studiolegaleastolfi.it

- Mauro Putignano (born 1969) graduated in law, University of Milan (*Università Cattolica del Sacro Cuore*), 1995.
- Admitted 1998, Milan. Supreme Court Barrister.

After a collaboration with the University of Castellanza and the University of Milan (*Università Cattolica del Sacro Cuore*), in 2014 Mauro Putignano joined Astolfi e Associati where he is an associate and collaborates, in particular, with the Life Science Group.

He has expertise in the field of administrative law, with particular reference to the pharmaceutical and healthcare area.

He is a member of the editorial board of the specialist legal journal, *Rassegna di diritto farmaceutico e della Salute*.

Francesco Tiboni
Tel: +39 02 885 561 / Email: francesco.tiboni@studiolegaleastolfi.it

- Francesco Tiboni (born 1981) graduated in law, University of Milan (*Università Cattolica del Sacro Cuore*), 2010.
- Admitted 2014, Milan. Supreme Court Barrister.

In 2020 Francesco joined Astolfi e Associati where he currently works as an associate and collaborates, in particular, with the Life Science Group.

He mainly works in the field of civil law as well as in the sector of pharmaceutical and health law (Life Science).

He is a member of the editorial board of the legal review "*Rassegna di diritto farmaceutico e della salute*".

Astolfi e Associati, Studio Legale

Via Larga, 8 – 20122 Milano, Italy
Tel: +39 02 885 561 / Fax: +39 02 8 855 622 6 / URL: www.studiolegaleastolfi.it

Japan

Kazuhiro Kobayashi
Oh-Ebashi LPC & Partners

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 such universal health insurance coverage.

Size of market

The Japanese health insurance market is the second largest in Asia and the third largest in the world.

Important issues

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 manufacturing and sale of drugs 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), and (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.[1] A Marketing Licence can be obtained from the governor of the prefecture as designated by the MHLW.[2] Such licence allows the holder to engage in the business of marketing pharmaceuticals, quasi-pharmaceutical products or cosmetics (the "Pharmaceuticals, Etc."). Depending on the type of products, there are several kinds of Marketing Licences, such as the First-class Marketing Licence for Pharmaceuticals, which is a Marketing Licence for prescription pharmaceuticals, and the Second-class Marketing Licence for Pharmaceuticals, which is a Marketing Licence for non-prescription pharmaceuticals. In order to obtain the Marketing Licence, (i) the methods of quality control for the Pharmaceuticals, Etc., must comply with the good quality practice (the "GQP") specified by the Ministerial Ordinance on Good Quality Practice for

Pharmaceuticals, Quasi-pharmaceutical Products or Cosmetics,[3,4] 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.[5,6]

Licence for Manufacturing

A Licence for Manufacturing is necessary to manufacture Pharmaceuticals, Etc. in Japan.[7] A Licence for Manufacturing can be obtained from the governor of the prefecture or the Director of the Regional Bureau of Health and Welfare as designated by the MHLW.[8] The Licence for Manufacturing pharmaceuticals shall be granted in accordance with the categories of (i) biological preparations, pharmaceuticals manufactured using a genetic modification 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).[9] Generally, the Pharmaceuticals and Medical Devices Agency (the "PMDA"), as designated by the MHLW, will conduct an investigation regarding any application for a Licence for Manufacturing.[10]

Additionally, a foreign manufacturer intending to manufacture Pharmaceuticals, Etc. that are exported to Japan can be accredited by the MHLW.[11] Generally, the PMDA, as designated by the MHLW, will conduct an investigation regarding such accreditation.[12]

Application for approval for marketing brand-name pharmaceuticals

A person who intends to market pharmaceuticals[13] must obtain approval from the MHLW for each such item.[14] Such person must hold a Marketing Licence[15] and such pharmaceuticals must be manufactured by the holder of a Licence for Manufacturing or must be imported from an accredited foreign manufacturer.[16] The methods to control manufacturing or the quality of the pharmaceuticals[17] 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.[18,19] However, if an item is a pharmaceutical (i) which is urgently needed in the prevention of the spread of a disease, etc. that may pose serious effects on the lives and health of the general public, for which no proper method of prevention is available other than the use of such pharmaceutical, and (ii) which are authorised to be marketed in a specified foreign country having a marketing approval system equivalent to that of Japan, the MHLW may grant special approval for such item even without certain requirements.[20] On May 7, 2020, such special approval was granted for Remdesivir as a treatment for severely ill COVID-19 patients. In addition, a person engaged in manufacturing, etc. of pharmaceuticals in foreign countries (the "Foreign Manufacturer") can apply for approval for marketing pharmaceuticals from the MHLW through a holder of a Marketing Licence designated thereby.[21]

Such person shall make an application by attaching data concerning the results of clinical studies and other pertinent data to their written applications.[22] The type of data that must be attached depends on the type of pharmaceuticals. In case of brand-name prescription pharmaceuticals, (i) data concerning the results of clinical studies collected by clinical trials,[23] which must be conducted in accordance with the good clinical practice (the "GCP") specified by the Ministerial Ordinance on Good Clinical Practice for Drugs,[24] 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.[25,26] In case of the Orphan Drugs (i) in which the number of subjects is lower than the number specified, and (ii) which shall have particularly excellent value for usage, and the Precursor Drugs, (i) which shall have different mechanisms of action, and (ii) which shall

have particularly excellent value for usage, and the Specialized Drugs, (i) which meet a demand for the specified usage greatly unsatisfied by other drugs, and (ii) which shall have particularly excellent value for usage, designated by the MHLW,[27] etc., the MHLW may exempt the applicant from attaching such data.[28]

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 the data described above.[29] 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, as designated by the MHLW, will conduct an examination regarding an application for marketing approval.[30] The MHLW may prioritise an examination for the Orphan Drugs, the Precursor Drugs, the Specialized Drugs, etc.[31]

In cases where the MHLW receives an application for approval for marketing of pharmaceuticals with new active components, etc. (the "New Pharmaceuticals"), the MHLW shall hear the opinions of the Pharmaceutical Affairs and Food Sanitation Council in advance.[32]

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.[33] In the case of orphan drugs, etc., such investigation period shall be 10 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 and one who has obtained a licence for sale of pharmaceuticals (the "Licence for Sale") can engage in the business of selling pharmaceuticals.[34] As mentioned above, however, a holder of a Marketing Licence can sell pharmaceuticals to a proprietor of a pharmacy and a holder of a Licence for Sale and a holder of a Licence for Manufacturing can 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, etc.[35] and one who establishes a pharmacy shall 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.[36] The Licence for Store-based Distribution shall be obtained from the prefectural governor for each store.[37] 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.[38] 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.[39]

A pharmacy can sell all kinds of pharmaceuticals; however, it can only sell prescription pharmaceuticals to those who hold a prescription.[40] A holder of a Licence for Store-based

Distribution can sell only Pharmaceuticals Requiring Guidance, which means behind the counter pharmaceuticals, and OTC Pharmaceuticals.[41] A holder of a Licence for Household Distribution can sell only certain OTC Pharmaceuticals.[42]

Health insurance system/who are the payers?

Kinds of health insurance

Under the Health Insurance Act, certain workers employed at certain places of business[43] are insured by the Japan Health Insurance Association (the "JHIA") and health insurance societies.[44] An employer who has one or more certain places of business regularly employing a certain number or more of such workers or employers can establish a health insurance society.[45] 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.[46] 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.[47]

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 the elderly aged 75 and over under the Act on Assurance of Medical Care for Elderly People.[48] 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[49,50] and a pharmacy providing services covered by health insurance shall fill a prescription with pharmaceuticals listed in the Drug Price Standard.[51,52]

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;[53] (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 billing therefor;[54] and (iii) health insurance providers pay to the payment agency upon being billed thereby.[55]

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; however, 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 can 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.[56] 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 of an application for listing in the Drug Price Standard is very high. The MHLW shall consult with the Central Social Insurance Medical Council (the "CSIMC") regarding the listing of such pharmaceuticals.[57] Then, the MHLW prepares a draft of the 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 can 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.[58] 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 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 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 50% of the New Pharmaceuticals. If such generic drug is a biosimilar, its Drug Price shall be approx. 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 the case that there 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 made approximately once every year. The MHLW may conduct a necessary survey to ensure the appropriateness of the Drug Price.[59] In 2021, the reduction rate was subdued because of the effect of COVID-19.

The Drug Price of the New Pharmaceuticals[60] 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 gradually lowered to the Drug Price of the generic drugs if the replacement rate of generic drugs is 80% or more.

If any pediatric 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, and (iii) the dosage or administration has changed, the Drug Price shall be reduced through a certain formula. In the extraordinary cases described in (i), (ii) and (iii) above, such reduction shall be made four times a year.

The Drug Price of generic drugs shall be consolidated into 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 the 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 that 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) a foreign price is listed therefor after they were listed therein.

Cost-Effective Evaluations shall be made for certain pharmaceuticals in large markets, for which the Similar Efficacy Comparison Method or the Cost Accounting System are used.

Policy issues that affect pricing and reimbursement

Expanding national medical expenditure

The cost of healthcare was 10.9% of GDP in Japan in 2016 and was not as high as in the United States and Switzerland, though the expenditure on pharmaceuticals and other medical non-durables was 18.8% of the expenditure on healthcare in Japan in 2014 and was higher than in the United States and Switzerland. From this perspective, it might seem to be unnecessary to hold down the payment to pharmacies under the health insurance system.

Whilst the percentage of elderly Japanese is increasing, the Japanese population is decreasing overall. Therefore, the amount of the nation's medical expenditure has been increasing. In order to maintain health insurance for elderly people, a new system was introduced which also is contributed to by other insurance providers, as described above. In addition, recently, the cost to develop 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 2021 or earlier.[61] Therefore, the form of the prescription written by a physician or dentist providing health insurance treatment shall 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 the medical expenditure under the health insurance system. The government then tries to switch prescription pharmaceuticals to Pharmaceuticals Requiring Guidance, such as pharmaceuticals of which the active component is a histamine-2 receptor antagonist. However, there are not many such pharmaceuticals.

Emerging trends

No new legislation is necessary to modify the Drug Price Standard. The MHLW may flexibly 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 to 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 a 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 should have a subsidiary in Japan and cause 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 generate 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.

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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").
2. 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").
3. Ordinance of the Ministry of Health and Welfare No. 136 of 2004.
4. Article 12-2 (i) of the Law.
5. Ordinance of the Ministry of Health and Welfare No. 135 of 2004.
6. Article 12-2 (ii) of the Law.
7. Article 13 (1) of the Law.
8. Article 13 (2) and 81-4 (1) of the Law and Article 281 (1) (i) 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").
9. Article 13 (2) of the Law and Article 26 (1) of the Regulation.
10. Article 13-2 (1) of the Law.
11. Article 13-3 (1) of the Law.
12. Article 13-3 (3) and Article 13-2 (1) of the Law.
13. With certain exceptions.
14. Article 14 (1) of the Law.
15. Article 14 (2) (i) of the Law.
16. Article 14 (2) (ii) of the Law.
17. With certain exceptions.
18. Ordinance of the Ministry of Health and Welfare No. 179 of 2004.
19. Article 14 (2) (iv) of the Law.

20. Article 14-3 (1) of the Law.
21. Article 19-2 of the Law.
22. Article 14 (3) of the Law and Article 40 (1) of the Regulation.
23. Article 2 (17) of the Law.
24. Ordinance of the Ministry of Health and Welfare No. 28 of 1997.
25. Ordinance of the Ministry of Health and Welfare No. 21 of 1997.
26. Article 43 of the Regulation.
27. Article 2 (16) and 77-2 of the Law, and Article 251 of the Regulation.
28. Article 14 (5) of the Law, and Article 45-2 and 45-3 of the Regulation.
29. Article 40 (2) of the Regulation.
30. Article 14-2 of the Law.
31. Article 14 (8) of the Law.
32. Article 14 (9) of the Law.
33. Article 14-4 of the Law.
34. Article 24 (1) of the Law.
35. Article 2 (12) of the Law.
36. Article 25 of the Law.
37. Article 26 (1) of the Law.
38. Article 30 (1) of the Law.
39. Article 25 (iii) of the Law.
40. Article 49 (1) of the Law.
41. Article 27 and Article 4 (5) (ii), (iii) and (iv) of the Law.
42. Article 31 of the Law.
43. Article 3 (1) of the Health Insurance Act.
44. Article 4 of the Health Insurance Act.
45. Article 11 of the Health Insurance Act.
46. Article 38 of the Health Insurance Act.
47. Article 5 of the National Health Insurance Act.
48. Article 48 of the Act on Assurance of Medical Care for Elderly People.
49. Article 70 (1) and Article 72 (1) of the Health Insurance Act, Article 40 of the National Health Insurance Act, and Article 19 of the Rules for Health Insurance-covered Medical Facilities and Medical Practitioners.
50. With certain exceptions.
51. Article 70 (1) and Article 72 (1) of the Health Insurance Act, Article 40 of the National Health Insurance Act, and Article 9 of Rules for Health Insurance-covered Dispensing Pharmacies and Pharmacists.
52. With certain exceptions.
53. Article 74 and Article 76 (2) of the Health Insurance Act, and Article 42 and Article 45 (2) of the National Health Insurance Act.
54. Article 76 (4) and (5) of the Health Insurance Act, and Article 45 (4) and (5) of the National Health Insurance Act.
55. Article 76 (1) and (2) of the Health Insurance Act, and Article 45 (1) and (2) of the National Health Insurance Act.
56. With certain exceptions.
57. Article 82 (1) and 76 (2) of the Health Insurance Act.
58. With certain exceptions.
59. Article 77 (1) of the Health Insurance Act.
60. With certain exceptions.
61. Basic Policy on Economic and Fiscal Management and Reform 2015 and 2017.

Kazuhiro Kobayashi
Tel: +81 6 6208 1409 / Email: k-kobayashi@ohebashi.com

Mr. Kobayashi has wide-ranging experience in corporate, M&A, compliance, intellectual property, antitrust, international transactions, product liability and dispute resolution. Mr. Kobayashi has conducted due diligences and prepared share purchase agreements, etc. in the health care industry. He has also handled investment in a foreign company and acquisition of Japanese company's business by a foreign company in the health care industry. Mr. Kobayashi has prepared and negotiated international licence agreements of pharmaceuticals. As a defence attorney for pharmaceutical companies, he has handled many cases of alleged contaminated medicines. Mr. Kobayashi has advised on pharmaceutical affairs not only for Japanese companies but also for foreign companies. Mr. Kobayashi has handled establishing foreign capital's entities and advising on their operations in Japan. Mr. Kobayashi has handled dispute resolutions in which foreign companies are involved.

Oh-Ebashi LPC & Partners

Nakanoshima Festival Tower 27F, 2-3-18 Nakanoshima, Kita-ku, Osaka 530-0005, Japan
Tel: +81 6 6208 1500 / URL: www.ohebashi.com

Korea

Kyungsun Kyle Choi & Yunjoh Lee
Kim & Chang

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 coverage levels 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 sought to expand NHI coverage under the "Mooncare" initiative, effectively bringing all therapeutic treatments under 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 NHIS negotiate the product's maximum reimbursement price ("MRP") based on factors such as the product's price in other countries, the local prices of comparable drugs, and the impact on the NHI budget. For certain oncology drugs, orphan drugs, antibiotics for which pharmacoeconomic ("PE") assessment is difficult, PE assessment is exempted. The company may enter into a risk-sharing agreement ("RSA") for certain oncology drugs or orphan drugs used for life-threatening diseases or for drugs that improve the quality of life for patients. The MRPs of generics and combination drugs are determined according to a set formula and reimbursement listing may be completed within three months. Due to the change in reimbursement scheme in 2020, all drugs, including generics and drugs under NHI coverage, must enter into supplementary agreements that secures sufficient supply of the drugs in the Korean market.

Market introduction/overview

As of 2019, 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 relatively large portion of products and services that are not reimbursed. 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 2020 was 6.86% of monthly income.

The projected population of Korea, as of the end of 2021, is expected to be 51.82 million and the average age is 43.4 years. As in other developed countries, the population is rapidly ageing – as of 2019, the life expectancy was 83.3 years, higher than the OECD average (80.7 years as of 2018) and 3.7 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 ageing 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 2019, *per capita* healthcare expenditure was US$3,384, much lower than the OECD average of US$4,224, and total health expenditure as a percentage of GDP was 8.0%, slightly lower than the OECD average of 8.8% (based on health statistics published by the OECD in 2020). 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 (or from convenience stores that are open for 24 hours, in the case of certain drugs classified as "safe drugs that should be readily available"). 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 must 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 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 NHIS include: managing the qualifications of insured persons and dependants; imposing and collecting premiums; and disbursing insurance payments.

Healthcare institutions including hospitals and pharmacies have the status of being "healthcare providers" 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), the cost of which is paid for by NHIS (up to the maximum reimbursement amount) and patients (co-payments). For some services or products, the patient must pay the entire cost 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 usefulness and to be cost-effective may be reimbursed under NHI. For certain drugs that have clinical usefulness but for which cost-effectiveness has yet to be proven, a provisional listing system is available whereby the drug is reimbursed under NHI for a certain period, following which its eligibility for formal NHI listing is reassessed.

New drugs, in order to be listed for reimbursement, must undergo PE assessment by HIRA, after which the company and 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 permit the PE review to proceed based on RSAs (where NHI listing is based on conditions such as the company refunding a certain portion of the drug price to 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 NHIS. 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 needing to negotiate with NHIS.

In the case of generics and combination drugs, the MRP is based on formulas set forth in the regulations without PE evaluation and MRP negotiation with NHIS (however, there must be negotiations with the NHIS in order to enter into supplemental agreement to ensure sufficient supply in the market) and reimbursement listing taking no longer than three months. Under

regulatory amendments that took effect in July 2020, the number of generic versions of a drug and the quality of the generic will be reflected in the MRP. Moreover, under the revised regulations, if a generic applies for listing, the generic company must negotiate with NHIS for a stable supply of such generic.

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 usefulness first, based on data such as articles on clinical studies, the product's reimbursement status in other jurisdictions and the applicable reimbursement criteria, 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 must submit PE data. If HIRA finds that there is no improvement to clinical usefulness, the company may get the product listed by accepting an MRP equal to 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 an RSA (based on which, for example, the publicly disclosed list price for the product may be set differently from the net price), or be exempted from having to submit PE data, in which case the "adjusted price" (ex-factory price, plus domestic distribution margin and VAT) of the product in the A7 countries would be regarded as the benchmark of cost-effective price. The relevant regulations were recently amended so that RSAs are now available for certain breakthrough drugs that help to enhance the quality of life. Moreover, the government amended the relevant regulations on PE exemption to allow the NHI listing of certain drugs that fall under the "Antibiotics, Tuberculosis treatments or antidotes for emergency use among the essential list of medicines as determined and announced by MFDS" category without the submission of PE data.

Once HIRA determines that the product is eligible for reimbursement under NHI, the company will negotiate with NHIS (except where the company is exempted from negotiation based on its acceptance of the WAP-based MRP; in this case, the final MRP will be determined as 90–100% of WAP). 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 countries, Taiwan, and Singapore, 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 NHIS break down, the product will not be listed and the company will 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 RSA, 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, although under recent amendments, the price of generics will be set differentially based on the number of generics approved for reimbursement and the quality of the generic.

Furthermore, as already stated above, the change in the reimbursement scheme in 2020 has instituted a procedure where manufacturers of all registered drugs under NHI coverage would need to enter into negotiations with the NHIS in order to execute a supplemental agreement that secures sufficient supply of the relevant drugs. If the agreed supply is not met by the manufacturer, the manufacturer faces administrative fines for breach.

Issues that affect pricing

As discussed above, PE data is a major factor considered in setting the MRP, and alternatives (such as MRP equivalent to the WAP of alternative treatments or a "adjusted price" that takes into account the domestic distribution margin) may also be available depending on the type of the drug.

There are several mechanisms through which the government may lower a product's MRP following MRP listing, including (i) for products that are being sold at below the MRP to hospitals (in which case the MRP may be reduced to reflect the actual transaction price), (ii) a "price-volume linkage" system under which the MRP of products that sell significantly above the volume forecasted by the company can be reduced, and (iii) reductions to the MRP or suspension of reimbursement (or imposition of a fine *in lieu* of reimbursement suspension) when a company is found to have provided kickbacks to healthcare professionals or medical institutions.

Policy issues that affect pricing and reimbursement

According to statistics published by the US Census Bureau, as of 2016, Korea had the most rapidly ageing 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%). According to Statistics Korea, the percentage of those over 65 has already reached 15.5% as of the end of 2019, and is predicted to increase up to 46.5% of the population by 2067.

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 NHIS to the National Assembly in 2019, health insurance expenditure doubled between 2009 and 2018, from KRW 39.3390 trillion to KRW 77.6583 trillion. During this period, the average annual rate of increase in health insurance expenditure was 7.8%; broken down by population segments, the average was the highest in the 65+ age group (11.0%). Total healthcare expenditure as a percentage of GDP was 8.1% as of 2018, 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

The Ministry of Health and Welfare recently added "cutting-edge regenerative medicine" (cell therapy utilising human cells and tissue) to the list of innovative medical technologies, which functions as a fast track for the health technology assessment process. Commercially, this change is expected to promote the development and use of products that use such technology, as it will become easier to obtain NHIS pricing and reimbursement.

Successful market access

Early planning is important in order to achieve successful market access in Korea. Companies are advised to plan their pricing and access strategy based on the product's clinical profile well before the product is approved in Korea. Other suggestions for consideration would include: involving personnel knowledgeable in the Korean regulatory landscape when planning clinical trials at the global level, to ensure that pricing-related considerations for Korea are adequately reflected; and reviewing data likely to be requested by HIRA in advance. If the relevant treatment is adopted in global treatment guidelines and/or textbooks, this would provide helpful support to the pricing and access strategy.

Kyungsun Kyle Choi
Tel: +82 2 3703 1119 / Email: gschoi@kimchang.com

Kyungsun Kyle Choi is a foreign attorney in the firm's Health Practice Group and is a member of the Mergers & Acquisitions and Corporate Investigations and White Collar Practice Group. Ms. Choi represents a broad range of companies in the pharmaceutical/medical device/food/cosmetic sectors, specialising in pharmaceutical regulation, pricing and reimbursement, compliance, bribery and competition law issues relating to promotional and marketing practices in the industry, anti-counterfeiting strategies, M&A, and restructuring of business operations. Ms. Choi's recent work has been in defending clients in pharmaceutical industry in a wide range of internal and government investigations for corporate fraud, corruption, fair trade law and anti-bribery allegations.

Yunjoh Lee
Tel: +82 2 3703 1466 / Email: yjlee1@kimchang.com

Yunjoh Lee is a senior attorney in Kim & Chang's Life Sciences Practice Group and advises global companies in the life sciences sector. She has extensive experience helping clients in the pharmaceutical and medical device industries navigate the hurdles of doing business in Korea's challenging environment, including responding to enforcement measures by Korean criminal, competition and anti-corruption authorities. She has advised global companies in restructuring their businesses in Korea and in forming, managing, and dissolving co-promotion and distribution relationships and other business alliances with local companies. Ms. Lee is known for her expertise on regulatory compliance and assists clients to design and implement effective compliance programmes.

Kim & Chang

39, Sajik-ro 8-gil, Jongno-gu, Seoul 03170, Korea
Tel: +82 2 3703 1114 / URL: www.kimchang.com

Mexico

Francisco Videgaray Ortega
Ortega y Videgaray, S.C.

Mexican health system

As provided in the Mexican Constitution, Mexico is a country with a mixed economy, allowing the public, social and private sectors to participate in the national economic development. The Constitution provides that "every person has the right to receive health protection" as a fundamental right. The Mexican General Health Law (*Ley General de Salud* "Law") establishes the fundamental principles for access to health care and services as well as the concurrence of the federal government and the federal entities in matters of general health. The right of every person to health protection and health care are inalienable rights.

The Mexican National Health System is formed by the federal and state governments together with all individuals and entities within the public, private and social sectors that provide health care services to the population.

In the public sector, the main and most important entities are: (i) the Mexican Institute of Social Security (*Instituto Mexicano del Seguro Social* "IMSS"), which provides health care services to all individuals working in the private sector; and (ii) the Social Security and Services Institute for State Employees (*Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado* "ISSSTE"), which provides health and social security services to all employees working for governmental entities.

The private sector is formed by all privately owned hospitals and clinics throughout the Mexican territory.

The social sector serves a large group of people that lacks social security and health care services provided by the public sector. The social sector is deemed vulnerable in both urban and rural areas, and it is mostly identified with the informal economy. Various assistance programmes controlled by the National Institute for Wellbeing (*Instituto de Salud para el Bienestar* "INSABI") serve the social sector.

The three sectors demand medicines and other health materials that are produced or imported by pharmaceutical companies established in Mexico or imported by the same pharmaceutical companies or by public institutions.

The public and social sectors must comply with the National Compendium of Health Materials issued by the General Health Council (*Consejo de Salubridad General*) to which said public institutions must comply for the provision of services. Such document describes, groups and codifies all medicines and medical devices to be used by public institutions.

Legal framework

Health care in Mexico is primarily regulated by the General Health Law (*Ley General de Salud*, the "Law"), which is a federal statute issued by the Mexican Congress and published

by the President of Mexico; it is applicable nationwide. The Law sets forth a number of general principles and goals which are the basis for the regulation of health care in Mexico. Thus, the Law relates to different aspects of human health, and among them, contains provisions on the production, manufacturing and commercialisation of medical products, foods, medical devices and cosmetics to be consumed by human beings.

Derived from the Law, there are various Regulations issued by the executive branch of the Federal Government (i.e., the President or administrative agencies), which set forth specific administrative rules. Also, administrative agencies in Mexico have the authority to issue official norms, which are regulations that establish technical specifications applicable to certain services or products offered or sold in Mexico ("NOMs").

The authorities that are responsible for enforcing the laws and regulations mentioned above are primarily the Ministry of Health (*Secretaría de Salud*, the "Ministry of Health") and the Federal Commission for the Protection against Sanitary Risks (*Comisión Federal para la Protección contra Riesgos Sanitarios* "Cofepris"). The Cofepris is an arm of the Ministry of Health primarily responsible for the enforcement of the health regulations, supervising their compliance and monitoring health risks in Mexico.

In accordance with the Law, a medicine is a substance or mixture, of natural or synthetic origin, with a therapeutic, preventive or rehabilitative effect, which is presented in pharmaceutical form and identified as such for its pharmacologic activity and for its physical, chemical and biologic elements. When a product contains nutriments, it will be deemed as a medicine if it contains concentrations (individually or associated with other substances) of: vitamins; minerals; electrolytes; amino acids; or oil acids in excess of those in natural foods and additionally presents a specific pharmaceutical form and has therapeutic, preventive and rehabilitative indications.

In addition to the Law, medicines are regulated by the various regulations. The main regulations applicable to the registration and commercialisation in Mexico of pharmaceutical products are the Regulations of Health Materials (*Reglamento de Insumos para la Salud*, the "RIS"). According to the RIS, a health material is a medicine, psychotropic substances, drugs, as well as the active ingredients, raw materials and additives that are necessary for the production of such products. Medical devices, surgical and healing materials and hygienic products are also deemed as health materials under the RIS, among others.

The RIS regulates the health and sanitary characteristics and conditions of health materials, packaging, labelling, their commercialisation and supply, importation and exportation. The RIS also provides the terms and conditions for the authorisations, health notices and the sanitary registrations of health materials, among other aspects.

For the commercialisation of medicines and other health materials in Mexico, it is necessary to have the approval issued by the Cofepris known as the "sanitary registration". Cofepris approves and issues sanitary registrations when the applicant submits sufficient evidence demonstrating that the manufacturing processes and the active ingredients comply with quality standards and are safe and effective. The Cofepris also verifies that the manufacturer complies with good manufacturing practices and the active ingredients have the required certifications. The sanitary registration is valid for a period of 5 (five) years and may be extended for an equal 5 (five) terms, pending the approval of Cofepris.

The RIS describes the technical and scientific information required to demonstrate the identity and purity, stability, therapeutic efficacy and safety, the prescribing information, the label and the packaging, among others.

In the case of generic medicines, the RIS describes the requirements on interchangeability tests, identification, and the certificate of good manufacturing practices issued by the competent authority of the country of origin. If the product is patented, it is necessary to submit proof of ownership of the patent or that the applicant has a licence to use the patent. The applicant must have a health licence or permit issued by the Mexican health authorities or by the health authority of the country of origin of the applicant authorising the applicant to manufacture and produce medicines or biological products for human use.

The NOMs applicable for the obtaining of the sanitary registration, among others, are: (i) NOM-059-SSA1-2015 Good Manufacturing Practices for Medicines; (ii) NOM-164-SSA1-2013 Good Manufacturing Practices for Pharmaceutical Products; (iii) NOM-073-SSA1-2005 Stability of Pharmaceutical Products and Medicines; and (iv) NOM-072-SSA1-1993 Labeling of Medicines.

The approval process for the sanitary registration of medicines

The applications for sanitary registrations of medicines must be resolved by Cofepris within a term of: (i) 180 days when the product contains active ingredients and therapeutic indications already registered in Mexico; (ii) 240 days when the products are not registered in Mexico but are commercialised in their country of origin; and (iii) in the case of new molecules, prior to the application for registration, it is necessary to request and hold a technical meeting on the Committee on New Molecules of Cofepris and thereafter, if applicable, the application may be submitted for approval, and Cofepris must resolve within a term of 180 days.

It is important to note, however, that in terms of Mexican administrative law, if Cofepris does not provide a resolution within the aforementioned terms, the application will be deemed as denied. In this case, the applicant may initiate a judicial action and bring the case before administrative courts.

In practice, it is common that Cofepris resolves applications for sanitary registrations within eight months or one year.

Patented, generic and biotechnological pharmaceutical products

Patented pharmaceutical products

The patents for pharmaceutical products are granted by the Mexican Institute of Industrial Property (*Instituto Mexicano de la Propiedad Industrial* "IMPI") and is valid for terms of 20 (twenty) years. Upon expiration of the patent, other companies may freely produce and commercialise generic versions of the products, which can be identified with a trademark or may be identified only by the generic version of their active principle.

Generic pharmaceutical products

There is a linkage system that forces Cofepris to consult with the IMPI when reviewing an application for sanitary registration to determine whether an existing patent is being evaded. Any company may file an application for the registration of a generic product within three years prior to the expiration of the patent, so that the applicant may carry out trials, tests and experimental production. Registration will be granted only upon expiration of the patent.

Biotechnological pharmaceutical products

Biotechnological products are defined as any substance that: (i) has been produced by molecular biotechnology; (ii) has therapeutic, preventive or rehabilitative effect; (iii) is presented in pharmaceutical form; and (iv) is identified as such by its pharmacological activity and physical, chemical and biological properties. Mexican law distinguishes

innovative biotechnological products (normally, patented products) from biocomparable biotechnological products.

Biocomparable biotechnological products, although not innovative, are those that have demonstrated to have quality, efficacy and safety comparable to an innovative product, also known as a reference product or patented product. The applicant for a sanitary registration of a biocomparable product may carry out trials, tests and experimental production within eight years prior to the expiration of the patent of the innovative product. Registration will be granted only upon expiration of the patent.

Prices of pharmaceutical products

Except for patented products, currently there is no price control in Mexico. This was the result of a Price Agreement (the "Agreement") entered into by and between the Mexican Ministry of Economy and the Mexican National Chamber of the Pharmaceutical Industry (*Cámara Nacional de la Industria Farmacéutica* "CANIFARMA") on September 12, 1996, as amended on October 1, 2004. The Agreement provides that companies will determine the prices of their non-patented products.

Conversely, the Agreement sets forth a procedure for companies to register the prices for their patented products. This procedure includes an opinion issued by an external auditor containing: (i) country or countries where the product is commercialised; (ii) active ingredients; (iii) trademarks; (iv) units sold in each country; and (v) an ex-factory price in each country.

To determine the maximum retail price of patented products, an international reference price will be taken from similar products, according to the following order of criteria:

i. those that have the active ingredient (molecule) in the same pharmaceutical form and presentation;
ii. those that have the active ingredient (molecule) in the same pharmaceutical form, but where presentation differs in concentration. The price will be determined in proportion to the total content of active ingredient; and
iii. those that have the active ingredient (molecule) in comparable pharmaceutical form (according to the criteria of the health authority). The price will be determined in proportion to the total content of active ingredient.

The result must be multiplied by a marketing factor and will be converted into Mexican pesos using the exchange rate of the day immediately following the application date.

The Agreement stipulates that the health authority must verify that the maximum prices of the patented products are observed. The authority may impose penalties in case of any price violation.

The distribution of medicines

The distribution of medicines in Mexico is carried out through specialised distribution companies. Such distribution companies must: (i) have warehouse facilities with the proper sanitary authorisations; and (ii) specialised transportation in compliance with the applicable regulations and with the capacity to deliver the medicines throughout the national territory. Distribution of medicines in Mexico for the private sector differs from the distribution within the public and social sector.

a. Private sector. Pharmaceutical companies generally do not directly commercialise products. The distribution is carried out by specialised companies that buy and acquire the products for further distribution. Such distribution companies have warehouse facilities in various strategic locations within the national territory.

b. Public and social sector. In this case, the distribution is made by specialised companies that, like those that distribute in the private sector, have warehouse facilities with the proper regulatory approvals and transportation equipment to deliver the products throughout the national territory to public health institutions, hospitals and clinics.

Notwithstanding the foregoing, the current government has not yet determined the terms and conditions under which these distribution companies must operate and has sought other avenues. Thus, the INSABI, which is controlled by the Ministry of Health, signed an Agreement with the United Nations Office for Project Services ("UNOPS") for the acquisition of medicines through public bids. Mexican and foreign companies have participated in the UNOPS international call to purchase medicines.

The companies participating in the bids, to which the purchase orders are awarded, deliver the products to a distributor authorised by the INSABI. Thereafter, the INSABI distributes the products within the national territory.

Code of integrity, ethics, transparency of pharmaceutical companies (the "Code of Ethics")

The pharmaceutical companies in Mexico affiliated to the Canifarma are bound to comply with the Code of Ethics, as well as other non-affiliated companies that have voluntarily agreed to be bound by such Code of Ethics, such as the companies affiliated to the Mexican Association of Pharmaceutical Research Industries ("AMIIF") and the National Association of the Pharmaceutical Industry ("ANAFAM").

An independent arm of Canifarma, the Council of Ethics and Transparency of the Pharmaceutical Industry (*Consejo de Ética y Transparencia de la Industria Farmacéutica* "CETIFARMA") oversees and enforces the Code of Ethics. The Board of Directors of CETIFARMA is formed by independent directors outside the pharmaceutical industry and of high reputation in matters of ethics and health. It is managed by a general director. The main functions of CETIFARMA are to review and give consistency to the internal procedures adopted by the pharmaceutical companies as well as to oversee and enforce the provisions of the Code of Ethics. CETIFARMA establishes alliances with related national and international organisations, receives complaints and carries out investigations, acts as a mediator, and imposes preventive or corrective measures, among other authorities.

The Code of Ethics contains a statement of principles, values and behaviours that must be observed as good practices for interaction with professional health institutions, the good practices of companies of medical devices and other health materials, and interaction with patient organisations, among other functions.

General Health Council

The General Health Council is an executive governmental agency which is directly under the control of the President of Mexico. The General Health Council has extensive authority in matters of the general country including issuing preventive general guidelines in case of pandemics/epidemics of a serious nature, as provided by the Mexican Constitution.

The General Health Council has various functions that are described in the Law such as: (i) the preparation of the National Compendium of Health Materials mentioned above; (ii) the participation in the consolidation and operation of the National Health System; (iii) the participation in the analysis of regulations pertaining to general health; (iv) the issuance of expert opinions on scientific research programmes and projects, as well as the training of

health human resources; and (v) the evaluation and certification on the quality of health care facilities, among other functions.

On March 30, 2020, the General Health published the declaration of the pandemic generated by the SARS-CoV2 virus (COVID-19) as a health emergency, ordering the Ministry of Health to determine all the actions that are necessary to attend the emergency.

In compliance with the aforementioned declaration, the Ministry of Health issued strict measures of health care and confinement, to avoid the transmission of COVID-19, which still prevail in many aspects.

Final comments

Investment and entry into the Mexican pharmaceutical market may be carried out directly through the purchase or incorporation of one or more Mexican companies. Mexican pharmaceutical companies can be fully owned by foreign investors. Depending on the needs and the specific business model, foreign investors have also opted to enter the Mexican pharmaceutical market through the association with a third party already established in Mexico without incorporating or purchasing a Mexican company.

Mexico is a country that welcomes foreign investment, job creation, and access to new and innovative products. However, the pharmaceutical industry in Mexico is a highly regulated industry, as such, it is always advisable to have adequate legal advice provided by lawyers with extensive experience and knowledge of the industry and its regulation.

Legislation and administrative processes are excessively formal in Mexico; it is always necessary to consider that all documents and information related to products, dossiers, permits, authorisations, among others, must be current, must be clear and must comply with all the laws, regulations and formalities of the country of origin.

To participate and enter the pharmaceutical market in Mexico, it is always advisable to contact, either through expert lawyers in the field, or through Canifarma or other associations of pharmaceutical companies, persons or entities in Mexico that serve as a contact with the industry, as well as to obtain different services as may be needed, such as warehouse services, analysis laboratories, pharmacovigilance, among others.

Francisco Videgaray Ortega
Tel: +52 55 5256 1754 / Email: fvo@oyv.mx

Francisco obtained his law degree in 1995 from Instituto Tecnológico Autónomo de México (ITAM) in Mexico City. He has a postgraduate degree in Commercial Law from Universidad Panamericana in Mexico City, and a Master in Laws (LL.M.) from Northwestern University, Pritzker School of Law, in Chicago. In 2002–2003, he worked as a foreign associate in Skadden, Arps, Slate, Meagher & Flom LLP in New York.

He has more than 20 years of experience advising Mexican and international companies on corporate matters, mergers, acquisitions and restructurings. For more than 15 years he has specialised in advising Mexican and transnational companies on health, pharmaceutical, cosmetic and food matters.

He is a partner of Ortega y Videgaray, S.C., a Mexico City law firm founded in 1972 specialised in offering legal advice to companies from different branches of industry and commerce, especially the pharmaceutical, cosmetic and food industry.

Ortega y Videgaray, S.C.

Yautepec 12, Colonia Condesa, Cuauhtémoc, 06140 Ciudad de México, Mexico
Tel: +52 55 5256 1754 / URL: www.oyv.mx

Netherlands

Koosje van Lessen Kloeke
Leijnse Artz

Abstract

The Dutch pricing and reimbursement system is quite complex and not set out in a well-defined set of rules and regulations. There is often more than one route or blockade to reimbursement. Which route will have to be followed, or how a blockade can be overcome, will depend on the circumstances and the parties involved. Because of this, a better understanding of the complexities of the Dutch healthcare market and the systems for pricing and reimbursement requires not only knowledge about the current rules and policies, but also about their history, the practical workings of the Dutch healthcare market, and the roles of different public and private bodies.

For better insight into the practical workings of the healthcare market, it is furthermore important to be aware of the Dutch term "polder model" of consensus-based economic and social policy making. Similar to other regulated markets in the Netherlands, the "polder model" is also used in pricing and reimbursement of pharmaceuticals. Much of the current pricing and reimbursement system is based on written and unwritten policies and practices, developed through consensus decision-making processes between governmental bodies and market parties such as private insurers, hospitals, doctors, and pharmacists. This makes for a quite complex and sometimes unpredictable system.

Many of the current policy issues are highly influenced by the public debate around pricing and reimbursement in the Netherlands. In recent years, this debate has become quite polarised. Many of these discussions are centred around themes such as financial sustainability of the healthcare system, patient access, pricing models, affordability, "evergreening" and transparency.

Market introduction/overview

The healthcare market

The 2006 reform of the Dutch healthcare system changed the role of the government from direct controller of volumes and prices to rule-setting and overseeing a proper functioning of the markets. The Dutch government is responsible for setting the basic health insurance package ("the basic package"), maximum prices for medicinal products on the Dutch market, and the available resources (funding). It also has the tools to intervene in the case of overspending. The government is ultimately responsible for:

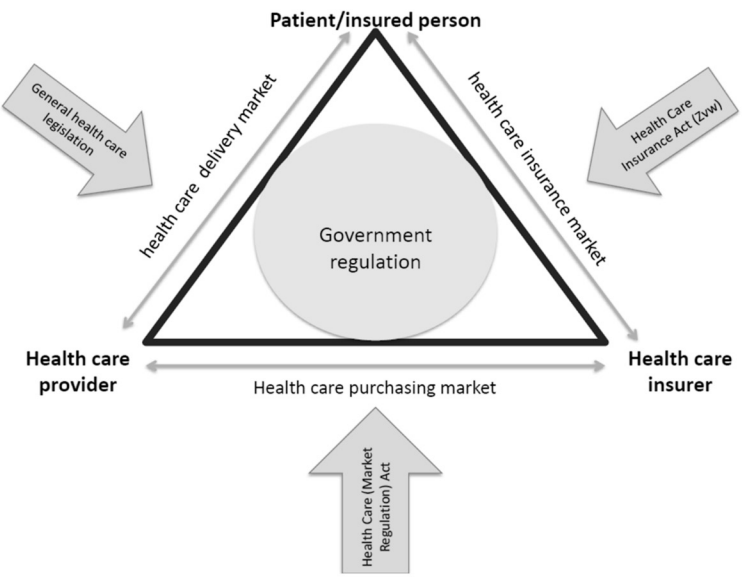
- price regulation of the maximum wholesale price ("*apotheekinkoopprijs*", or "AIP") based on a system of reference pricing and reference countries, laid down in the Medicine Prices Act ("*Wet geneesmiddelenprijzen*", or "Wgp");
- price influencing via the rules concerning the reimbursement of medicinal products laid down in the Healthcare Insurance Act ("*Zorgverzekeringswet*", or "Zvw"), including the

internal reference pricing of the Medicine Reimbursement System ("*Geneesmiddelen vergoedingssysteem*", or "GVS"), the "lock chamber" ("*sluis*") for inpatient medicinal products, and health technology assessment ("HTA") processes; and

- funding of outpatient pharmaceutical care and inpatient treatment with medicinal products in hospitals under the Healthcare (Market Regulation) Act ("*Wet marktordening gezondheidszorg*", or "Wmg").

Furthermore, the government has other, non-regulated instruments at its disposal to control healthcare spending, such as *de facto* outsourcing of budget controls to healthcare insurers and hospitals, prescribing conventions, sector agreements or "covenants", horizon scanning,[1] managed entry agreements ("financial arrangements"), and "appropriate use arrangements" which, for example, monitor the appropriate use of medicinal products through patient registries.

The interplay between the different instruments and markets is sometimes visualised as follows:



Moreover, the Netherlands together with Austria, Belgium, Ireland and Luxembourg is a member of the cross-country collaboration initiative Beneluxa,[2] which aims to improve collaboration on pharmaceutical policy, including horizon scanning, pricing and reimbursement, and HTA.

Roles of government bodies and non-governmental bodies

As mentioned above, much of the workings of the system are based on written and often unwritten policies and practices, developed through consensus decision-making processes between several governmental bodies and market parties.

The following government bodies are involved in these discussions: the Minister for Medical Care/Ministry of Health, Welfare and Sport ("MoH");[3] the National Healthcare Institute ("*Zorginstituut Nederland*", or "ZIN");[4] the Dutch Healthcare Authority ("*Nederlandse Zorgautoriteit*", or "NZa");[5] and the competition authority the Netherlands Authority for Consumers and Markets ("ACM").[6]

Other important non-government actors are the associations of insurers ("*Zorgverzekeraars Nederland*", or "ZN"),[7] hospitals and other healthcare institutions (NFU,[8] NVZ,[9] ZKN,[10]

Actiz),[11] doctors (KNMG,[12] "*Federatie Medisch Specialisten*",[13] etc.), pharmacists (KNMP,[14] NVZA,[15] "*Netwerk Gespecialiseerde Bereidingsapotheken*"),[16] patient representatives and industry associations (VIG,[17] BOGIN,[18] HollandBIO).[19]

The MoH is in charge of the overall pharmaceutical policy. The Minister for Medical Care decides on the maximum wholesale price (Wgp). He also takes decisions with regard to the contents of the basic health insurance package. The Minister is furthermore ultimately responsible for the main instruments to control healthcare spending, such as the *de facto* outsourcing of budget controls to healthcare insurers and hospitals and preference policies, sector agreements and covenants with insurers, hospitals and other healthcare providers, centralised financial arrangements and cross-country collaboration initiatives such as Beneluxa.

ZIN advises the MoH as well as healthcare insurers on the reimbursement of care, including medicinal products used for outpatient treatment ("extramural care") and for inpatient treatment ("intramural care"). As part of such advice, ZIN can perform HTA. Further to a draft advice concerning the reimbursement of a medicinal product or a group of products, ZIN will not only consult the company involved, but also representative organisations for the insurers, healthcare providers and patients. ZIN is furthermore responsible for the Dutch Horizon Scanning Initiative, and, as of October 2021, the selection of "lock candidates" and advising the MoH concerning the application of the lock chamber.[20] Input from pharmaceutical companies is requested, which is then further assessed in "working groups" consisting of representatives of the government (MoH, ZIN), physicians, pharmacists and insurers.

The NZa is tasked with the market regulation. It sets the tariffs and the treatment descriptions for the funding of healthcare, including pharmaceutical care in the outpatient setting and so-called "add-ons" in the inpatient setting. When drafting its policies and regulations, the NZa will consult representatives of the insurers and healthcare providers. The NZa is also tasked with the supervision of compliance with the WMG and the Zvw by insurers and healthcare providers.

The ACM is charged with competition oversight, including in the pharmaceutical market. Since 2018 one of the key priorities of the ACM is the prices for prescription-only medicines. In 2018, the ACM published the "ACM Working Paper: Reconciling competition and IP law: the case of patented pharmaceuticals and dominance abuse",[21] launched a sector inquiry into anti-rheumatic drugs, and submitted a paper for the OECD named "Excessive Pricing in Pharmaceutical Markets".[22] In 2019 the ACM announced[23] that it sees opportunities for lower prices of authorised "expensive prescription drugs" by instead using unlicensed "magistral preparations" made by pharmacies (i.e. replacement compounding). Furthermore, the ACM published the results of its sector inquiry into anti-rheumatic drugs[24] and an evaluation of the "Guidelines on collective procurement of prescription drugs",[25] and used this opportunity to inform hospitals and health insurers about the room that the competition rules offer for collective procurement of prescription drugs for medical specialist care. With regard to excessive prices of drugs, ACM is currently conducting investigations into specific cases, including an investigation into the prices of the orphan drug CDCA Leadiant.[26]

Relative size of the market

The Netherlands spends relatively little on pharmaceuticals compared to other countries. Compared to the Gross Domestic Product ("GDP"), expenditures on pharmaceuticals and medical devices in the Netherlands are 1.24%. The average expenditure in the European Union is 1.81%. The expenditures for total healthcare in the Netherlands are similar to those in other wealthy countries, due to the fact that the Netherlands spend a relatively large amount

on hospital care and long-term care. Over the past decade, the total government expenditures on healthcare have increased from EUR 56 to EUR 74.7 billion. The expenditures for pharmaceuticals increased to EUR 6.2 billion, excluding the pharmacy remuneration. The share of pharmaceuticals in the healthcare budget decreased in this period from 8.9% to 8.3%. The 2019 version of the State of Health in the EU's Country Health Profile on the Netherlands,[27] the 2020 "Facts and Figures" overview by the Dutch Foundation for Pharmaceutical Statistics ("SFK")[28] and the 2021 "Medicines Monitor" of the Association Innovative Medicines ("*Vereniging Innovatieve Geneesmiddelen*", or "VIG")[29] provide quite helpful, recent and concise overviews of the demographic and socioeconomic context in the Netherlands, as well as a general description of healthcare in the Netherlands.

Pharmaceutical pricing and reimbursement

Regulatory classification

The Dutch rules and regulations concerning medicinal products and their classification are based on Directive 2001/83/EC, which has been transposed into the Medicines Act. There are three main regulatory classes of medicinal products:

1. prescription-only medicinal products ("*UR-geneesmiddelen*"); and
2. medicinal products which are not subject to prescription, the categories of which are subdivided as the following:
   a. "[p]harmacy-only medicinal products" ("*UA-geneesmiddelen*"), which consumers may purchase without a prescription but only from a pharmacy;
   b. "[p]harmacy-and-drugstore-only medicinal products" ("*UAD-geneesmiddelen*"), which consumers may purchase without a prescription but only from a pharmacy or a drugstore; and
   c. "[g]eneral sale medicinal products" ("*AV-geneesmiddelen*"), which consumers may purchase without a prescription.

The regulatory criteria for classification of a medicinal product as a prescription-only product are based on Article 71 Directive 2001/83/EC. The regulatory classification of a medicinal product not subject to prescription (i.e. UA, UAD or AV) will depend on factors such as the need for medication monitoring, information or supervision when the product is dispensed, the active substance, the dosage and the pack size. The competent authority for the classification of medicinal products in the Netherlands is the Dutch Medicines Evaluation Board.

Medicinal products not subject to prescription are generally not eligible for reimbursement, and do not have to comply with maximum prices.

Pricing

The Wgp aims to safeguard the accessibility and sustainability of healthcare by bringing the price level of authorised medicinal products in the Netherlands closer to the European average price level. When purchasing medicinal products, pharmacists may not pay more than the maximum prices and the manufacturer/wholesaler is not permitted to charge a higher price than the maximum price. The MoH has the authority to set maximum allowable prices for authorised medicinal products on the Dutch market. The maximum prices are determined twice per year (as per 1 April and per 1 October) by the Farmatec unit of the CIBG (a department of the MoH),[30] based on an arithmetic average of the list prices for similar medicines in four reference countries.

Since the Wgp's introduction in 1996, the reference countries had been Belgium, France, Germany and the United Kingdom ("UK"). In 2019 Germany was replaced with Norway, and the maximum prices of medicinal products in the Netherlands are currently set by comparing

prices for similar products in Belgium, France, Norway and the UK. Germany was replaced for expenditure reasons. Although the Dutch Parliament was concerned that the amendment of the Wgp could have a negative impact on the availability of medicinal products on the Dutch market, especially of generics, the MoH expected that the risk that amendment of the Wgp would contribute to shortages would be limited because the list prices of generics are generally lower than the maximum prices further to the Wgp.

The preparation of a decision to amend the list of maximum prices is subject to the so-called uniform public preparatory procedure. The draft regulations are published in the Government Gazette, usually in December and in June, and interested parties have the opportunity to submit a statement of views further to the proposed maximum prices. If an interested party fails to submit a statement of views against a proposed maximum price, it could lose the right to appeal the final price. Interested parties can furthermore apply for an increase of a maximum price.

Reimbursement: the basic package

(a) *Government regulation and competitive private insurance*

The Dutch reimbursement system is characterised by a mix of competitive private insurance for curative care and government regulation. The social insurance scheme is regulated by the government, and is carried out by competing private insurers. The contents of the basic health insurance package are determined by the government and are the same for everyone. All residents are required to take out an insurance policy that covers the basic package. Premiums are paid through a combination of employer/private individual's contributions. Insurers must accept all applicants and are expected to contract with healthcare providers based on quality and price. One of the recurring adages in that context is "cheap where possible, expensive where necessary" ("*goedkoop waar het kan, duur waar het moet*").

At present, there are 11 health insurance companies (groups) that have one or more labels, insurers and/or proxies. The four largest health insurers are: Zilveren Kruis (Achmea); VGZ; CZ; and Menzis. Of everyone who is required to choose health insurance, 85% (in 2021) is insured with one of these four companies.[31]

Out-of-pocket payments are necessary for non-insured care, e.g. aesthetics. Since 2019 the government has set a maximum personal contribution (co-payment) for medicinal products of EUR 250 per person. Before 2019, there was no maximum. In addition, there is a deductible for insured care which also applies to medicinal products. The deductible is a maximum of EUR 385 per year for adults (or more if you have opted for a voluntary deductible). No deductible excess applies to children.

It is possible to take out supplementary insurance. In that case, the insurer determines the premiums and corresponding coverage. This is often used for dentistry, physiotherapy, etc.

(b) *The "double-dual system"*

In order to understand the mechanisms built into the reimbursement system in the Netherlands, the first distinction to be taken into account is between the reimbursement of medicinal products used for outpatient treatment (extramural pharmaceutical care) and medicinal products used for inpatient treatment in hospitals (intramural medical care).

The system for the reimbursement of medicinal products is sometimes also referred to as a "double-dual system" ("*dubbel duaal stelsel*").[32]

- The extramural system is characterised by positive lists of reimbursed medicines with reimbursement limits (a closed system) and open-end funding (no fixed budget).
- For the intramural system, the scope and contents of care are determined by "established

medical science and medical practice" ("*stand van de wetenschap en praktijk*") (an open system). In exceptional cases, a medicine may be placed on a negative list (the so-called "lock chamber" or "*sluis*"). Furthermore, the intramural system is characterised by overall budget restraints ("*prestatiebekostiging*", i.e. performance costing).

Pursuant to Articles 10 and 11 Zvw, insured persons in the Netherlands have the right to receive the care that they require, as defined in a Decree, including extramural pharmaceutical care and intramural medical care with medicinal products. The relevant Decree is the Healthcare Insurance Decree ("*Besluit zorgverzekering*", or "Bzv"). Detailed rules on the content of the different types of care are set out in the Healthcare Insurance Regulations ("*Regeling zorgverzekering*", or "Rzv") and its Annexes. The totality of the forms of care to which insured persons are entitled – and which healthcare insurers are obliged to offer further to the Zvw – are commonly referred to as the "basic health insurance package" or "basic package" ("*basispakket*").

The Wmg applies to "*zorg*" or care, being all care or services defined by the Zvw. This means that the Wmg also applies to the services ("*prestaties*") and tariffs ("*tarieven*") related to extramural pharmaceutical care, as well as to the intramural medical care with medicinal products. The NZa determines what types of "care" can be charged to patients by healthcare providers, and specifically for medicinal products used for inpatient treatment in hospitals, the maximum amounts ("add on tariffs") that can be charged for such healthcare. For most treatments, healthcare insurers and healthcare providers negotiate and agree upon arrangements about what each treatment entails, what its quality should be, and what price can be charged for it.

Both in the extramural system and the intramural system, there are different mechanisms to enhance the purchasing power of healthcare insurers and healthcare providers (pharmacies hospitals) *vis-à-vis* marketing authorisation ("MA") holders of medicinal products. In the extramural system, healthcare insurers are permitted to apply so-called "preference policies" for preferred medicines, so that patients who use a different brand may have to pay the difference in costs or the total amount. Such policies can also be implemented by hospitals. The Dutch competition authority, the ACM, has condoned the formation of purchasing combinations between hospitals and cooperation with insurers in order to purchase such medicines jointly. In practice, discounts are regularly negotiated by hospitals or their purchasing vehicles ("*inkoopcombinaties*"). These sorts of purchasing policies will often set out preferred products for a particular indication, and can also establish guardrails on dosage, strength and duration of use, and/or off-label use.

As a general rule, prescribing clinicians must prescribe products based on their common name ("INN") or active substance rather than by brand name. There are exceptions to this, notably for biologics and certain other products. This means that pharmacists are free to dispense any prescription-only medicinal product with this prescribed INN/active substance. If the pharmacist can choose between several options (e.g. generics and/or parallel imports), any arrangements made with the insurers (extramural care: a preference policy or other policy from the insurer; intramural care; or contractual arrangements made with the hospital) and/or arrangements with manufacturers of competing products offering higher discounts, are likely to influence the product of choice.

In practice, prescribing clinicians will be reluctant to prescribe products that are not (fully) reimbursed by the insurers and/or that imply negative financial consequences for the hospital (in case of inpatient care). This applies, in particular, in those cases where from a therapeutic point of view reasonable alternatives exist.

(c) *Main reimbursement criteria*

The main reimbursement criteria are not laid down in the law, but in explanatory notes, policies and reports and (unpublished) case-law, in some cases explanatory notes, policies and reports based on repealed legislation.

The main reimbursement criteria are:

(1) Necessary care ("*noodzakelijkheid*"): is the disease serious enough, in light of the burden of disease?
(2) Effectiveness ("*effectiviteit*"): is there proof that the treatment works? Is the treatment at least as good as the current standard of care?
(3) Cost-efficiency ("*kosteneffectiviteit*"): are the treatment costs proportionate to its benefits?
(4) Feasibility ("*uitvoerbaarheid*"): is inclusion in the basic package feasible from a practical point of view? Is it reasonable that the costs should be for a patient's own account and accountability?

(d) *Horizon Scanning and financial arrangements*

In 2012 the Dutch MoH started a pilot for negotiations between the MoH's "*Bureau Financiële Arrangementen*" (Drug Price Negotiation Unit) and pharma companies concerning financial arrangements. Such arrangements are also called "centralised financial arrangements" because they are concluded between the State of the Netherlands (Minister) and the company. The MoH's reimbursement decision will depend on the outcome of negotiations.

In order to facilitate early access to information on the development and market introduction of new pharmaceutical products for the government, payors and purchasers, and the identification of "candidates" for a financial arrangement, the future-oriented method of "horizon scanning" was introduced. ZIN coordinates the *Horizonscan Geneesmiddelen*,[33] using information from the European Medicines Agency ("EMA"), the Dutch Medicines Evaluation Board ("CBG"), clinical studies, R&D pipeline overviews, and input from insurers, clinical experts and pharma companies.

The pilot for negotiations between the Bureau and pharma companies ended in 2016 and since then, the Bureau operates on a structural basis. It should be noted, however, that neither the Bureau nor financial arrangements between the State (MoH) and pharmaceutical companies and/or price negotiations with the State (MoH) have a (clear) legal basis in the Zvw.

In practice there are several types of arrangements, for example, (confidential) price/volume agreements, a public price cut, (confidential) discounts and/or (confidential) budget caps. It is possible to combine such measures in a financial arrangement. The MoH has stated that it is open to discussing other types of financial arrangements such as performance-based agreements, but there have not yet been examples of such arrangements with the State.

The State (MoH) applies the instruments of negotiations and financial arrangements to extramural *and* intramural medicines. Arrangements are generally in force for an average of three years. Under these centralised arrangements there will be an annual payment of a return amount to a Trusted Third Party ("TTP"), with the insurers as the beneficiaries.

In most cases the details of the financial arrangements between the State (MoH) and a company are confidential (but this is not explicitly laid down in the law), unless the company agrees to a non-confidential arrangement.[34]

(e) *Reimbursement of extramural pharmaceutical care*

In principle, only authorised extramural medicinal products are eligible for reimbursement. Pursuant to Article 2.8(1)(a) Bzv, pharmaceutical care to which patients are entitled includes

"supply of, or advice and guidance that pharmacists normally provide, for the purpose of assessment of medication, and responsible use of authorised medicines designated by Ministerial Regulation", as well as certain exceptional situations regarding unauthorised medicinal products, such as pharmacy preparations and named patient use, provided that such a product can be considered "rational pharmacotherapy".

(i) *Procedure*

The authorised medicinal products "designated" for reimbursement pursuant to Article 2.8 Bzv are listed in Annex 1 Rzv, commonly known as the GVS. This is a positive list within the meaning of Article 6 Directive 89/105/EEC.

The Minister for Medical Care ("Minister") is the designated competent authority for all GVS decisions. Pursuant to Article 2.50 Rzv, a request to "designate" a medicinal product is submitted to the Minister, and requires advice from ZIN. In practice, a request for GVS inclusion is made by submitting the "Farmatec application form"[35] and the application dossier to the Farmatec unit of the CIBG and to the ZIN.

In its assessments, the ZIN will usually be supported by its Scientific Advisory Board ("*Wetenschappelijke Adviesraad*", or "WAR") for the scientific and practical assessment of the data and the determination of the cost-effectiveness, as well as its Package Advisory Committee ("*Adviescommissie Pakket*", or "ACP") for the societal assessment. Further to draft advice concerning the reimbursement of a medicinal product or a group of products, ZIN will not only consult the company involved, but also representative organisations for the insurers, healthcare providers and patients. The ZIN's Executive Board will adopt the final advice and will send it to the Minister for a final decision on GVS inclusion.

In principle the time limit for the entire application procedure should be 90 days (as set out in Article 6 Directive 89/105/EEC) but in practice this is rarely the case, at least not for new products.

(ii) *Criteria*

The basic concept of the GVS is that medicinal products are classified in groups ("*clusters*") of therapeutically substitutable products (i.e. having equivalent therapeutic value or "*gelijke therapeutische waarde*").

Products are considered "substitutable" ("*onderling vervangbaar*") if they have: (i) a similar indication; (ii) a similar route of administration; and (iii) are generally indicated for the same age category. In principle this means that products with different active substances and slightly different therapeutic indications can be classified as therapeutically "substitutable" if the abovementioned conditions have been met.

Notwithstanding the above, medicinal products are not considered therapeutically substitutable if: (i) the medicinal products have different characteristics; (ii) these differences occur or can occur in the entire patient population in which the products are used; and (iii) if it is apparent from the reimbursement application dossier that these different characteristics, taken together, are the determining factor for the doctor's choice to prescribe the medicinal product.

If a medicine is considered to be substitutable, it is placed in a cluster on Annex 1A to the Rzv, and the reimbursement level of the medicine is calculated based on the prices of categories of products within the cluster, at a certain reference date (1 October 1998). This reimbursement level is called the "*vergoedingslimiet*". If the actual price of a product is higher than the reimbursement level, patients will be required to make a co-payment ("*eigen bijdrage*") to the cost of the product. This co-payment will have to be made by the patient

to the pharmacist, either directly when the patient fills the prescription, or indirectly via the patient's healthcare insurer. Since 2019 there is a maximum co-payment for medicinal products of EUR 250 per person.

If a medicinal product is not considered therapeutically substitutable, in principle it will not be included in the GVS. However, the Minister can decide to fully reimburse unique, non-interchangeable medicinal products further to their added therapeutic value ("*therapeutische meerwaarde*") and their cost-effectiveness ("*doelmatigheid*"). Such products are listed on Annex 1B to the Rzv.

Usually all the authorised indications for a medicinal product are tacitly accepted. However, some conditions may apply to the reimbursement of a product, such as a confirmation of medical need by a medical specialist or no off-label use. Such reimbursement conditions are set out in Annex 2 Rzv.

The Minister may decide that, taking into account the ZIN advice, the medicinal product is too expensive in relation to the added value that it provides for patients. In that case, the Minister may refer the applicant to the MoH's "*Bureau Financiële Arrangementen*" which will then enter into negotiations for a financial arrangement with the applicant.

(iii) *Reimbursement of unauthorised extramural medicinal products*

As mentioned above, in principle, only authorised extramural medicinal products are eligible for reimbursement. However, pursuant to Article 2.8(1)(b) Bzv, insurance coverage exists for certain unauthorised medicinal products, provided that such a product can be considered "*rationele farmacotherapi*e" (rational pharmacotherapy). This concerns, *i.a.*, "magistral preparations", i.e. pharmacy compounded preparations, that meet the requirements of the Dutch Medicines Act, but also named-patient use in case of a rare disease, i.e. a disease affecting no more than 1 in 150,000 persons in the Netherlands, and named-patient use in case of shortages.

(iv) *Funding*

As mentioned above, the extramural system is characterised by open-ended funding (no fixed budget). The rules for funding of pharmaceutical care are provided by the NZa, based on the Wmg. The NZa has provided "*prestatiebeschrijvingen*" or performance descriptions, including performance descriptions for the charging of the costs of authorised medicines by a pharmacist to an insurer, and the reimbursement of these costs by the insurer to the pharmacist. The NZa has also provided certain rules regarding the costs of "magistral preparations", i.e. pharmacy compounded preparations. As of 2019 a "magistral preparation" may be charged even if there is an equivalent or alternative authorised and prescription-only product available on the market. In a recent ruling the Trade and Industry Appeals Tribunal ("*College van Beroep voor het bedrijfsleven*", or "CBb") confirmed that it is permitted to give a patient nonetheless a compounded product, e.g. for economic reasons.[36]

(f) *Reimbursement of inpatient medical care*

As set out above, the reimbursement system for "inpatient" medical care contains multiple market mechanisms for exercising the bargaining power of the healthcare system.

Pursuant to Article 2.4 Bzv, insured patients have the right to receive "medical care", which includes care that is commonly provided by medical specialists. Specialist care includes specialist medicines, i.e. medicines used as part of a treatment by or under the responsibility of a medical specialist, administration as part of specialist diagnostics, therapy and/or prevention.[37]

The scope and contents of medical care are determined based on "established medical science and medical practice", or "*stand van de wetenschap en praktijk*" (Art. 2.1(2) Bzv). This

means that care is insured if it is sufficiently tried and tested by international medical science (in principle, this is the case if the product has an MA), or absent scientific testing, has been accepted in daily practice as correct and responsible. Pursuant to these provisions, insured patients in the Netherlands should, in principle, have direct access to new specialist medicines and hospitals would normally be required to purchase such medicines in order to comply with the standards of good care.

The intramural system is in principle an open system: there are no positive lists of reimbursed products designated by the Minister/MoH. In exceptional cases the Minister may place a medicine on a negative list (the so-called "lock chamber" or "*sluis*"). Furthermore, the intramural system is characterised by overall budget restraints ("*prestatiebekostiging*", i.e. performance costing).

(i) *The lock chamber*

In order to manage the budgetary impact of new, expensive medicinal products, the Ministry has established a "lock chamber" ("*sluis*"), pursuant to which there is no automatic entry into the open reimbursement system for intramural products. In that case patients are *not* entitled to receive new, expensive medicinal products as part of medical care until negotiations for a "financial arrangement" with the MA holder have been completed.

After being first applied in 2015 to nivolumab, the "*sluis*" was formally introduced in the law in 2018 (Article 2.4a Bzv). Since then the MoH has further developed the processes, criteria and standard agreements. That being said, several parties still feel that there is a lack of clarity and processing times. Furthermore, the lock procedures are not always in line with current procedures and practices. In consultation with the MoH, the association for innovative medicines in the Netherlands, the Association Innovative Medicines (VIG) has published a guidance document concerning the lock.[38]

The lock decision will be published in the *Government Gazette* ("*Staatscourant*"), and must be taken within one month (i.e. four weeks) after (i) the granting of an MA for the product indication(s), *or* (ii) publication of a treatment guideline or protocol concerning the product's off-label use. Further to Article 2.4a Bzv, the lock will only be applied in cases where there are "unreasonable high costs per year or per treatment" based on price (unclear if it concerns gross, net or, for example, US prices) and including costs of combination treatment, the number of patients eligible for treatment, and the risk of inappropriate use.

According to the current criteria applied by the MoH, a medicinal product qualifies for the lock chamber if:

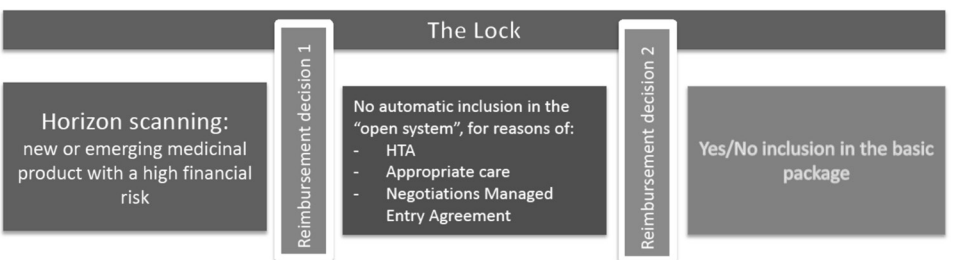
- the projected overall macro costs related to one or more of the authorised therapeutic indications of the product is EUR 40 million or more (based on the Horizon Scan and/or other public information); or
- if the threshold of EUR 40 million is not met, but the treatment costs per patient per year are EUR 50,000 or more and the projected overall macro costs of the new treatment are EUR 10 million or more per year (based on the Horizon Scan and/or other public information).

These criteria have not been laid down in the law but follow from the explanatory notes to Article 2.4a Bzv and individual lock decisions, as published in the *Government Gazette*. As of October 2021, ZIN will be responsible for the selection of "lock candidates" and advising the MoH concerning the application of the lock chamber.[39]

If a medicinal product is placed in the lock chamber, the product is included on Annex 0 to the Rzv. This is a so-called negative list of products that are not reimbursed. The Minister

will only take a product out of the lock chamber after ZIN has advised on, *i.a.*, the therapeutic value and cost-effectiveness of the product. Depending on the outcome of the advice of ZIN and negotiations between the Bureau and the company about a centralised financial arrangement, the product can either be (temporarily) placed out of the lock (successful negotiations), or remain in the lock. If a product is temporarily placed out of the lock, this will be indicated in Annex 0 to the Rzv.

In the explanatory notes to Article 2.4a Bzv this is illustrated as follows:[40]



One of the main challenges of the lock chamber and negotiations is that it remains uncertain if and when the product will become available for patients and treating physicians/hospitals, because there are no fixed timelines. Especially in cases where there is an urgent unmet medical need, companies can be pressured to provide the product free of charge during the lock period. Whether or not this is possible or feasible should be assessed on a case-by-case basis, also taking into account competition law and the advertising rules for medicinal products.[41]

Another issue is that the MoH's decisions to place a product in the lock chamber do not seem to be based on a transparent risk analysis and balancing of interests, based on objective and verifiable criteria. Furthermore, the procedure is not transparent. Once a product is placed in the lock, a financial arrangement is inevitable. It could provide an incentive to ZIN to always advise the MoH to negotiate, even if the outcome of the HTA shows that the treatment is cost-effective.

Furthermore, the lock is used as a *centralised* negotiating instrument while the intramural system is based on *decentralised* negotiations with insurers and/or hospitals. In practice, decentralised arrangements with insurers or agreements with hospitals cannot prevent placement in the lock chamber as the conditions of such arrangements will usually be confidential. The MoH will take a decision based on public information, such as the information of the Horizon Scan. Decentralised arrangements can be an alternative for a central arrangement with the State (MoH/*Bureau Financiële Arrangementen*) after the ZIN has issued its advice. Such decentralised arrangements or agreements do not have to be public, but the MoH should be granted full access and there should be guarantees to cover the long-term financial risks of treatment with the product. Until now, there has been only one example where the MoH decided that the decentralised arrangements with insurers and hospitals were sufficient to cover certain financial risks.[42]

Finally, there is an ongoing debate in the Netherlands about the legal remedies against lock chamber decisions, and compliance with EU law. For example, there is an ongoing discussion if Annex 0 to the Rzv is in fact a combination of a negative and a positive list within the meaning of Articles 7 and 6 Directive 89/105/EEC. Until now, the MoH takes the position that Annex 0 Rzv is merely a negative list within the meaning of Directive 89/105/EEC,

which would mean that the time-limits, etc. as set out in that Directive do not apply to the lock process and the assessment by ZIN. Furthermore, it is still unclear if the "lock chamber" is in fact a combination of a pricing and reimbursement measure within the meaning of Directive 89/105/EEC. As regards the legal remedies against lock decisions, the current position of the MoH is that a lock decision cannot be appealed before an administrative court because it should be considered an amendment of legislation. This position has not yet been tested by the highest administrative court, the Dutch Council of State.

(ii) *The "decentralised" lock*

An intramural medicine (inpatient medical care) is automatically included in the basic package if it is considered established medical science and medical practice (open system). Further to guidance (a "*duiding*") by the ZIN, or a position of a professional organisation, insurers can take the position that the product is not established medical science and medical practice.

In practice, add-on funding is essential for obtaining market access for medicinal products costing more than EUR 1,000 per year per patient. Normally, a hospital can charge insurers for providing "treatments" ("*diagnose behandel combinatie*", or "DBC"), and it is up to the hospital to purchase the medicinal products needed to provide state-of-the-art care. However, if an add-on request is granted, hospitals will be permitted to charge insurance companies separately for the price paid for the "add-on" medicinal product to treat their patients with the product. This is why healthcare providers and hospitals will equate the add-on with reimbursement. In practice hospitals tend to only use medicinal products after an add-on has been obtained, even though patients were already entitled to reimbursement due to the open system.

The add-on application procedure is not part of the lock procedure. However, many pharmaceutical companies regard the procedure as used and applied by insurers for obtaining an add-on as a "decentralised lock" ("*decentrale sluis*").

An add-on is a combination of a performance description and a maximum tariff, meaning that hospitals and insurers can negotiate a price for the add-on medicine below the NZa maximum tariff.

In order to alleviate the budgetary burden that would be incurred by hospitals if they have to pay for expensive specialist medicinal products out of their general budget, a so-called "add-on" request can be submitted to the NZa.[43] Currently an add-on can be obtained for authorised medicinal products costing more than EUR 1,000 per year per patient, as well as for unauthorised pharmacy preparations and advanced therapy medicinal products ("ATMPs") under the hospital exemption ("HE"). Furthermore, the product must be listed in the price list of the Z-Index.[44] It is possible to obtain an add-on for an unauthorised pharmacy preparation or ATMP under HE if an authorised equivalent or alternative product is available on the market.

An add-on request cannot be submitted by an MA holder. The add-on form[45] must be submitted jointly by (i) one or more hospitals, and (ii) one or more insurers, either directly or through their trade associations.[46] Via their trade organisation ZN, the insurers work together in the Committee for the Assessment of Add-on Medicines ("*Commissie Beoordeling Add-on Geneesmiddelen*", or "CieBAG"). This committee consists of representatives of the different insurers.

In practice the add-on application process works as follows:[47]

- A healthcare provider submits the add-on form[48] together with a written confirmation of the professional association of medical specialists to the CieBAG. The submission should include information with regard to the indication, the patient population and costs, budget impact, effectiveness and cost-effectiveness.

- The CieBAG will advise on the reimbursement status of new products. In case of a positive assessment by the professional association (i.e. the treatment is considered established medical science and medical practice) or positive assessment by ZIN, the CieBAG will change the reimbursement status of the product from NO to YES in the G-Standard. In the absence of an assessment by the professional association or ZIN, the CieBAG can make its own assessment. The CieBAG can furthermore advise to attach conditions to reimbursement, such as certain quality criteria for the hospitals (which will usually be set in consultation with the professional association), an appropriate use arrangement or a financial arrangement with the pharmaceutical company.
- After signing of the add-on application form by the healthcare provider and the CieBAG, the application is submitted to the NZa.
- The NZa will provide representatives from the healthcare providers (NVZ, NFU, ZKN and Actiz), healthcare insurers (ZN) and the pharma company the opportunity to respond to the application.[49] In case of an add-on application for an unauthorised pharmacy preparation or ATMP under HE, the NZa will provide the company that markets an authorised alternative or equivalent the opportunity to submit a statement of views.
- The NZa takes a decision, which will be published by the NZa and in the G-Standaard (Z-Index).

Policy issues that affect pricing and reimbursement

The MoH's Medicines Plan ("*Geneesmiddelenvisie*")

In 2016 the MoH launched its first Medicines Plan for the coming years. The plan highlights a multi-faceted approach. Each year the MoH provides an update of the Medicines Plan. Many of the topics that were listed in the first Medicines Plan have been implemented or are still in the process of being implemented.

One of the recurring themes of the plan is the accessibility of innovative medicines. The plan lists several tools to tackle high prices, such as joint procurement by insurers and hospitals, a reform of the reimbursement system (GVS), financial arrangements between the government and pharmaceutical companies for their products, and cross-country collaboration (e.g. Beneluxa). The plan also highlights the importance of the development of new business models, price transparency, public-private partnership ("PPP"), and subsidies. Replacement compounding (i.e. replacing authorised medicinal products by pharmacy-compounded preparations for economic reasons) is considered an opportunity to tackle high prices of authorised medicinal products. Other themes are the appropriate use of medicinal products and encouraging the use of generics and biosimilars. The MoH furthermore announced that it wishes to review the IP and regulatory rewards, such as Supplementary Protection Certificates ("SPCs") and market exclusivity for orphan drugs.

Emerging trends

It is suggested that medicine prices are rising exponentially, due to patents, SPCs, market exclusivity for orphan drugs and other mechanisms that are deemed "market monopolies" vulnerable to misuse/abuse by companies. Examples of instruments identified by the MoH, Parliament and government agencies to tackle high prices are compulsory licensing in cases where a company refuses to lower its price for a patented product, and pharmacy compounding to replace authorised medicinal products.[50] This has, *inter alia*, led to the introduction of the "pharmacist exception" in the Dutch Patents Act 1995, allowing pharmacists to engage in compounding without infringing process patents or product patents,

MoH "guidance" with a numerical definition of what is considered "small scale" *vs.* "large scale" compounding, an announcement by the ACM that it sees opportunities for lower prices of authorised "expensive prescription drugs" by instead using unlicensed "magistral preparations" made by pharmacies (i.e. replacement compounding), and an amendment of the reimbursement rules. The discussions about affordability and pricing have led to the introduction of new forms which require applicants to submit certain information about costs (see, e.g. the new Budget Impact Analysis template of ZIN), and discussions about pricing models, such as cost-plus pricing. Other notable developments include:

- The introduction of group assessments and therapeutic indication assessments by ZIN.
- The new conditional reimbursement of orphan medicinal products and medicinal products with a marketing authorisation granted under exceptional circumstances or a conditional marketing authorisation.
- The MEB-ZIN Parallel Procedures pilot, which allows a parallel assessment by the MEB and ZIN.[51]
- The modernisation of the GVS as per 1 January 2023.[52] By letter of 10 May 2021, the Minister for Medical Care informed the Parliament that a decision on the details of the GVS modernisation has been temporarily put on hold pending the outcome of the formation of the government. The Ministry will prepare a recalculation of the reimbursement limits with the outlined alternative safety net (i.e. the maximum reimbursement of the patient's own GVS contributions). If a new cabinet decides in favour of this interpretation, it can be implemented as of 1 January 2023 in accordance with the target set in the coalition agreement.[53]
- The introduction of add-on rules for unauthorised pharmacy preparations[54] in the intramural setting.[55] These new rules also apply to ATMPs under the HE. It is possible to obtain an add-on for an unauthorised pharmacy preparation or ATMP under HE if an authorised equivalent or alternative product is available on the market. In May 2021, the NZa set the first add-on for a pharmacy preparation (lutetium-dotatate).[56]
- The granting of a government subsidy of EUR 30 M for a multi-center, randomized head-to-head non-inferiority clinical trial of point of care ("PoC") CAR T *vs.* authorised CAR T. One of the secondary endpoints is cost-effectiveness. The expectation is that PoC CAR T will lead to substantial cost savings compared to the use of authorized CAR T. Within six months after completion of the trial, ZIN will adopt a position on whether or not the homemade CAR T treatment is considered established medical science and practice. If so, the treatment will directly enter the basic reimbursement package (i.e. no lock procedure, no prior pricing & reimbursement negotiations with the MoH or insurers).[57]
- The launch of the DRUG Access Protocol, which aims to make promising medicinal products that are not yet covered by basic medical insurance available in a faster, controlled and coordinated manner. The DRUG Access Protocol is an initiative of ZIN, ZN (insurers), the Dutch Association for Medical Oncology (NVMO) and the Antoni van Leeuwenhoek hospital. For the time being, the following hospitals participate in the protocol: Antoni van Leeuwenhoek, Erasmus MC, Maastricht UMC+, Radboudumc and UMC Groningen. Cemiplimab is the first product to be used in the context of the Protocol.[58]
- The start of the "Pilot project Regulating the influx of new non oncological, intramural orphan drugs in the Netherlands", which will run until 1 January 2023. During the pilot period, selected orphan drugs and/or new indications of orphan drugs that fall within the scope of orphan drugs that fall within the scope of inpatient care, are immediately set to NO in the G Standard upon introduction. This will remain on NO until clarity has been obtained and agreements have been made about a number of points.

Successful market access

The Dutch pricing and reimbursement system is quite complex and not set out in a well-defined set of rules and regulations, and it involves may stakeholders, both government and non-government. There is often more than one route or blockade to reimbursement. Which route will have to be followed, or how a blockade can be overcome, will depend on the circumstances and the parties involved. Successful market access there requires a thorough understanding of the market.

Many of the current policy issues are highly influenced by the public debate around pricing and reimbursement in the Netherlands. Many of these discussions are centred around themes such as financial sustainability of the healthcare system, patient access, pricing models, affordability, "evergreening" and transparency. Unfortunately, this can also make the system and the healthcare market unpredictable. This underlines the importance of public affairs and stakeholder engagement to increase the likelihood of success.

* * *

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Koosje van Lessen Kloeke
Tel: +31 10 244 43 44 / Email: k.vanlessenkloeke@leijnseartz.com

Koosje specialises in Life Sciences and Healthcare regulation under EU and Dutch law, both contentious and non-contentious. Her practice covers pharmaceuticals, medical devices, biotech, and healthcare. She advises several prominent life sciences companies and industry associations on a broad range of regulatory matters, such as marketing authorisations, pricing and reimbursement, managed entry agreements ("financial arrangements"), Beneluxa, patient access to unauthorised/unlicensed products, regulatory status of borderline products, clinical trials, cross-border healthcare, government transparency and data protection issues (in the context of the "Dutch FOIA"), and regulatory compliance and enforcement actions by competent authorities. Koosje has extensive experience representing clients in procedures before regulatory authorities, as well as with judicial review proceedings. Koosje is the author of the only comprehensive commentary on the Dutch Medicines Act (Kluwer, Tekst & Commentaar Gezondheidsrecht) and a regular speaker at conferences on topics concerning pharmaceutical law. Furthermore, she is co-founder and honorary member of the Dutch Pharmaceutical Law Association ("VFenR").

Leijnse Artz

Blaak 555, 3011 GB Rotterdam, Netherlands
Tel: +31 10 244 43 44 / Fax: +31 10 244 00 91 / URL: www.leijnseartz.com

Poland

Monika Duszyńska
Law for Lifesciences

Abstract

We present below basic information on the healthcare system in Poland. In the further part of this chapter, we provide more detailed comments on pricing and reimbursement of medicinal products and medical devices in the Polish regulations and in practice.

Market introduction/overview

In Poland, there is a mixed healthcare system, with a strong dominance of public healthcare. In line with the Constitution of the Republic of Poland, Polish authorities are required to ensure equal access to healthcare services financed from public funds, on terms provided for in separate laws. It is worth noting that services financed from the public resources may be provided in Poland both by the public and private healthcare providers.

To deliver healthcare financed from public sources, any provider, both public and private, should conclude a contract for the provision of healthcare services. Applicants seeking to obtain this must meet specific requirements and go through special proceedings. The contract with the public payer is usually for one year (the maximum term is three years). Public facilities, and public hospitals in particular, in practice nearly always obtain these contracts, while private entities are required to strongly compete, and many do not obtain them. A large part of the basic healthcare and some part of ambulatory care is provided by private healthcare providers; there also some private hospitals. The private sector may deliver care either on a fully commercial basis, where patients pay for care they obtain or services are prepaid (monthly fees paid by employers or individuals), or under contracts with the public payer, where care is financed from public sources.

Since the public healthcare system is not capable of meeting all patients' requirements, the gap is largely filled by private healthcare. Deficiencies concern similarly priced pharmaceutical products and medical devices. Unfortunately, the level of co-payment in Poland is high. Also, many medicines and products, reimbursed in other EU countries, are not listed in Poland at all, which means that their costs are either imposed on the patient or, if expensive, they remain unavailable. Numerous new medicines used to treat severe chronic diseases, if just recently authorised by the European Commission, or orphan medicines, are either unavailable, or their access though reimbursement is significantly delayed.

Products may be financed or co-financed from public sources if they are recorded by their proprietary name on a special reimbursement list (medicinal products, medical devices and certain food for special nutritional purposes) or covered by a special Regulation of the Minister of Health (only certain categories of medical devices). The reimbursement list is updated every two months, following reimbursement decisions granted for each of the listed products, after special proceedings before the Minister of Health.

Since 2016 there has been a special list of reimbursed medicines for elderly persons entitling persons aged at least 75 years to obtain, under specific conditions, reimbursed medicines entirely free of charge. The conditions are: age (at least 75 years); the medicine should be included on the list 75+ (at present, there are over 2,000 medicines, containing c. 180 active substances); the patient should require this medicine in a given indication disclosed on the list 75+; and a prescription is required.

Pharmaceutical pricing and reimbursement

Regulatory classification

The Polish regulations regarding the marketing authorisations are harmonised with the European Union laws on pharmaceuticals. Therefore, an authorisation to market a medicine in Poland may be granted following EU procedure (centralised, MRP, decentralised) or through the national procedure.

The Polish Pharmaceutical Law provides for detailed rules of the proceedings aimed at obtaining the national marketing authorisation. The proceedings should be concluded within 210 days from the submission of the application, however, they usually last much longer, since each time there is a need to submit any additional document or comments in reply to deficiency letters, there is a clock stop. In practice, obtaining the national market approval may require up to two to three years.

The authority granting marketing authorisation is the President of the Agency for the Registration of Medicinal Products, Medical Devices and Biocides, while the Chief Pharmaceutical Inspector is responsible for supervision of distribution and promotion and advertising of medicinal products. The Minister of Health takes decisions on pricing and reimbursement of medicines and other products eligible for reimbursement, while the public payer is the National Health Fund (NFZ).

Medicines are authorised and further dispensed either on prescription or as OTC medicines, as per their marketing authorisation. Also, medical devices and food for special nutritional purposes, if financed from the public funds, are dispensed on prescription only (they do not require a prescription if dispensed out of reimbursement). In Poland, most of the innovative medicines are authorised, however, their actual access to patients is strongly dependent on reimbursement. Polish authorities widely recommend the use of generic medicines, which are often prescribed and used, and relatively easily obtain reimbursement. It is worth noting that Poland has a number of domestic manufacturers of generic medicines.

Who is the payer?

The payer for the reimbursed medicines is the NFZ, which is a country-wide agency. It is headed by the President with a wide scope of responsibilities and a huge impact on how the system operates in practice. The President issues ordinances and communications that implement, explain and develop the rules established in legal laws and regulations, so its powers and impact on the Polish reimbursement system and access to healthcare is very significant.

The Fund is operated through 16 divisions, one in each of the Polish voivodships (Polish administrative regions). Contracts regarding the provision of healthcare, including these relating to financing certain hospital medicines within the reimbursement systems, are concluded at the regional level. Likewise, settlements of payment for medicines dispensed in open pharmacies are made regionally.

The remaining expenses on healthcare, including medicines, which are not financed by the public payer, are covered through self-pay. There are no other public payers in Poland.

Private healthcare insurance is available on the Polish market; to some extent it may cover certain expenses on medicines and medical devices, but a limited number of Polish citizens have such insurance and the scope of healthcare services covered by them is not significant.

It is worth noting that numerous public hospitals host or have foundations which collect funds from private sources to finance certain healthcare services, and in particular not reimbursed medicines. Often new medicines which are lifesaving or used in rare diseases, or which are very expensive, are financed from such funds. Parents of ill children raise money in various fundraisers (available online or through social media), which are then transferred on the account of such foundations, and are used to cover costs of medicines in hospitals providing the treatment (the medicine is purchased against the funds collected by the foundation).

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

Securing reimbursement for a new product is quite clearly regulated in the law. It is, however, its practical application that may turn out to be a tough adventure.

a) *Reimbursement decision*

Reimbursement is granted in an administrative decision, issued by the Minister of Health following proceedings regulated in detail in the Act of Reimbursement of Medicinal Products, Food for Special Nutritional Purposes and Medical Devices, applied since 1 January 2012 (Reimbursement Act). The Reimbursement Act is completed by numerous regulations. A reimbursement decision determines detailed terms of reimbursement and a fixed price of the reimbursed medicine. Other terms of reimbursement include a channel in which a medicine is reimbursed (pharmacy or hospital), co-payment level (only pharmacy medicines), the limit group in which a reimbursed medicine is included (all medicines in such a group have the same financing limit – please see our further comments), and any risk sharing schemes. Reimbursement decisions are issued for a defined term – first for two years (unless issued for generics to already reimbursed medicinal products), and then for a three years' term.

b) *Products eligible for reimbursement*

In Poland, the following products are eligible for reimbursement: medicinal products on prescription; medical devices; and food for special nutritional purposes. A product subject to reimbursement should be authorised and available on the Polish market (in practice, a sales invoice should be provided).

Certain medicines which do not possess a regular market authorisation, or are unavailable on the Polish market, may get reimbursed under separate terms and in separate reimbursement proceedings. These are usually medicines recently authorised by the European Commission and not yet available on the Polish market, including orphan drugs, or medicines not yet authorised in the EU. From the perspective of the applicants, which – unlike in regular reimbursement proceedings – are individuals seeking care for their children or themselves, it is a very difficult path and it is often that refusal to grant reimbursement under these proceedings is challenged in complaints brought to administrative courts.

Certain categories of medical devices may be reimbursed in a very special regimen, without a reimbursement decision. In Poland, only two categories of medical devices are reimbursed in reimbursement decisions: dressings; and strips to measure glucose or ketones in blood or urine. Other medical devices, if at all, are reimbursed, if a category, to which they belong, is mentioned in a special Regulation of the Minister of Health (no brands are listed there, but only categories of reimbursed medical devices, such as prosthesis, wheelchairs, ostomy equipment, and many others). To sell medical devices falling into a category listed in that Regulation, their manufacturer or distributor is required to conclude a special contract with the public payer, setting terms of the reimbursement of the device.

A product eligible for listing may be reimbursed in all its authorised indications, or only in selected ones (it is very common, in particular, in the majority of hospital drug programmes where strict criteria of use of the reimbursed medicine are applied). A medicine may also be reimbursed out of its authorised indications (reimbursement in off-label indications). Reimbursed products are divided into so-called limit groups, according to indications in which they are reimbursed. Products falling into one limit group have a common financing limit. In case of pharmacy medicines, the payer covers its price only up to this limit, which is the same for all the medicines belonging to that group, while the difference between the limit and the price must be covered by the purchaser (e.g., the patient, in case of pharmacy medicines). The Reimbursement Act provides for detailed terms of calculating the amount of the limit in limit groups, but basically, the limit equals the price of the cheapest medicine in the group (but a medicine which price sets the limit should achieve a certain market share though). The limit is subject to frequent changes, which in turn impact the amount of co-payment. Pharmacy medicines in which prices exceed this limit will always require co-payment.

c) *Reimbursement proceedings*

Application for reimbursement

In principle, reimbursement is granted only upon a special application (with some exceptions). Requirements vary depending on whether an application regards an innovative medicine, or a generic or biosimilar. An application for reimbursement for an innovative medicine should be accompanied by determined HTA analysis (including clinical, economic and budget impact analyses). Applications for reimbursement of generics are simpler, only a budget impact analysis is required. Reimbursement proceedings should be concluded in principle within 210 days (with some exceptions) following submission of the application, but any request from the Minister of Health to complete the application triggers a clock-stop, therefore, in practice they are much longer (usually at least a year).

Any applicant, irrespective of whether for an innovative or generic medicine, is required to disclose detailed information on the prices and other terms of reimbursement, including any rebates, both in Poland and in other EU countries. It is also necessary to provide, among others, both daily and average costs of the therapy with the medicine subject of application, and the duration of the therapy. WHO-defined daily dose (DDD) system is widely used. The applicant should also make a warranty to supply the product on a continuous basis and declare determined volumes to be supplied on the Polish market in each year of the term of the reimbursement decision.

Fees

Applications are subject to various regulatory fees; their amount vary depending on the type of the application (a pharmacy or hospital medicine, innovative or generic). The basic fee is c. EUR 735 (PLN 3,300), a fee for a medicine to be reimbursed in a hospital drug programme (reserved for most expensive hospital medicines) is c. EUR 2,200 (PLN 9,900). In case of innovative medicines that would require a HTA assessment, in addition to the regular fee, a special fee of c. EUR 22,570 (PLN 101,574) should be paid.

Proceedings are sometimes suspended at the request of the applicant, in particular, when there is an impasse in the negotiations of the financial terms of reimbursement of certain innovative, expensive medicines. Thanks to such suspension (that cannot exceed three years), the applicant does not loose fees already paid for the application for reimbursement, and it may wait until the change of circumstances, collection of new clinical evidence supporting its application, or a more favourable position of the Minister of Health toward its financial proposals (this possibility may be removed, however, in the next amendment of the Reimbursement Law, already disclosed for public consultations).

The course of the proceedings

The proceedings include a formal review of the application, review and assessment of the HTA analysis (for innovative medicines) by a special body – the Agency for Assessment of Medical Technologies and Tariffs (AOTMiT), followed by financial negotiations with the Economic Commission and finally the decision of the Minister.

The assessment of HTA analysis is a complex process and concludes with a detailed report on clinical, economic and others aspect of reimbursement, called a verification analysis. This report should also include a recommendation on whether the medicine should be listed or not and on its highest acceptable price, and the terms of its reimbursement in other countries, with their detailed analysis. The President of AOTMiT then issues its recommendation for reimbursement, or recommends a conditional reimbursement (e.g., the price should be adjusted to CEE threshold), or expresses its negative opinion. The statement of the President of AOTMiT should include detailed terms of any future reimbursement, covering indications, in which the medicine may be reimbursed, suggested co-payment category, a recommended limit group in which the medicine should fall, and risk sharing schemes. It should also include detailed rationale of its conclusions, referencing clinical, financial, economic and other data.

Negotiations with the Economic Commission are conducted at the meetings attended in person (or online during the COVID-19 pandemic) by the applicant's representatives. They are widely reported as being very challenging, because the Economic Commission often expects financial terms which are difficult to accept. These concern the price and the terms of risk sharing schemes – commonly the Economic Commission from its own initiative proposes such schemes. Interestingly, both foreign and domestic applicants complain about a huge pressure to lower offered prices. It is quite common to reschedule the agreement of reimbursement terms, since the applicants, having heard expectations of the Commission, cannot respond right away and often letters with further fee proposal follow the meetings with the Commission (this may be restricted, as per a recent draft amendment of Reimbursement Law). The negotiations conclude with a protocol, where an agreement or disagreement on the terms of reimbursement (such as the price offered by the applicant and the price expected by the Economic Commission) are determined.

The last step is the decision of the Minister of Health, who adopts it based on numerous determined criteria, listed explicitly in the Reimbursement Act. The Minister may issue a decision on reimbursement of a product (only if the Minister finally agrees on terms offered by the applicant), or it may refuse to reimburse it. Please note that the applicant cannot appeal or submit official objections against either statement of the President of AOTMiT, or a position of the Economic Commission. In contrast, a decision (especially a refusal decision) of the Minister of Health can be appealed against, however, since the Minister of Health is the highest authority in the administrative proceedings, the appeal is brought to the same authority, that is the Minister of Health. In consequence, the appeal rarely leads to a change of the issued decision, unless there are obvious and justified allegations challenging the decision on the merits or procedurally.

A final decision of the Minister of Health may also be challenged in a complaint lodged with the administrative tribunal, in proceedings permitting review of the administrative decision in two court instances. The proceedings before the administrative tribunal are lengthy (at least one year, in case of two instances – up to three years), however, in some cases may lead to waiving of the challenged decision. In such cases, the Minister is required to review the application again, in line with guidelines from the tribunal, nevertheless, in many cases he/she issues the same (refusal) decision.

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

The prices of reimbursed products are set by the Minister of Health in an administrative decision, where a product gets reimbursement. Therefore, these two matters are inseparable.

Since 2012, in Poland all prices of reimbursement medicines are fixed. The reimbursement decision sets a price to the first independent wholesaler, which also includes VAT (a statutory sale price). Further in the distribution, the statutory wholesale margin is added (fixed margin of 5%), and at the end the retail statutory margin for pharmacy medicines (retail margins are degressive). There is one exception in case of hospital medicines, since in sales to hospitals, under certain specific circumstances, the fixed prices change into maximum ones.

The price proposal made by the applicant in its application for reimbursement, and other proposed financial terms, are reviewed and assessed during reimbursement proceedings and strongly negotiated. In line with the legal provisions, the Minister of Health should set the statutory price of a reimbursed medicine based on numerous criteria listed in the Reimbursement Law such as: the position of the Economic Commission; the lowest prices applied in Poland and in other EU countries (both if listed or not; in particular, prices applied in the countries having similar GDP *per capita* are taken into account as reference prices); and the amount of statutory sale prices of other medicines, also of other molecules, having similar therapeutic properties, if reimbursed in the same indications and having similar efficacy (comparators). Other criteria include the need of balancing the interests of patients and manufacturers and distributors, financial capacity of the payer (NFZ) (all these factors truly matter), and research and development, and investments activity of the applicant in healthcare, in Poland and in other EEA countries (the latter is rather a formal criterium, with less practical value).

So-called risk sharing schemes, often of great importance, are agreed between the applicant and the Minister, and their terms are articulated in an exhibit to the final reimbursement decision (not in a civil contract). Almost exclusively, risk sharing schemes consist of either: (1) an obligation of the applicant to return to the public payer an agreed share in revenues generated from sales of reimbursed medicines (used more often in the past); and (2) a warranty of the applicant to ensure that the wholesalers will sell the reimbursed medicine at an agreed maximum price (the applicant will be required to obtain such warranty from wholesalers to which it will sell the reimbursed medicine). In practice, this particular scheme is equivalent to an agreed rebate to be applied in the distribution of the reimbursed medicine. A common practice is to agree on determined caps (such as a limit of number of packages of medicines subject to reimbursement, or a limit of number of patients whose therapy with reimbursed medicine will be financed through reimbursement). There has been a long discussion in Poland over the last few years to introduce outcomes-based risk sharing schemes. However, due to insufficient tools to measure, monitor and record the clinical outcomes, they are still rare.

The reimbursement decisions in Poland are temporary. The price determined in any consecutive reimbursement decision cannot be higher than the price determined in the existing decision. The prices of first generics and biosimilars to be reimbursed cannot exceed 75% of the price of the reimbursed reference medicine.

During the term of a reimbursement decision, the applicant may apply for an increase in price. This request should be properly justified. In Poland there is a statutory price decrease after the expiry of market exclusivity (by 25% with respect to the existing price). Certain manufacturers apply for a price increase just before the statutory price decrease due to expiry of market exclusivity, to mitigate lower revenues from sales after such decrease (this also will probably be restricted, as per a new draft amendment of the Reimbursement Act).

Co-payment

All reimbursement medicines are divided into so-called 'limit groups' that have a common limit, up to which they are financed from public sources. With regard to medicines used in an outpatient setting, the patient is required to pay: a difference between the limit and the retail price of a pharmacy medicine; and a determined share in the limit. This share depends on the category of co-payment determined in the reimbursement decision. Pharmacy medicines may obtain one of the following categories of co-payment: free of charge; available for a lump sum (at present, less than one Euro); 50% of the limit; or 30% of the limit. The remaining share in the limit, not financed from the public sources, is paid by the patient.

Issues that affect pricing

Due to quite frequent changes in the level of the limit in a group, following, e.g., adding of a cheaper medicine to the group, holders of reimbursement decisions for medicines whose price started to exceed the limit in the group, in order to reduce or avoid the co-payment by the patient, sometimes apply for a price decrease. This is also because co-payment over the value of the limit often results in lowering sales of the reimbursed medicine (it regards mostly generic medicines or older medicines which have numerous substitutes).

A pharmacist is required to inform the client on availability of a substitute of the medicine prescribed, if the retail price of this substitute does not exceed the limit and the price of the prescribed medicine (pharmacy substitution). Pharmacies are required to have such substitute in stock. These obligations on pharmacists favour sales of the cheapest reimbursed medicines. In hospitals, in the case of both regular generics, but also of biological medicines, automatic substitution is permitted and strongly recommended, and even sometimes imposed by the public payer.

In addition, hospital group purchasing of reimbursed medicines, with the aim to purchase cheapest products, is strongly favoured. Certain medicines are purchased in nationwide public tenders.

Policy issues that affect pricing and reimbursement

In Poland, the population is slowly decreasing (at present, c. 37,600,000 inhabitants), despite certain legislative instruments that were aimed to increase fertility, Poland faces the same challenges as societies in Western Europe, and in particular a growing number of elderly persons and, similarly, a growing number of people affected by chronic diseases. The Polish population is relatively younger than the population of the majority of the EU Member States, however, as Eurostat prognosticates, the difference will gradually disappear and by 2050 both median age, and the percentage of people over 65 years old, will probably exceed the average in the EU. The biggest number of deaths is caused by cardiovascular diseases, including strokes, cancer and car accidents. The most frequent chronic diseases are cardiovascular diseases, hypertension, obesity, diabetes and tumours.

Expenses on healthcare, both public and private, are considered to be much below the average in the EU, even if their nominal value is raising slowly. Private expenses account for c. 30% in overall expenses on healthcare, and are also considered very high. A share of all the public expenditure on healthcare in GDP is still very low and amounts to c. 4.5%. However, in line with Polish laws, this share should raise until 6% in 2025.

The share of expenditure on medicines in the general expenditure on healthcare is also insufficient and it amounts to c. 15–16% of the overall expenditure of the public payer NFZ on healthcare. The Polish Reimbursement Act imposes a rule that expenses on reimbursement

cannot exceed 17% of the overall prognosticated expenses on healthcare services financed from the public funds. Nevertheless, this share does not reach even 16% of the overall expenses on all healthcare services, despite the declaration of the government, articulated in the strategic document *The Drug Policy of the Government for the years 2018–2022*, that this percentage will be kept between 16.5% and 17%. The pharmaceutical industry and numerous experts and stakeholders have been bringing up the issue of insufficient expenses on reimbursement of pharmaceuticals for many years, however, so far without noticeable effects.

In recent years, there has been a very animated discussion over the use of biosimilars. It is widely criticised in Poland, especially among the clinicians, that access to biological treatment is very limited, especially if compared with other EU countries. The Polish authorities promote and use various tools to even enforce use of biosimilars and automatic substitution from original biologicals into biosimilars, especially in hospitals; however, their relatively quick reimbursement by the Minister of Health does not result, unfortunately, in a greater access to biological treatment. This is caused, to a great extent, by restrictions in availability of biological treatments articulated in so-called hospital drug programmes, in which biological medicines are reimbursed. These programmes establish quite strict inclusion and large exclusion criteria for patients eligible to reimbursed treatments, which in many respects are more restrictive than provisions of SmPC for the medicines used in these treatments.

To summarise, in Poland great changes are still required to increase access to affordable medicines and healthcare in general. The most urgent issues that are mentioned most frequently are the need to increase expenses on reimbursement, reducing existing restrictions to medicines reimbursed in hospital drug programmes, including biological medicines, and reducing co-payment.

The COVID-19 pandemic has had a huge impact on access to healthcare in Poland. The most critical problems that were reported are delayed diagnosis and, in consequence, delayed starts of treatments. In addition, a reduction in medical consultations, which was followed by a significant decrease in the number of prescriptions, and then, in delayed or no treatment at all during the lockdown, and poor or insufficient diagnosis at on-line consultations, were also widely reported.

Emerging trends

Reimbursement and access to medicines are a widely discussed topic and often stakeholders report a need to modify provisions of the existing regulations, bringing to the public attention various issues and requirements. There has been an important change in terms of access to very special reimbursed care, reserved to cases in which no other reimbursed treatment is available (*RDTL*). Before, a hospital treating the patient and wishing to ensure a medicine under *RDTL* was required to obtain special approval of the Minister of Health, issued in a very complicated and bureaucratic procedure, while at present the access to this way of financing the treatment is more dependent on the treating physician (however, within the limits of the countrywide fixed budget).

On 30th June 2021 a new draft amendment to the Reimbursement Act has been published and brought to the public consultation. This draft proposes numerous significant changes. These include an automatic transfer of the reimbursement applications in case of, e.g., corporate changes, the secrecy of the negotiations in the reimbursement proceedings, the rule that any revenues paid by the holders of reimbursement decisions to the public payer,

and coming from reimbursement (payback) or risk sharing schemes, should be spent on the reimbursement of medicines, and not on general healthcare (as it has been so far, which has been widely criticised), what would possibly allow for an increase of public sources dedicated to finance pharmaceuticals. Many other proposed changes raise numerous concerns, such as widening of discretion powers in changing and setting up limit groups, also during terms of reimbursement decisions (which would affect co-payment levels), privileges to products and API manufactured in Poland, and certain mechanisms aimed at keeping the prices and other terms of reimbursement at the level the most convenient to the payer.

Irrespective of the said draft amendment, it has been widely discussed recently how to increase access to orphan drugs and in general to treatments of rare diseases. Another topic has been quicker access to most innovative medicines, newly authorised, before they get reimbursement, to those who cannot wait and for whom they would be lifesaving therapies. Also, access to biological treatment still awaits improvement. There is still a lot to do and change to increase access to care to the extent clearly noticeable to patients.

Another emerging trend is hospital group purchasing, or even central (country-wide) public tenders. The idea has become quite popular, however, it is also criticised for triggering a risk of eliminating losing competitors, which may finally lead to an increase in prices.

Successful market access

Even if in Poland there is a growing openness to finance innovation, the price and financial terms offered by the pharmaceutical company still play a huge role in the final outcome of the negotiations of the terms of reimbursement. A pharmaceutical company, unless it offers a medicine with exceptional clinical benefit, should be ready to face a strong pressure to offer the best terms possible, even if it would mean the lowest prices in Europe. While negotiating the price, especially with the Economic Commission, it is important to explain the reasoning behind the financial proposal as detailed and accurately as possible, and to be very flexible and open to elaborate various financial solutions. Financial risk sharing schemes are often agreed, so it may be very helpful to have a proposal in mind while starting negotiations. Also, the quality of the clinical data are very significant. This is especially regarding clinical superiority, if substantiated, which may be important in obtaining a decision on reimbursement.

Therefore, a high quality of the HTA analysis and a reasonable financial proposal, along with flexibility in negotiations, certainly are useful tools in reimbursement proceedings.

Monika Duszyńska
Tel: +45 60 910 64 38 / Email: monika.duszynska@md-law.pl

Monika Duszyńska is a Polish-qualified advocate with 23 years of professional experience.

Monika's experience includes regulatory issues, advertising and marketing of medicinal products and medical devices, clinical trials, manufacturing, distribution and compliance. Monika also advises clients in reimbursement matters, and represents them in proceedings before the Minister of Health, advising on risk-sharing instruments and negotiations' strategy. She also has a wide-range of experience in drafting contracts including distribution and licence agreements (IP).

Monika also advises the Polish pharmaceutical industry chamber and a number of patients' organisations. Monika is a frequent lecturer at various events for the industry, and a contributor to a number of publications (including university publications) on various regulatory topics, such as early access to medicines and access to the treatment of rare diseases.

Law for Lifesciences

L. Rydygiera 13/271, 01-793 Warsaw, Poland
Tel: +48 22 100 43 24 / URL: www.md-law.pl

Spain

Jordi Faus, Lluís Alcover & Joan Carles Bailach
Faus & Moliner

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 2020, the pharmaceutical market in Spain reached €19.5 billion, of which €7.8 billion corresponds to the hospital market, and €11.7 billion to products dispensed through retail pharmacies. Growth was around 11.8%, with expenditure in hospital products exceeding 5.6% over 2019, whilst growth in retail pharmacies was 3.4%. In 2021, YTD figures (until February 2021) show a 0.9% decrease in the hospital market with respect to the same period of 2020 and a 1.4% decrease of the retail market with respect to the same period in 2020.[1]

In 2019, Spanish public pharmaceutical expenditure (approx. €18.7 billion) is said to account for approx. 1.5% of the gross domestic product and public pharmaceutical expenditure accounted for 26.1% of all public healthcare financing (approx. €75 billion).[2]

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 €12.1 billion per year); and by comparison with other sectors in Spain, it has a higher concentration of more stable, qualified and diverse employment (95% of its workers are permanent, 66% have university studies, and 50% are women).

As regards demographics, in July 2020 (last data available), 47.4 million inhabitants lived in Spain, with a gross birth rate of 7.6 births per 1,000 inhabitants and an average maternal age of 32 years. Life expectancy at birth reached 83.6 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")[3] show that steady growth in births may be expected during the next 10 years at rates that may be near 0.5% but with 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 recognise universal access to healthcare.[4]

However, measures[5] 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.[6]

Put into practice, these measures imply that some of the population do 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 the 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 ("NHS").[7]

During the year 2018 (last data available), 1,419 presentations of medicinal products were included in the provision of the NHS.[8] 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 the 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 always be subject to a medical prescription. This is the case for those medicines that

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 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 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 must 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 must 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 that 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. 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 carried out by evaluation teams who handle the dossiers prior to the meeting of the ICPM.

The AEMPS has a very important role in the reimbursement process when issuing its Therapeutic Position Report ("IPT"). This may vary in the near future because Spain is planning to reform its IPT process in 2021. This reform has already led to the set up of a new pharmaceutical network called REvalMED which will be responsible for the coordination of the whole IPT process from late 2021 onwards. REvalMED will comprise a therapeutic evaluation group (led by the AEMPS), an economic evaluation group (led by MOH) and therapeutic area specialists. Within REvalMED, the AEMPS will still retain significant power, especially with respect to the therapeutic evaluation of the product, but this power will be shared with the General Directorate of Pharmacy of the MOH which will increase its influence on the IPT process, mainly with respect to the economic evaluation. It is also very important to note that the 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. Autonomous Regions will also have an important role within REvalMED, providing input to the therapeutic and economic teams led by the AEMPS and the General Directorate of Pharmacy, respectively, and appointing "expert reviewers" that will be entitled to review and provide comments on ITPs drafts before their approval.

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[9] 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. Regarding the right of access to the information provided by the interested company, we refer to the Confidentiality and transparency section below.

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 NHS 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 Coordination Group of REvalMED shall approve, 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 currently having in Spanish practice; 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. Further, it is worth mentioning that due to a recent modification of the Spanish Law on Medicines and Medical Devices made by Royal Decree-Law 7/2020, the MOH may now establish maximum retail prices for non-reimbursed products sold in Spain (including non-prescription medicinal products) that may be needed for the protection of public health in the context of exceptional health crisis (such as the COVID-19 crisis). The only condition that the law imposes on the MOH is that its decisions must be based on objective factors and must be transparent. The fixed prices will remain valid throughout the duration of the exceptional circumstances that motivated the administrative intervention.

Finally, 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 of 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 into 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.

Finally, we note that alternative pricing and reimbursement rulings, such as payment based on results, are becoming increasingly popular in the last years, especially for medicinal products with high budgetary impact and with an important R&D component such as CAR-T medicinal products. In this respect, on 22 October 2019, an information system[10] to support the collection and processing of health outcomes (the so-called "VALTERMED") was officially presented by the MOH.

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 the case that 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.

Finally, it also relevant to highlight that IPTs, which will start including economic evaluations, are expected to significantly increase its influence on pricing and reimbursement negotiations going forward.

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 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 that penalises companies for defending their position – provided this is carried out 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 having the same level 5 of the Anatomical Therapeutic Chemical ("ATC") Classification System of the World Health Organization 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 at the same ATC 5 level to establish a maximum price for the dose necessary for a day of treatment with this substance, which is the maximum price that the NHS will satisfy when the presentations with this substance are dispensed or administered to the patient charged to public funds. Whether reference price groups must be created with presentations having the same "active substance" or the same "ATC 5 Classification" has been a controversial matter in Spain since 2014. While art. 98 of the Law on Guarantees and Rational Use of Medicines ("LGRUM") used to unambiguously contemplate that reference price groups had to be created with product presentations having "the same active substance", it was not unusual for the MOH to conform groups with presentations having the same ATC 5 level rather than the same active substance. This way of acting of the MOH led to many claims before Spanish Courts where companies argued that the MOH was inadequately including product presentations with different active ingredients in the same reference pricing group. In 2017 the Supreme Court declared that if the MOH wanted to include two product presentations in the same reference price group on the basis of the ATC 5 Classification, the MOH had to provide sufficient evidence that the active ingredients of the two presentations were the same; otherwise such presentations could not be included in the same group. This 2017 Supreme Court decision was followed by many others with the same rationale. In view of these Court rulings, the MOH changed its criterion and in 2020, it updated many reference price groups following the active-substance-criterion. However, right after this decision, Article 98 of LGURMPS was amended to specifically contemplate the ATC 5 criterion to conform reference price groups. 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).

Between 2019–2021, Spanish courts ruled on several cases related to reference pricing.

A first group of cases revolve around the interpretation of the requisites laid down in Spanish law for the creation of reference price groups. In October 2019, the Spanish *Audiencia*

Nacional had the chance to rule on an interesting case regarding the creation of reference groups when no generic or biosimilar exists in Spain.[11] In that case, the plaintiff was the MAH of an exenatide product with two presentations (an immediate release formulation and a delayed release formulation). The plaintiff claimed that the MOH inadequately created a reference price group with both presentations because such presentations were, in fact, the same medicinal product. The Court did not share this view, and resolved that the creation of the group had been correctly carried out by the MOH because the two presentations were to be considered different products for reference price purposes. The Court supported its position with the fact that the two presentations had separate marketing authorisations and were commercialised under different trademarks. The Court did not consider the fact that the two presentations were part of the same global marketing authorisation for data protection purposes. An appeal against this Judgment has been presented to the Supreme Court. On 1 October 2020, the Supreme Court admitted the appeal and clarified that the controversial matter that was sufficiently relevant to be submitted to the Supreme Court was "whether a reference price group may be created exclusively with presentations of the same medicinal product that, despite being commercialised under different names/trademarks, are owned by the same company". The resolution of the appeal is still pending. Our opinion is that this ruling of the Spanish *Audiencia Nacional* may be questionable from the point of view of the economic rationale of the reference price system. In this respect, we think that the reason why Spanish law contemplates that reference prices may appear even in the absence of generics or biosimilars is that at the time such reference price would start applying, there should exist in the market at least one product which does not incorporate the research effort done by the reference one, thus opening the door to price competition not conditioned by R&D costs. In this regard, one may argue that this opening to competition not conditioned by R&D costs does not occur in situations like the one described in this case where two presentations of a product are owned by the same company and are the result of the same company's R&D effort. We shall wait for the Supreme Court position on this.

A second group of judgments refer to matters related to the challenging of already formed reference price groups. In this group we find particularly interesting a judgment of the Spanish *Audiencia Nacional* published in October 2019 which discussed the test that should be done to determine whether the commercialisation of a product is economically viable after the price reduction operated by its inclusion in a reference price group.[12] The Court considered that such test should compare the ex-factory price with the actual commercialisation and manufacturing costs of the product, and disregard any profit margin. Although the Court finally refused the plaintiff arguments on the basis that the plaintiff did not provide sufficient evidence about the costs associated to the product, the message conveyed by the Court is relevant to the extent it expressly recognises that a product may be deemed economically inviable if the plaintiff can prove that its ex-factory price falls below its manufacturing and commercialisation costs. As a final comment, we note that in the recent past, Spanish courts have usually been reluctant to accept this type of economic rationale when companies challenge the inclusion of its products in reference price groups.

A third group of judgments refer to cases where plaintiffs argued that the MOH was inadequately conforming reference price groups on the basis of the ATC Classification System. Such cases, however, have become moot because, as mentioned, the law was changed with effect as from 1 January 2021 to contemplate that reference price groups must be created with presentations having the same ATC 5 Classification rather than the same active substance.

Finally, we note that on 2 June 2020, the Spanish Government approved a resolution pursuant

to which it was declared that orphan medicinal products with no therapeutic alternative (or with a therapeutic alternative but providing a significant benefit with respect such alternative) would not be subject to the reference price system.

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

The 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. Actual sales of the product being greater than the sales forecast submitted by the company during the price and reimbursement proceeding is one of the reasons that may trigger an *ex officio* price review. In this respect, we note that on 5 June 2020 the High Court of Justice of Madrid confirmed that the price reduction of a product because of a 15% deviation between the forecasted and actual sales of such product was in accordance with the law.

From January 2020 until March 2021 (last period with available information),[13] the ICPM has reviewed the price of 106 products. Such reviews ended with 49 price increases and 57 price reductions.

As one may expect, the *ex officio* 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 1015/2009, 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 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; 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 are 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 (Article 31 of Royal Decree 1090/2015 on clinical trials).

We note that Royal Decree 1015/2009 is under review and it is likely to be replaced in the near future. A public consultation with respect this initiative was run in December 2020–January 2021 with the objective to inform all relevant stakeholders and citizens and to invite them for feedback. The need to differentiate the regimes (currently unified under Royal Decree 1015/2009) applicable to access to non-authorised products and to access to authorised but not commercially available products has been identified as one of the topics expected to be addressed with the reform.

What happens with products for which reimbursement is denied?

Up until 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 on the market for patients or hospitals who wish to acquire the product 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 purchased by hospitals, approval is required from the regional authorities where the hospital is located and are 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 1718/2010 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 1718/2010 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 1718/2010, or of any other law or regulation in Spain, which supports the idea that when Royal Decree 1718/2010 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.

In 2019, a Spanish Court had the chance to rule on a very relevant case regarding the payment by regional authorities of medicinal products for which a ruling expressly denying reimbursement had been adopted.[14] In this case, the plaintiff (a minor patient with a severe genetic disease) claimed against the decision of a regional authority that refused to pay for the treatment that the doctor had prescribed. One the one hand, the plaintiff alleged that the refusal of the regional authority to pay for the treatment constituted a violation of its fundamental rights, including the "right to life", the "right to equality" and the "best interest of the child". The defendant regional authority argued that no fundamental rights were infringed and that there were no reasons to justify the payment of a product that the MOH had decided not to reimburse. The Court ruled in favour of the plaintiff and required the regional authority to pay for the treatment after recognising that the position of the regional authority infringed the right to equality of the patient (other patients in other Spanish regions were receiving the product free of charge) and the best interest of the child. The Court did not accept any violation of the right to life. As a final note, we point out that although this judgment does not specifically refer to the report of the General Director of Pharmacy mentioned above, it provides for a solution that is contrary to that of the report.

In 2020–2021 Spanish Courts have ruled on two new cases regarding access to non-reimbursed medicines. In both cases, as occurred with the 2019 case outlined in the preceding paragraph, the Court ruled in favour of the plaintiffs (patients) after recognising that the conduct of the administration being sued amounted to an infringement of the right to equality of such patients: patients in the same exact situation were treated differently without any objective reason.

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.

Until 2019, in cases where the Spanish Council on Transparency received complaints against the MOH denying access to pricing and reimbursement rulings, it decided that the MOH should deliver these rulings to the party that had requested them, only not disclosing 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 took 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.

Between 2019–2021, the Spanish Council on Transparency has had the chance to rule on

several matters regarding access to pricing and reimbursement rulings. The position of the Transparency Council on this matter has been rather erratic during this period. On the one hand, the Transparency Council has issued several resolutions ordering the MOH to disclose copies of the rulings whereby the MOH accepted to reimburse certain products and fix their ex-factory price ("PVL"). On the other hand, the Council has adopted the contrary position in other cases. In this respect, in September 2019 the Council denied the right of a citizen to have access to the price and reimbursement ruling of a medicinal product (and, therefore, to its PVL) on the basis that such access would damage the legitimate interests of the company. In this case, the Council assessed the value of keeping the PVL confidential from a public interest point of view, claiming that if prices were not confidential in the EU, they would tend to be fixed at a level that could be low for richer countries but too high for countries with less economic capacity, thus making access to certain products difficult.

On another note, it is worth pointing out that the information that the MOH makes public when uploading the minutes of the meetings of the ICMP on its website has increased since mid-2019.

In view of the foregoing, 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).

Between 2019–2021, the Spanish Council of Transparency has also had the chance to rule on several cases regarding requests to disclose supply prices offered to hospitals. The position of the Council in this matter, again, has also been erratic. On the one hand, the Council has ruled in favour of a citizen who requested the disclosure of a list of all the medicinal products purchased by four specific hospitals from 2016 to 2018 (including units and prices paid for them by the hospitals); and also in favour of another citizen who requested access to the quantities of certain products (and their price) purchased by Spanish hospitals in 2018. On the other hand, the Council has issued decisions whereby disclosure requests have been denied. In this respect, the Council ruled against the disclosure of the "annual expenditure of hospitals in Madrid for three specific medicinal products" on the basis that the disclosure would harm the economic and commercial interests of the companies and would distort competition in the market. In some rulings, the Council relied on Law 1/2019 on Commercial Secrets to support the denial to release information on unit prices. It is also relevant to mention that during 2019–2021, the Spanish Transparency Council has issued four Interpretative Criteria (1/2019, 2/2019, 3/2019 and 1/2020) on how to evaluate access requests. Regarding access to price & reimbursement rulings, the Interpretative Criterion 1/2019[15] on how to evaluate whether disclosing certain information may cause harm to economic and commercial interests is especially relevant. In this document, the Transparency Council states that when the requested information qualifies, in whole or in part, as a business or commercial secret under the terms of Law 1/2019 on Commercial Secrets[16] or is affected, in whole or in part, by a declaration of confidentiality contained in a law or established under the terms of the law, access must be denied by application of the limit of protection of economic and commercial

interests established in Article 14.1.h of Law 19/2013 on Transparency, Access to Public Information and Good Government.

With respect to the position of the Spanish Courts, we can say that the judgments published in the period 2019–2021 do not provide for a clear and unequivocal criteria on this matter and, as occurs with the Spanish Council of Transparency, their position has been rather erratic. In this respect, the three most recent rulings regarding access to price and reimbursement rulings (April 2020) and disclosure of supply prices offered to hospitals (May 2020 and March 2021) reach different conclusions. On the one hand, one judgment annulled a resolution of the Spanish Council on Transparency which required the disclosure of the reimbursement terms of a new product on the basis that the MOH did not hear the affected company. The Court recognised the right of the affected company to be heard and indicated that the process before the MOH should be started again from the beginning. On the other hand, the other judgment (May 2020) confirms a resolution of the Council that ruled in favour of the disclosure of the price for medicinal products paid by Spanish public authorities during 2018. This judgment was appealed and annulled. A Spanish Court ruled (March 2021)[17] that providing such information would violate the guarantee of confidentiality established in Article 97 of Royal Legislative-Decree 1/2015. In addition, this judgment of March 2021 recognises that providing this information would affect the economic and commercial interests of the pharmaceutical companies that market them.

Finally, we note that in March 2021 the Supreme Court issued an important judgment confirming that if there is a risk that the disclosure of a document undermines the protection of commercial interests of a third party, the Spanish Council of Transparency (and not only the institution that initially receives and denies an access request) must consult with such third party before granting access to the document. The Supreme Court further stated that if the Council does not know the identity of such third party and does not have any data that allows such identification (this may happen when the institution that receives the access request at first does not consult with the third party before denying access), then the Council must order the proceeding to be resumed at the point where the institution that received the access request (e.g. the Ministry of Health) should have had consulted such third party.

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 (the "Farmaindustria Agreement"), 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.

The Farmaindustria Agreement has been fully effective until 30 June 2020. Farmaindustria and the Spanish Government are currently negotiating an extension of the agreement.

With respect to the implementation of the Farmaindustria Agreement so far, it is worth mentioning that the follow-up committee of the agreement agreed in July 2019 (with respect to financial year 2018) on a claw-back payment of approx. €120 million to be paid by the members of Farmaindustria to the Government. The Committee also agreed on other non-monetary measures to be made by members of Farmaindustria for a value of approximately

€97 million. The agreed claw-back for 2019 amounted to approximately €270 million. As per year 2020, the situation is still very open because of the open negotiations regarding the Farmaindustria Agreement and the expected slowdown of the GDP.

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.

Action Plan to promote the use of generic and biosimilar products[18]

In September 2019, the Interterritorial Council of the Spanish NHS (a committee on which the MOH sits together with representatives of all the Autonomous Regions) approved a draft of an Action Plan to foster the use of generic and biosimilar products. Later on, the MOH published the Plan for public consultation and asked all relevant stakeholders to submit observations and proposals with respect to the Plan. Such observations will be assessed in the Interterritorial Council of the Spanish NHS and, afterwards, the MOH will publish a revised version of the Plan.

As specifically stated in the Plan, its main and general objective is to foster the use of generics and biosimilar products (the so-called "regulatory" medicinal products) by facilitating the price and reimbursement proceeding for such products. Other specific objectives contemplated in the Plan include reducing the time elapsed between the authorisation of a generic or biosimilar and its inclusion in the reimbursement, increasing the competitiveness of the pharma sector, promoting the generic and biosimilar industry, increasing the use of generics and biosimilars in the NHS, and enhancing the level of information regarding generics and biosimilars.

For the achievement of these objectives, the Plan proposes specific actions in the following areas: (i) reimbursement; (ii) Pharmacotherapeutic Guide of the NHS; (iii) prescription; (iv) dispensation; and (v) information and training.

The publication of the Plan has generated a lot of interest and many stakeholders have actively submitted observations and proposals to the MOH.

Plan for the Consolidation of Pharmaceutical Therapeutic Positioning Reports

In 2020, the Permanent Commission of Pharmacy of the Interterritorial Council of the Spanish NHS approved the Plan for the Consolidation of Pharmaceutical Therapeutic Positioning Reports. This Plan, which was presented in November 2020 by the General Directorate of Pharmacy of the MOH, aims to review the whole HTA process in Spain and consolidate Therapeutic Positioning Reports ("ITP") as a key element of such HTA. The Plan includes two major action lines. First, setting up a new pharmaceutical evaluation network called REvalMED which will be responsible for the coordination of the ITP process. REvalMED will comprise a therapeutic evaluation group (led by the AEMPS), an economic evaluation group (led by the MOH) and therapeutic area specialists mainly appointed by the Autonomous Regions. Second, improvement of the methodology of IPTs. Such methodology, which will include health economic evaluations, will be based on guidelines developed by the Group for the Evaluation of Innovations, Standardisation and Research in Drug Selection ("GENESIS") of the Spanish Society for Hospital Pharmacy ("SEFH"). As per GENSIS, the therapeutic positioning criteria will be mainly defined by both the incremental cost-effectiveness ratio and budget impact.

Spanish Recovery and Transformation Plan (*Plan de Recuperación, Transformación y Resiliencia*)[19]

At its meeting of 17–21 July 2020, the European Council agreed to create Next Generation EU, a temporary recovery fund additional to the multiannual budget of the European Union for 2021–2027. Such funds are envisaged to be used to tackle the consequences of the COVID-19 pandemic and boost economic recovery. To access these resources, Member States must design "recovery and resilience plans" that will be evaluated by the European Commission ("EC").

Spain presented its first version of its "recovery and resilience plan" in January 2021 and sent it to the EC in April 2021. The Plan includes several references to the pharmaceutical sector in its 18th component (page 161) under the section "strengthening of the capabilities of the National Health System".

The 18th component contemplates funds amounting to Eur 1,069M and includes two subsections: "reforms" and "investments". Both the reforms and the investments are listed but not described in detail. With respect the reforms we highlight Sec. C 18.R5 which contemplate "the approval of a national plan to rationalise the use of medicinal products and to promote sustainability", including measures such as the "reform of the regulatory framework for medicines and medical devices to introduce elements to foster competence and to facilitate access to new treatments". With respect the investments, we outline Sec C 18.15 which foresees "the approval of a national plan to rationalise the use of medicinal products and to promote sustainability" (C18.15). This national plan is expected to include measures to foster the use of economic evaluation in HTA assessments and to promote the use of generic and biosimilar products in Spain.

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

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Jordi Faus
Tel: +34 93 292 21 00 / Email: jfaus@faus-moliner.com

- Graduated in Law, Autonomous University of Barcelona, 1986.
- Diploma in Advanced Legal European Studies. College of Europe, Bruges (Belgium), 1987.
- Executive Management Programme at IESE, 2003.

Jordi Faus has been practising law for over 30 years. In 1997 he founded Faus & Moliner, a Spanish boutique law firm specialised in legal matters typical of the pharmaceutical industry and of other companies which operate in the life sciences sector. Faus & Moliner has been recognised as the leading firm in pharmaceutical and life sciences law in Spain by various Spanish and international publications.

Jordi Faus is the author of several publications on pharmaceutical law and EU law. His works include Pharma, a journey through the pharmaceutical industry (2008) and the Pharmaceutical Law Treaty co-authored with Professor José Vida (2017).

Lluís Alcover
Tel: +34 93 292 21 00 / Email: lalcover@faus-moliner.com

- Graduated in Economics, University Pompeu Fabra, 2010.
- Graduated in Law, University Pompeu Fabra, 2012.
- Master in Business Tax and Legal Advice, ESADE, 2014.
- Executive Management Programme, ESADE, 2017.

Lluís Alcover joined Faus & Moliner in 2017 coming from PwC, where he worked for four years as part of the transactions legal team (M&A). Lluís Alcover has experience in investment operations, restructuring and due diligence processes, drafting and negotiation of all types of commercial contracts, as well as in regulatory matters affecting companies operating in the life science sector, including price and reimbursement proceedings.

Joan Carles Bailach
Tel: +34 93 292 21 00 / Email: jcbailach@faus-moliner.com

- Graduated in Political and Administration Sciences, University Pompeu Fabra of Barcelona, 2015.
- Graduated in Law, University Pompeu Fabra, 2017.
- LL.M. in Professional Legal Practice at UPF-Barcelona School of Management, 2018.
- Master's degree in Economic criminal law & Compliance at UPF-Barcelona School of Management, 2019.

Joan Carles Bailach has been practising law for over three years. He joined the team of Faus & Moliner in 2019.

Faus & Moliner

Rambla Catalunya 135, 08008 Barcelona, Spain
Tel: +34 93 292 21 00 / URL: www.faus-moliner.com

Sweden

Odd Swarting & Per Hedman
Cirio Advokatbyrå AB

Abstract

This chapter provides an overview of the model for pricing and reimbursement of pharmaceuticals 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 instead introduced a value-based pricing and reimbursement scheme. Thereby and since, to a large extent Sweden has led the way on value-based pricing for pharmaceuticals. 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 within the reimbursement scheme. The use of cost-effectiveness analysis in reimbursement decisions aims to relate and balance the reimbursement price to the social value of the pharmaceutical, but does not necessarily result in (or intend to result in) the lowest possible price.

The regions are solely responsible for the funding of in-patient pharmaceutical expenditure and the costs are covered by taxes.

Costs for out-patient pharmaceuticals included in the reimbursement scheme are formally financed by the regions but are almost exclusively covered by state 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, regions and municipalities. The state is responsible for the overall health and medical care policy, while the regions 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 the elderly, immigration constitutes the largest demographic change and primarily increases the population that is of working age.

Manufacturing of pharmaceuticals and medical devices is one of the largest industries in Sweden, and accorded a high priority by the Swedish Government. For 2020, Sweden continues to be the EU innovation leader according to the European Innovation Scoreboard. During 2020, the Swedish pharmaceutical market had a turnover of SEK 52.4 billion, an increase of 4% compared to 2019. In 2020, close to 211 million pharmaceutical packages were sold in Sweden. Approximately 51% of these packages were prescription pharmaceuticals, while approximately 44% were non-prescription pharmaceuticals.

The Swedish pharmacy state monopoly was abolished in 2009. Since then, the number of pharmacies has increased by almost 500. Currently, there are over 1,400 outpatient pharmacies in Sweden and the industry is dominated by five pharmacy chains. In addition to out-patient pharmacies, there are hospital pharmacies, dose-dispensing pharmacies and distance pharmacies. 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 regulatory framework for pharmaceuticals 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 pharmaceuticals 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 Products 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). These directives will thus be repealed and replaced by Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices. The former regulation will enter into force on 26 May 2021 and the latter regulation will enter into force on 26 May 2022. The Medical Devices Act is intended to be replaced by, *inter alia*, a new law with additional provisions to the EU regulations on medical devices and a law with supplementary provisions on an ethical review of the EU regulations on medical devices. The Medical Devices Act shall, however, continue to apply to in relation to in vitro diagnostic medical devices until 26 May 2022.

The legal framework concerning the granting of marketing authorisation of a pharmaceutical 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 if and to what extent a pharmaceutical 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. *förordning om läkemedelsförmåner m.m.*) (PBO). TLV also issues regulations and general advice.

In addition, Sweden has a system for substitution of generically equivalent pharmaceuticals.

The MPA decides which pharmaceuticals shall be substitutable (generic substitution) 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 to the cheapest pharmaceutical within the reimbursement scheme. The system demands that pharmacies dispense the least expensive generic product available to the patient, regardless of the prescribed product, unless the prescribing healthcare professional has opposed substitution for medical reasons in writing or the dispensing pharmacist oppose to the substitution. The patient may also refuse substitution if he or she is willing to pay the difference between the prescribed medicine and the generic alternative.

Prescription (out-patient) vs. requisition (in-patient)

Pricing and reimbursement procedure and regulation of pharmaceuticals primarily depends on whether the specific product is a *prescription pharmaceutical (out-patient)* or a *requisition pharmaceutical (in-patient)*.

Prescription is the case when a pharmaceutical is prescribed to a patient and dispensed to the patient by an out-patient pharmacy. The price of prescription pharmaceuticals included in the reimbursement scheme is determined by TLV, while the pricing of prescription pharmaceuticals outside this system are set freely (see below).

Requisition, on the other hand, means the requisition of pharmaceuticals 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 pharmaceuticals to publicly owned healthcare providers are procured and priced pursuant to public procurement procedures carried out by the Swedish regions. Privately owned healthcare providers who perform healthcare on behalf of the Swedish regions can make call-offs from these agreements unless they want to arrange their pharmaceutical supply on their own.

It is possible for a specific pharmaceutical 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 will, in connection with being granted a Swedish marketing authorisation, be classified either as a prescription only or a non-prescription pharmaceutical. The MPA will decide the classification for the pharmaceutical depending on its intended use and characteristics. A prescription-only pharmaceutical must be subject to either prescription or requisition in order to reach the patient. Non-prescription pharmaceuticals, on the other hand, do not require prescription or requisition; however, nothing prevents non-prescription pharmaceuticals from being prescribed or requisitioned.

Products eligible for reimbursement

The general rule is that only prescription-only pharmaceuticals are eligible for reimbursement under the reimbursement scheme, 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 pharmaceuticals being eligible for reimbursement. According to the TLV regulation TLVFS 2003:2 (regarding non-prescription pharmaceuticals in accordance with PBA) (last amended by TLVFS 2012:3),

non-prescription pharmaceuticals may be eligible for reimbursement (as of the date of this chapter, non-prescription pharmaceuticals eligible for reimbursement include, e.g. certain allergy pharmaceuticals and pharmaceuticals for skin and stomach problems). In addition to pharmaceuticals, there are also other products that are eligible for reimbursement. Further, such pharmaceuticals and products must be prescribed by healthcare professionals to be reimbursed.

As stipulated in Section 18 of the PBA, only some medical devices are eligible for reimbursement. Medical devices eligible for reimbursement, called consumables, only includes products used: (i) in connection with stoma; (ii) to induce a pharmaceutical into the human body; and (iii) for self-monitoring of medication. Stoma-consumables are covered by the same rules regarding reimbursement as pharmaceuticals 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 pharmaceuticals included in the reimbursement scheme is regulated and the cost of such pharmaceuticals dispensed in pharmacies to patients is to a large extent indirectly financed 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 writing this chapter, the maximum amount is SEK 2,350 (approx. €230). 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 chapter SEK 1,175 (approx. €115)), 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 pharmaceuticals 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 pharmaceuticals included in the reimbursement scheme are free for all women under the age of 21.

As stated above, the prices for requisition pharmaceuticals used in publicly institutional and non-institutional healthcare are negotiated in public procurement processes. Prices for requisition pharmaceuticals used in privately owned institutional and non-institutional healthcare will depend on whether the healthcare provider has made call-offs from regional agreements or not.

For publicly financed healthcare a patient will pay the applicable standard fee for the healthcare which includes the cost for any requisition pharmaceuticals.

Most non-prescription (over-the-counter) pharmaceuticals are not part of the reimbursement scheme and, thus, not subject to regulated pricing.

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

TLV decides on the basis of the PBA if and to what extent a pharmaceutical shall be reimbursed after an application by the manufacturer. For a pharmaceutical 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 pharmaceutical meets the applicable legal requirements. In the application, the applicant shall state the requested price of the pharmaceutical 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 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 pharmaceutical 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 pharmaceuticals, as long as the devices are to be used by patients and prescribed by a healthcare professional. However, the rules regarding substitution of pharmaceuticals 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 pharmaceuticals 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 to be included in the reimbursement scheme are that: (i) the costs of using the pharmaceutical appear reasonable from a medical, humanitarian and socioeconomic perspective; and (ii) there are no other available pharmaceutical(s)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.

In order to estimate the cost for the use of the pharmaceutical, TLV requires information regarding the relevant patient group and volume; for instance, the number of patients that will need the pharmaceutical and for how long. Furthermore, TLV considers whether there is a risk that the pharmaceutical is used outside a potential limitation of the subsidy – which, in that case, risks being a usage that is not cost-effective.

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 is eligible for reimbursement for its entire approved area of use, while restricted reimbursement means that the pharmaceutical is included in the reimbursement scheme only for a certain area of use or a specific patient group. One of the reasons why TLV grants a restricted reimbursement may be that the pharmaceutical is only considered to be cost-effective for a limited and specific group of patients. TLV may also stipulate special conditions for a reimbursement decision (conditional reimbursement), e.g. that the applicant, after some time, must present new data on the use of the pharmaceutical in the healthcare system.

There are no further statutory law 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.

In 2003, TLV issued general guidelines (TLVAR 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, 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.

TLV's practices on the conditions for determining the subsidy and price has over time been developed by the administrative courts.

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

There are various pricing procedures for pharmaceuticals; for example, through decisions by TLV, the regions' 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 regions and pharmaceutical companies may enter into managed entry agreements, where one of several factors is considered when TLV makes decisions on price and reimbursement. So far, such agreements have been seen as a tool to ensure cost-effectiveness and reduce the increasing costs for new pharmaceuticals by way of flat rebates. However, the 2021 agreement between the Swedish regions and the Swedish government concerning financing of pharmaceuticals provides for a halt of new rebates agreement with regions *outside the three-party negotiation process*, and include a mechanism intended to disincentives the regions for entering into new such agreements.

Furthermore, the pharmacies have a limited right to negotiate pricing of pharmaceuticals that differ from the price of pharmaceuticals determined by TLV, a right that mainly extends to parallel imported pharmaceuticals.

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, however, regulated for non-prescription drugs that are included in the reimbursement scheme, and the patient makes a co-payment. It should be noted that most over-the-counter pharmaceutical products are not included in the reimbursement scheme.

The MPA decides which medicinal products that shall be substituted at the pharmacies and publishes a list of groups that includes such products (including products outside the reimbursement system). 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 in principle 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 pharmaceuticals within the publicly owned healthcare are set in the county council's public procurement processes, which are regulated by the Swedish Public Procurement Act (2016:1145) (Sw. *lagen om offentlig upphandling*). However, prices for requisition pharmaceuticals used in privately owned institutional and non-institutional healthcare will depend on whether the healthcare provider has made call-offs from regional agreements or not.

In publicly financed healthcare, the patient only pays the patient fee that applies for the in-patient treatment concerned, and except such flat fee, and the full cost of the pharmaceuticals used in in-patient case are borne by the regions.

Issues that affect pricing

Generic substitution

As stated above, the MPA approves pharmaceuticals with regard to their quality, safety and efficacy, and the MPA also decides which pharmaceuticals 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. All pharmaceuticals, whether or not, included in the reimbursement scheme, are subject to substitution, if there is an equivalent pharmaceutical in the reimbursement scheme. The pharmacies are obligated to dispense the least expensive that is available on the market. 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 branded original pharmaceuticals that have lost their 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 price, or withdrawing from the reimbursement scheme.

Price reduction after 15 years

Certain rules apply for the pricing of some older pharmaceuticals approved for reimbursement (see TLV's regulation TLVFS 2014:9, last amended by HSLF-FS 2018:30). Based on these rules, TLV may reduce the price of pharmaceuticals 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 pharmaceuticals that recently have 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?').

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 pharmaceuticals 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 regions. 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 regions, 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 regions 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 across the country, 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. As of the date of this chapter, no governmental bill has been presented.

In 2014, a three-party negotiation process involving the regions, TLV and the pharmaceutical company in question were introduced. The three-party negotiations are intended to facilitate a more dynamic process for pricing and reimbursement assessments of pharmaceuticals, as well as facilitate access to new, innovative treatment options for patients while maintaining a general price control and price reduction for the society. 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 more comprehensively 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 regional 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 regions 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.

As mentioned above, in June 2020 certain amendments to the PBA entered into force, enabling the substitution of prescribed pharmaceuticals not included in the reimbursement scheme, to equivalent cheaper pharmaceuticals that are included in the reimbursement scheme. As a result of these amendments, TLV initiated a reassessment of several reimbursed pharmaceuticals, to either adjust medicines subject to restricted reimbursement and make them generally reimbursed, or in some cases harmonise reimbursement restrictions within

specific substitution groups (regarding general and restricted reimbursement, respectively, see section 'How is the reimbursement amount set? What methodology is used?', 'Pharmaceutical Pricing and Reimbursement' above). As a result, in April 2020, several decisions by the TLV entered into force, adjusting the reimbursement status for approximately 680 pharmaceutical products. The intention with the legislative amendment and the TLV's reassessments was, *inter alia*, to enable more patients to receive their prescription drugs within the benefits scheme and subject to high-cost protection.

TLV was in 2020 assigned by the Swedish government to develop models for health economic assessments, and to analyse viable payment models, for gene and cell therapies (ATMP), and TLV reported its conclusions in May 2021 through the report 'How shall we value and how shall we pay?'. As regards the models for health economics assessment, the TLV report addresses, among other things, combination products (including pharmaceuticals and diagnostics combinations) and the room to include new value factors in the models to capture the type of uncertainties that are particularly common for ATMPs. In the report, TLV expresses its willingness to explore outcome-based payments models, a type of managed-entry agreement that until now have been rare in Sweden (if any). TLV concludes that it sees outcome-based models as a tool to bridge value differences and to reduce payor risk, where TLV envisions payments tied to value realisation over time. Although deferred payment models for ATMPs may offer financing benefits for payors, TLV concludes that it does not see it as a viable in a Swedish context. The report also argues for benefits in allocating at least partial responsibility for the financing of ATMPs on the national government.

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 regions for in-patient use.

The three-party negotiations with the regions and TLV are a natural path for a large share of new pharmaceuticals to reimbursement and the Swedish market. Given the dynamic nature of the process, careful preparations are essential and access of in-house or external experience with experience of the three-party process will be key.

It is worth noting that reimbursement and pricing decisions within the reimbursement scheme by TLV are appealable decisions that can be tried by the administrative courts, and there are generally no restrictions against resubmitting an application to TLV (e.g. including a more comprehensive health economic analysis) for a second-round evaluation.

Odd Swarting
Tel: +46 70 644 12 13 / Email: odd.swarting@cirio.se

Odd Swarting works as legal advisor to public and privately held clients in various industry branches and has more than 25 years of experience and focus in the healthcare, pharmaceutical, medical devices and food sector. In addition to transactions, collaborations and other commercial contracts, his practice also largely involves research and development projects, pricing, substitution and other regulatory matters and various issues pertaining to the public sector. Odd also has substantial experience counselling clients during financial crises. Odd has been engaged as a speaker at various seminars and conferences and has written many articles within, *inter alia*, the Life Sciences area. He has been ranked for many years as a leading Swedish Lawyer by many institutes.

Per Hedman
Tel: +46 76 617 09 21 / Email: per.hedman@cirio.se

Per Hedman's practice focuses on businesses that have a significant reliance on IPR, and primarily the life science and health sector (being biotech, pharma, medtech, e-health, wellness and foods, as well as healthcare and elderly care). Per advises companies in all aspects of their business and legal affairs, including regulatory advice, R&D arrangements (such as non-disclosure, material transfer, clinical trial and joint development agreements) and commercial relationships (such as manufacturing, supply and distribution agreements). Per is regularly invited to speak at conferences and seminars on life science and healthcare topics.

Cirio Advokatbyrå AB

Mäster Samuelsgatan 20, 8th floor, 111 44 Stockholm, Sweden
Tel: +46 8 527 916 00 / URL: www.cirio.se

Switzerland

Dr. Oliver Künzler, Dr. Carlo Conti & Dr. Martina Braun
Wenger Plattner

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 must 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 2019, healthcare costs amounted in total to 82.08 billion Swiss francs (provisional result). Compared to the general domestic product, healthcare spending represented 11.3% in 2019 (provisional result). Every resident in Switzerland paid on average 798 Swiss francs per month (provisional result) for the healthcare system in 2019 (*cf.* https://www.bfs.admin; last visited on 21 May 2021). The corresponding numbers for 2020 are not yet available.

In 2020, there was a historical decline in both exports and imports from and to Switzerland due to the COVID-19 pandemic. The total value of goods and services exported from Switzerland amounted to 225 billion Swiss francs (provisional result), which corresponds to -7% compared to the previous year, whereas the value of imported goods and services amounted to 182 billion Swiss francs (provisional result), which corresponds to -11% compared to 2019. A new record surplus balance of 43 billion Swiss francs (provisional result) in favour of Switzerland resulted therefrom, compared to a positive balance of 36 billion Swiss francs in 2019. The most important part of Switzerland's exports were chemical and pharmaceutical products, which constituted 51.5% of the exports (116 billion Swiss francs). According to the Swiss Federal Customs Administration, exports of chemical and pharmaceutical products bucked the general downward trend registered by the other product groups (*cf*. Key figures 2020, available under the following link: https://www.ezv.admin.ch; last visited on 21 May 2021). Chemical and pharmaceutical products further constituted the second-largest group of imported products (51 billion Swiss francs respectively 28% of the imports). It must be noted that all numbers stated above are provisional results (*cf*. Key figures 2020, available under the following link: https://www.ezv.admin.ch; last visited on 21 May 2021).

According to the Association of research-based pharmaceutical companies in Switzerland ("**Interpharma**"), in 2019, reimbursable therapeutic products represented approximately 84.5% of the total pharmaceutical market (*cf*. Interpharma, Health Panorama 2020, p. 32).

In 2019, 47,500 people in Switzerland were employed by the pharma sector alone (*cf*. Interpharma, Health Panorama 2020, p. 71). Over 496,200 people in Switzerland (corresponding to approximately one in 12 of the working population) worked in the entire healthcare industry and the pharmaceutical sector in 2017 (*cf*. Interpharma, Healthcare Switzerland, 2019, p.38).

In Switzerland there is a very high density of hospitals which offer a wide range of medical services. In 2019, 281 hospitals and maternity units (38,057 beds) and 1,565 homes for elderly and care (92,838 residents per 31 December 2019) were registered in Switzerland (*cf*. https://www.admin.bfs.ch; last visited on 21 May 2021). The density of general practitioners is, however, relatively low compared to other countries.

Contrary to certain countries, such as the USA, most therapeutic products cannot be sold via supermarkets. Hence, pharmacies still remain the most important sales channel for medicines: 65% of all medicine packs (corresponding to approximately half of the sales in terms of value) were sold via pharmacies in 2020. In certain cantons, doctors are permitted to dispense medicines themselves. In terms of value, self-dispensing doctors and hospitals each account for approximately another quarter of sales of pharmaceuticals (*cf*. Interpharma, Health Panorama 2020, p. 30).

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*. https://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 50 approved non-profit insurance providers currently offer basic mandatory insurance and optional daily allowance insurance.

The insurers offering compulsory health insurance must treat all insured persons equally. In particular, they are not permitted 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 must 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 (for further information, *cf.* "The compulsory health insurance system", a guide published by the FOPH, available under the following link: https://www.ezv.admin.ch; last visited on 21 May 2021).

In case of congenital diseases, basic health insurance pays the same costs as in the case of disease, if such costs are not covered by invalidity insurance (article 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 must 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 a public consultation every five

years 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: https://www.bfs.admin.ch (last visited on 21 May 2021).

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*. https://www.admin.bfs.ch; visited last on 21 May 2021).

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*. https://www.admin.bfs.ch; last visited on 21 May 2021).

The hospitalisation ratio per 1,000 residents was 118.3 in 2019, while infant mortality stood at 3.3‰, in 2019 (*cf*. FSO, Health – Pocket Statistics 2020, available under the link: https://www.bfs.admin.ch; last visited on 21 May 2021).

2.2 million people living in Switzerland are affected by a non-communicable disease (cancer, cardiovascular diseases, chronic respiratory diseases, diabetes and diseases of the musculoskeletal system). This corresponds to a quarter of the Swiss population. A growing number of people living in Switzerland is affected by dementia as life expectancy increases (*cf*. Interpharma, Health Panorama 2020, p. 8). The most common causes of death in Switzerland are cardiovascular diseases (approx. 30.7% of the deaths in 2018) and cancer (approx. 25.9% of the deaths in 2018; for more details, *cf*. FSO, Health – Pocket Statistics 2020, available under the link: https://www.bfs.admin.ch; last visited on 21 May 2021). 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: https://www.bfs.admin.ch; last visited on 21 May 2021).

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 at the 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 16*c* TPA). On request, Swissmedic renews the authorisation if the requirements are still fulfilled (article 16*b* TPA). In principle, the renewed marketing authorisation is valid for an unlimited term. However, Swissmedic may put a time limit on it (article 16*b* 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: https://www.spezialitätenliste.ch (last visited on 21 May 2021).

If a therapeutic product is more than 10% more expensive than a third of all therapeutic products listed on the specialty list with the same composition, the insured must pay 20% of the costs exceeding the deductible (article 38*a* 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 must file an application to the invalidity insurance.

Consequently, non-listed therapeutic products must 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 must 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 been expedited and should not exceed 60 days from the date of the marketing authorisation (article 31*b* 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 and composition of the therapeutic product in question by taking into account clinical-pharmacological and galenic considerations, possible side effects and the risk of misuse (article 33 OBHI). Finally, a therapeutic product is deemed economically efficient if the indicated therapeutic effect is reached most cost-efficiently (article 65*b* 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 Austria, Belgium, Denmark, Finland, France, Germany, Great Britain, Netherlands 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 65*b* OHI and articles 34*a 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 65*b* paras 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 65*d* and 65*e* 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 2019 is expected to reach the age of 81.7 (men) or 85.4 (women) (*cf.* https://www.bfs.admin.ch; last visited on 21 May 2021). 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, 15.0% lived in retirement homes per 31 December 2019 and 29.2% needed care at home, and that the total costs of retirement homes alone amounted to 10.550 million Swiss francs in 2019 (*cf.*

FSO, Health – Pocket Statistics 2020, available under the link: https://www.bfs.admin.ch; last visited on 21 May 2021), 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 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

The Swiss legislation regarding integrity and transparency has recently been revised. The previous provision with respect thereto (article 33 TPA) has been abolished and replaced by two new provisions (article 55 TPA and article 56 TPA), which entered into force on 1 January 2020. Further, the HIA has been amended. The details are set forth in the new Ordinance on Transparency and Integrity of ("**OTI**"; *Verordnung über die Integrität und Transparenz im Heilmittelbereich, VITH*), which also entered into force on 1 January 2020.

Pursuant to article 55 TPA, it is prohibited for persons who prescribe, dispense, use or purchase for this purpose prescription-only medicinal products as well as for the organisations that employ them, to solicit, be promised or accept any undue advantage for themselves or for the benefit of a third party. Further, it is prohibited to offer, promise or grant an undue advantage to any such person or organisation for their benefit or for the benefit of a third party. Article 55 para. 2 TPA contains a list of contributions, which are not regarded as undue advantages. Those are (i) material benefits of modest value (300 Swiss francs per medical professional and year at maximum), which are of relevance for the medical or pharmaceutical practice, (ii) subject to certain criteria, support for research, education and training, (iii) compensation for equivalent services in return, in particular for those provided in connection with orders and deliveries of therapeutic products, and (iv) price discounts or refunds granted on medical purchases, provided they have no influence on the choice of treatment.

Compared to the previous regulation regarding benefits and kick-backs, the personal scope of application has been extended (for example, purchasers of medicinal products, such as members of medicines' commissions in hospitals, homes for elderly or nursing homes and purchasers of medicinal products for practitioners' networks are now covered). In contrast, the material scope of application has been reduced from all medicinal products to prescription-only medicines. However, with regard to the current medical device revision, the integrity provision will be extended to benefits related to the prescription, supply and use of medical devices. This will require a partial revision of the VITH, which is expected to enter into force in 2025 at the earliest.

In addition, for the purpose of transparency, according to article 56 TPA, all price discounts and rebates granted on purchases of medicinal products must be shown on the receipts and invoices and in the accounts of both the selling and the purchasing persons and organisations and must be reported and disclosed to the FOPH upon request. This obligation does not apply to remedies with a low risk potential, such as over-the-counter therapeutic products (category E) or classical medical devices of class I according to annex IX of the EU Directive 93/42/EEC on Medicinal Devices (e.g. plasters, thermometers or walking aids) available in the retail trade (article 10 OTI).

Finally, service providers (e.g. doctors, hospitals, pharmacists) are obliged to pass on price discounts and reimbursements granted to them to patients or insurers (article 56 HIA).

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 new regulations 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 were revised. The revision aimed at improving the population's access to therapeutic products and the conditions for biomedical research and industry. Certain provisions entered into force on 1 January 2018, the remaining revision of the TPA and the corresponding ordinances entered into force on 1 January 2019 and 1 January 2020, respectively.

Further, Switzerland has adapted its legislation in view of the developments regarding medical devices and *in vitro* diagnostics in the EU. The new regulations regarding medical devices were originally scheduled to come into force on 26 May 2020. However, in connection with the COVID-19 pandemic, implementation of the Medical Devices Regulation ("**MDR**") in the EU was deferred by one year. As Switzerland wishes to achieve equivalence with the EU legislation, the entry into force of the revised Swiss medical device legislation were also deferred by one year, to 26 May 2021. With the coming into force of the new provisions, the transition of the EU regulations regarding medical devices into Swiss law has been completed. In a final step, *in vitro* diagnostic medical devices shall be regulated in a separate ordinance on *in vitro* diagnostics.

In parallel to the above-mentioned legislative projects regarding medical devices and *in vitro* diagnostics, the Agreement between the EU and Switzerland on mutual recognition in relation to conformity assessment ("**MRA**"), which aims at overcoming technical barriers to the trade of numerous industrial goods (including medical devices), shall be updated, to maintain facilitated reciprocal market access between Switzerland and the EU and to ensure joint implementation of the regulations. However, the EU Commission has made the update of the MRA conditional upon progress being made on the Institutional Agreement between the EU and Switzerland. As the negotiations on the Institutional Agreement have been closed end of May 2021 without success, the Federal Council has adopted supplementary provisions regarding the new medical device legislation, which also entered into force on 26 May 2021, in order to mitigate the negative consequences of the lack of an update of the MRA. The revision of the legislation will however be continued based on equivalent EU provisions, so that the MRA could still be updated within the next one to two years.

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.

Acknowledgment

The authors would like to thank Melanie Müller for her invaluable contribution to this chapter. Melanie Müller is an associate at the firm's Basel office. She is a member of the IP and IT team as well as the Life Sciences and Health Law team. She advises national and international companies as well as individuals on the full range of intellectual property matters, focusing primarily on trademarks, copyright and licensing.

Prior to joining Wenger Platter, Melanie Müller completed an LL.M. in Boston with a focus on IP law, and worked, among other positions, as a law clerk at the civil court in Basel.

Tel: +41 61 279 70 00 / Email: melanie.mueller@wenger-plattner.ch

Dr. Oliver Künzler
Tel: +41 43 222 38 00 / Email: oliver.kuenzler@wenger-plattner.ch

Oliver Künzler is a partner in Business Groups Corporate and Commercial and Life Sciences and Healthcare. He deals primarily with international and national M&A transactions, restructurings and reorganisations, private equity and venture capital transactions and financings and has a specific focus on the Life Sciences and Healthcare sector. He also advises shareholders and companies on all aspects of contract, commercial and corporate law. He further specialises in advising small and medium-sized enterprises, particularly with respect to business succession and structuring.

Oliver Künzler regularly publishes and speaks on topics of contract, commercial and corporate law. He is active in several national and international professional organisations and serves as an expert on business succession.

Dr. Carlo Conti
Tel: +41 61 279 70 00 / Email: carlo.conti@wenger-plattner.ch

Carlo Conti is a partner in the field of Life Sciences and Health Law. He is a member of a number of boards of directors. He is also a lecturer on Health Law at the University of Basel Law School and regularly speaks at national and international conferences.

He has many years of professional experience and deep knowledge of all areas of Life Sciences and health law. He has held executive positions in the pharmaceutical industry for more than 15 years. Carlo Conti then served as member of the State Council of Basel where he was head of the public health department. He was also president of the Swiss Conference of the Public Health Ministers and vice-chairman of the agency council of Swissmedic.

Dr. Martina Braun
Tel: +41 43 222 38 00 / Email: martina.braun@wenger-plattner.ch

Martina Braun is a senior associate and a member of the IP & IT and of the Life Sciences & Health Law teams of Wenger Plattner. She advises and represents clients on all aspects of intellectual property law and information technology, with a particular focus on copyright, trademarks and data protection. One of her key areas of expertise is advising on contract law. She also deals with a wide range of health law matters and the related regulatory issues. She completed her doctoral thesis on copyright law and worked at the Centre for Business Law at the University of Lausanne and at a district court before joining Wenger Plattner.

Wenger Plattner

Seestrasse 39, P.O. Box, 8700 Küsnacht, Zurich / Aeschenvorstadt 55, 4010 Basel /
Jungfraustrasse 1, 3000 Berne, Switzerland
Tel: +41 43 222 38 00 (Zurich) / +41 61 279 70 00 (Basel) / +41 31 357 00 00 (Bern)
URL: www.wenger-plattner.ch

United Kingdom

Grant Castle, Brian Kelly & Raj Gathani
Covington & Burling LLP

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 depending on product type and settings. Reasons for this include a growing and ageing population with specific needs, the prevalence of costlier high-tech and rare disease medicines, the COVID-19 pandemic and to an extent the effects of Brexit. Although the Government has increased funding for the NHS, particularly in response to COVID-19, there continues to be significant downward pressure on budgets and pricing. In light of this, there is a clear trend for the NHS and other state organisations to involve themselves directly and indirectly in drug pricing and policy. Commercial negotiations with the NHS and procurement initiatives often have a significant effect on the actual selling price of a product. As such, the landscape for pricing and reimbursement is increasingly multi-layered. Moreover, potentially significant changes are on the horizon. At the time of writing, NICE's processes are being reviewed and updated. Significant reforms are also underway to enable rapid market access. The NHS' system for commissioning and procuring products is also set to change.

Market overview

The UK comprises four constituent nations: England; Wales; Scotland; and Northern Ireland.

The UK has a population of approximately 66.8 million people, with the vast majority (approximately 56.3 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 £20.9 billion on medicines in 2019/20, without taking discounts into account. That represents a 9.9% increase on the prior year, a sharp increase from the average 5% annual growth rate since 2010/11. That growth is largely attributable to: (i) the COVID-19 pandemic; and (ii) to other medicines dispensed in hospital settings (*i.e.*, secondary care).

In 2019/20, spending on hospital medicines accounted for 55.9% of the NHS's total expenditure on medicines, which increased by 14% on the previous year. Meanwhile, spending on medicines in primary care increased by a more modest 5.2% in 2019/20. This reflects spending priorities geared towards acute, specialist, hospital-based therapies.

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 created 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) a competent regulatory authority, such as the Medicines and Healthcare products Regulatory Agency ("MHRA") 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, the NHS 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 (although this autonomy is diminishing as the NHS takes a more centralised approach to achieving cost-efficiency). 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. As noted below, this landscape could alter dramatically pursuant to proposed organisational changes. Prescribers in secondary care settings usually only deviate

from set 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 by a small minority of patients (usually, adults aged under 60 in full-time employment and earning over a certain threshold). The UK has a smaller – but ever 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:

- Commissioning in secondary care is effectively the responsibility of approximately 100 local Clinical Commissioning Groups ("CCGs").[6] CCGs receive funding from the NHS and, in principle, it is for each CCG to obtain value for money in terms of the products and services it makes available. That said, the NHS has become an increasingly centralised force in the way it obtains value.
- Responsibility for funding products in primary care falls to the NHS centrally (albeit, for administrative reasons, there are many local-level partnerships). As such, the reimbursement mechanism in primary care is centralised under the Community Pharmacy Contractual Framework. Community pharmacies who largely dispense products in primary care will receive a fixed reimbursement price for a particular product.
- The NHS 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 allow the NHS to provide centralised funding for high-cost products that individual CCGs may be reluctant to fund.
- The NHS is responsible overall for commissioning certain "public health" services (such as vaccination programmes).
- In February 2021, the Government set out plans to restructure much of the NHS around an integrated care model. By April 2022, the proposals would see local Integrated Care Systems ("ICS") replace CCGs and assume some of the commissioning responsibility from NHS England (discussed further below).

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 the NHS 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.

In response to COVID-19, NICE has published a number of rapid-review guidelines, which focus on the use of products during the pandemic. These are not subject to NICE's standard

procedures and methodologies and are continuing to evolve. As such, this chapter does not provide a detailed commentary on these rapid-review guidelines.

NICE's methods and procedures for appraising products and treatments is currently under review, with potentially significant changes anticipated to be in place from January 2022.

NICE topic selection

NICE's aim is to conduct a health technology appraisal for all new significant drugs and indications launched in the UK. NICE would typically scan for significant new products and indications 15 to 20 months before regulatory approval. Manufacturers of new products may make suggestions for an appraisal though UK PharmaScan (an industry horizon-scanning directory).

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 noted above, NICE is evaluating how it conducts such assessments and plans to implement a new system by January 2022. 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

For most conventional products, 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 considered "life extending" in end-of-life scenarios (*e.g.*, many oncology products fall into this category). In those situations, NICE may recommend a product with an ICER of up to £50,000.

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 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 the NHS to bring the overall cost down. If these negotiations are unsuccessful, the NHS may apply to NICE to delay funding the product by up to three years, or longer in exceptional cases. The Budget Impact Test was a controversial measure, as many felt it undermined NICE's independent role and brought it closer to helping to manage the NHS' budget. 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 it a positive recommendation if the drug's supplier alters its commercial proposition through an agreed Patient Access Scheme. These are formal pricing agreements, provided for under the VPAS (see section, "How are drug prices set? What is the relationship between pricing and reimbursement?", below) between a supplier and the NHS 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 the NHS 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 a 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 14 pieces of final guidance in more than seven 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. So far, 82 new oncology drugs treating 170 different indications have benefitted from CDF review. 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. The CDF has provided a route to NHS funding for a number of highly innovative, high-cost oncology technologies, including CAR-T and certain immuno-oncology therapies.

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"; or (iii) 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 usually 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. However, that is not always the case and the NHS will take a price-focused approach to secondary care products.

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

The Secretary of State for Health has 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 ("VPAS"); or the so-called "Statutory Scheme". The UK Government aims for "broad commercial equivalence" between the two schemes, though there are some differences. In terms of membership, the VPAS is by far the more popular scheme, though some companies continue to prefer the alternative.

VPAS

As the name suggests, the VPAS 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 VPAS has been running in the UK since 1957. The current scheme came into effect on 1 January 2019 and runs for five years.

The VPAS contains complex arrangements for price and profit control. Below are some key features:

- The VPAS aims to cap increases in the amount the NHS spends on branded medicines to 2% growth *per annum*. To stay within this cap, the scheme's members ("Members") must pay the Department of Health a fixed percentage of their net sales of branded medicines supplied to the NHS ("Scheme Payments"), subject to certain exceptions. Scheme Payments are designed to offset anticipated growth above the agreed 2% limit.

Scheme Payment percentages are fixed for one calendar year and apply scheme-wide. The percentage payable depends on the difference between the agreed growth rate and projected growth in sales. Scheme Payments are set at 5.1% of net sales for 2021 (the figure was 5.9% in 2020 and the original prediction for 2021 was 9%).

- 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 VPAS 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 VPAS agreement, the NHS made a number of commitments aimed at improving access to medicines. These include that from 2020, all new innovative medicines should receive NICE appraisals unless there are clear reasons not to assess them. There was also a commitment to increase commercial flexibility, giving the NHS scope to engage with industry and agree bespoke pricing and access deals with companies. With this greater scope, the NHS in England has struck some very significant pricing and access deals for certain products.

Statutory Scheme

Manufacturers or suppliers of branded medicines to the NHS who do not participate in the VPAS 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 amendments between 1 January 2019–1 April 2020. Currently, the 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 is 10.9% 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); (iii) if the product contains a new active substance; and (iv) estimated profits and other financial parameters, *etc*.
  - Unless the VPAS 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 VPAS than the alternative. In both schemes, the rebates that the industry must pay back to the Department of Health are broadly aligned and have fallen from initial projections.

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. The importance of those aspects has grown in recent years, which reflects the increasingly multi-layered landscape for drug pricing in the UK. Often, the discounts that a company is prepared to offer the NHS will affect its level of uptake and use.

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 heavy use of tendering for branded medicines has received criticism from various commentators who say it undermines the VPAS and Statutory Schemes by giving Government "two bites at the discount cherry". The UK Government intends to reform its public procurement laws, including those for the NHS. The proposed changes could see certain types of purchases falling outside the need to tender, particularly in the health space.

Recent years have witnessed the NHS in England adopting an increasingly centralised and joined-up approach to procurement and achieving lower medicines costs. For example, the NHS has established several national and regional procurement groups to co-ordinate and support medicines procurement, sharing information and expertise. This may affect the ability to give local, volume-based discounts. 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. The NHS often has a complex internal system to incentivise hospitals and local commissioning bodies to adhere to centrally negotiated formularies and price structures, which again erodes local autonomy.

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, that in general the UK prohibits generic or biosimilar substitution in pharmacies for a brand-name prescription. However, certain exceptions apply. For example, substitution may be permitted in hospitals in some cases. Also, pharmacy-level substitution is lawful if provided for under a "Serious Shortage Protocol" (which is a statutory mechanism that amends pharmacy dispensing rules if the Department of Health considers there is a serious shortage of one or many medicines in the UK).

The NHS generally avoids intervening in the market for generic products, relying on market forces to regulate it. However, over the last four years, the NHS has experienced severe shortages in the supply of certain generic medicines. Reportedly, Brexit-related uncertainty contributed to shortages, but a variety of other supply-side issues have persisted since the UK left the EU. 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;
- prioritising health spending, particularly in light of the COVID-19 pandemic;
- 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, the funding invested to fight the pandemic, 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 66.8 million people in 2019 to approximately 69.4 million people by 2028. In that time, the proportion of the population over the age of 65 in England would increase from 18.2% to 20.7%. 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, diabetes and the unknown costs of Long COVID.

As noted above, the volume and cost of drugs used in and/or reimbursed by the NHS is on a steady upward trajectory, which has spiked in the last year. Population and demographic changes, as well as fighting the pandemic, are major contributing factors. Another reason is an increase in high-cost innovative medicines NHS, particularly those used in hospital and specialist settings.

Historically, while the overall NHS budget continued to grow, this growth was outpaced by the rising cost of medicines (both in terms of volume and price). That context affected the UK's approach to controlling the price of medicines (particularly when the Voluntary and Statutory Schemes were re-cast in 2018/19). The Voluntary and Statutory Schemes have so far delivered savings to the public purse. The percentage amounts that the industry must pay back as rebates under both schemes has fallen in 2020 from early projections, which suggests

the rising cost of branded medicines is better controlled than before, so less must be "paid back". Nevertheless, the NHS remains focused on delivering efficiencies and focusing on priority areas. The multi-layered landscape that affects drug pricing, uptake and procurement is likely to evolve and be further enhanced.

Emerging trends

The pricing and reimbursement landscape in the UK is constantly evolving, with 2021 set to be a year of major change. We discuss some of the key aspects:

Current trends

- Although a review is underway, NICE's current cost-effectiveness criteria and Budget Impact Test are rigid and have remained so for several years. In effect, this means that pharmaceutical companies (particularly those who develop high-cost drugs) increasingly have little choice but to negotiate bespoke agreements with the NHS (*e.g.*, through Managed Access Agreements or Patient Access Schemes) to achieve a positive NICE recommendation. Usually, that involves significant discounts from the product's list price.
- Bespoke NHS agreements go hand in hand with the NHS exercising its mandate to negotiate pricing and access deals with pharmaceutical companies either alongside or outside the parameters of a NICE appraisal. For example, in March 2021, the NHS announced a "smart deal" with Novartis for its life-saving spinal muscular atrophy drug, Zolgensma.
- Price confidentiality continues to be controversial. 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. The NHS' infrastructure encourages pricing information to be shared throughout the organisation. This includes sharing confidentially agreed prices between NHS bodies in England, Scotland, Wales and Northern Ireland (each of which funds products separately).
- For the time being, co-ordinated procurement continues to be a key tool for the NHS to achieve best-value in purchasing medicines for hospital or specialist settings. As a result, particularly in a competitive market, pharmaceutical companies find themselves under pressure to offer further discounts to the NHS at the tendering stage (beyond those built in through the NICE process, the VPAS and/or the Statutory Scheme). Many of these tenders are complex and highly co-ordinated, which sometimes leads to medicines procurement litigation. For instance, in early 2019, there was 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 structure and policies often incentivise local organisations to purchase "best value" products, particularly generics and biosimilars. NHS organisations that fall short of this are potentially vulnerable to financial penalties or disincentives.
- Linked to the move towards generics and biosimilars is the growing tendency for the NHS to support using unlicensed products (or licensed products off-label) to cut costs. 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 takes the 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 High Court, Court of Appeal and Supreme Court litigation in respect of reformulated bevacizumab for intra-ocular use.

- The end of the Brexit transition period on 31 December 2020 resulted in major changes to the medicines regulatory landscape in the UK. The consequences of this are still unfolding, but the Government has revealed its intention to accelerate the approval of, and access to, new, innovative medicines. Flexing these post-Brexit ambitions, the UK launched the so-called Innovative Licensing and Access Pathway ("ILAP") on 1 January 2021. ILAP aims to reduce market-entry time for medicines that hold "innovation passports". These passports enable companies to engage with the MHRA and NICE at a very early stage to generate evidence for cost-effective value-proposition and/or expediting managed access into the NHS.

On the horizon

- NICE's long-running review of its own procedures and methods is due to complete by December 2021, with a new paradigm set to be in place for January 2022. The outcome of the review will undoubtedly change the way NICE evaluates the cost-effectiveness of medicines, and by extension which products receive a positive recommendation for NHS funding and at what price. The changes may include how NICE could accommodate clinical or outcome uncertainty; and an acknowledgment of disease severity.
- The proposed structural changes to the NHS – including the replacement of CCGs with Integrated Care Systems – are designed to nurture local-level commissioning, co-operation and reduced bureaucracy. In Secondary Care, there may be shift away from the "payment by results" model, towards a more collaborative system to fund population-health. In practice, that may make it easier for the NHS to develop local-level funding and tariff structures. The proposals also create more flexibility over when the NHS must use competitive procurement processes to purchase healthcare services.
- The long-term impact of COVID-19 on the NHS and the medicines funding landscape is unknown. The Government has committed to providing significant, albeit temporary, resources to the NHS and supporting life-sciences companies. However, one could not rule out significant changes in the medicines pricing and reimbursement environment. This could be for budgetary reasons. More likely, there may be changes to the way in which Governments and the NHS can procure medicines relevant to population health.

Successful market entry

Formulating a successful strategy for market entry will depend on the type of product in question, its place in the NHS' complex architecture and on the outcome of proposed reforms to NICE and the NHS. The following are some general points to consider:

- **NICE appraisal**. A company should investigate whether its product will be subject to a NICE appraisal and if so, whether it could meet NICE's cost-effectiveness criteria, including the Budget Impact Test. For high-cost products, companies should get ahead of the curve by planning Patient Access Schemes or some other commercial offer to the NHS.
- **Innovative access pathways**. Innovative access pathways, such as ILAP, could significantly streamline regulatory approval and the NHS reimbursement process. Companies should assess whether they might benefit from such schemes.
- **Specialised commissioning categories**. Falling within the scope of Specialised Services, Highly Specialised Services or the Cancer Drugs Fund could materially affect the likelihood of a high-cost product receiving NHS funding. Companies should explore whether a product falls within these categories early on.
- **Factoring in the NHS' multi-layered approach to commissioning and procurement**. It is critically important to appreciate the NHS' multi-layered approach to medicines

pricing and purchasing. The pricing and reimbursement framework in the UK often cumulatively "chips away" at the amount a company might receive for a product (*e.g.*, through the VPAS, the NICE process or tendering). Companies should therefore consider their pricing strategy in a holistic way, and be prepared for downward pressure from multiple angles. Companies should also be aware that the NHS is now likely to share pricing information internally.

- **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, so understanding them is important.
- **Watch this space**. With the scale of change likely to take place over the course of 2021, companies should be prepared for a volatile and uncertain climate. Successful market entrants will need to stay on top of these changes and adjust their strategy accordingly.

* * *

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, 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.

Grant Castle
Tel: +44 20 7067 2006 / Email: gcastle@cov.com

Grant Castle is a partner in the London office of Covington & Burling LLP, practising in the areas of life sciences regulatory law, with an emphasis on pharmaceutical and medical device regulation and associated compliance issues. He has assisted clients with a variety of UK pricing and reimbursement issues, including representing suppliers of pharmaceutical products and medical devices and other interested parties in a number of successful NICE appeals and administrative proceedings in the UK and EU courts. He speaks and lectures frequently on regulatory issues in both the pharmaceutical and medical device areas at the University of Surrey, the University of Wales and Cranfield University. He received a BSc in chemistry with first-class honours from Imperial College of Science, Technology and Medicine in London in 1991 and a Ph.D. in organic chemistry from Trinity College, University of Cambridge in 1994.

Brian Kelly
Tel: +44 20 7067 2392 / Email: bkelly@cov.com

Brian Kelly is a partner in the London Life Sciences group, whose practice focuses on EU food and drug regulatory law, public and administrative proceedings, public procurement matters, European Union law and product liability and safety.

Mr. Kelly has advised and successfully represented a variety of clients in respect of NICE appeals. He has advised clients on establishing joint working and risk-sharing relationships with the NHS in England and Wales. Mr. Kelly has also successfully represented life-sciences clients in judicial reviews and other administrative proceedings in the UK in respect of NHS procurements. Mr. Kelly holds a degree in neuroscience and is an honorary lecturer at University College London.

Raj Gathani
Tel: +44 20 7067 2266 / Email: rgathani@cov.com

Raj Gathani is an associate in Covington & Burling LLP's London office. Mr. Gathani's practice includes advising clients on a variety of UK pricing and reimbursement matters, including Drug Tariff listing and the Voluntary and Statutory Pricing Schemes. He has first-hand experience of drug reimbursement matters, having spent eight years operating a pharmacy business prior to joining Covington & Burling LLP.

Covington & Burling LLP

22 Bishopsgate, London, EC2N 4BQ, United Kingdom
Tel: +44 20 7067 2000 / URL: www.cov.com

USA

Rujul Desai, Anna Kraus & Kristie Gurley
Covington & Burling LLP

Abstract

The United States ("U.S.") accounts for the largest share of drug spending and innovation in the world, and its drug pricing regime is the most complex given its multi-payer model and unique overlay of market access requirements that collectively impact drug pricing and reimbursement decisions in the U.S.

The U.S. health care system includes both private and public health insurance coverage. Whether a drug product is covered, and at what price, is determined by each payer's coverage, coding, and payment criteria for health insurance plans. The largest government-funded programs are Medicare and Medicaid, under which plans are subject to detailed requirements set forth by statute or regulation. Private plans, which cover far more Americans than public plans, have more flexibility to make coverage and reimbursement determinations. All plans implement various cost containment measures which may impact plan beneficiaries' access to certain drug products. For Americans that either do not have insurance or have inadequate coverage to support their drug purchasing needs, a number of public safety net programs or private assistance programs (including manufacturer assistance) may be available to ensure access to needed medications.

Drug prices are highly dependent on the complexities of the U.S. drug supply chain. Between the initial manufacturing and ultimate dispensing of a given drug product, numerous transactions must take place among manufacturers, wholesalers, pharmacies, pharmacy benefit managers ("PBMs"), providers, and payers. These transactions typically involve price concessions in the form of discounts or rebates, as well as other fees. As a result, there is a significant gap between the list price a manufacturer initially sets for a drug product, and what is sometimes referred to as the "net price" – the actual amount of money received by the manufacturer.

Successful market access requires navigating this complex pricing and reimbursement system in a way that ensures drug products are available to patients, reimbursable by patients' private or public plans, and appropriately valued to ensure favorable coverage. These efforts also must comply with overlapping regulatory requirements and minimize risk related to enforcement action for violating regulatory or compliance obligations. Manufacturers should be aware of policy proposals and emerging trends that may significantly affect drug pricing and reimbursement in the U.S.

Market introduction/overview

The U.S. health care market

Health insurance

The U.S. health care system consists of a complex mix of payers and institutions.

Government-funded programs include Medicare (a federal program that primarily covers individuals 65 years of age and over) and Medicaid (a joint federal-state program that provides coverage for individuals with limited income and resources), as well as programs for military personnel, veterans, uninsured children, and others. Private health insurance, which covers 68% of the population, is more prevalent than public health insurance.[1] Most private insurance is offered through employer-sponsored plans, although Americans can also purchase coverage directly. Coverage for prescription drugs is an important component of both private and government health insurance programs.

Over 90% of Americans have health insurance through such private or public plans, but a significant number of Americans do not have any form of health insurance coverage. In 2019, the latest year for which coverage data is available, the U.S. population of 324.5 million had coverage as follows:

- 221 million received coverage under private plans, including 183 million through employment-based plans;
- 58.8 million received coverage under Medicare;
- 55.9 million received coverage under Medicaid;
- 3.2 million received coverage through the Veterans Health Administration and the Civilian Health and Medical Program within the Department of Veterans Affairs, and TRICARE (previously known as Civilian Health and Medical Program of the Uniformed Services); and
- 26.1 million were uninsured.[2]

Underinsurance remains a significant challenge. Many Americans face relatively high out-of-pocket health care costs in the form of premiums, deductibles, coinsurance, and copayments required by private and government payers for covered services, as well as costs for services not covered by insurance. In 2017, more than 1 in 50 Americans who interacted with the health care system had out-of-pocket costs above $5,000, and 1 in 200 had costs over $10,000.[3]

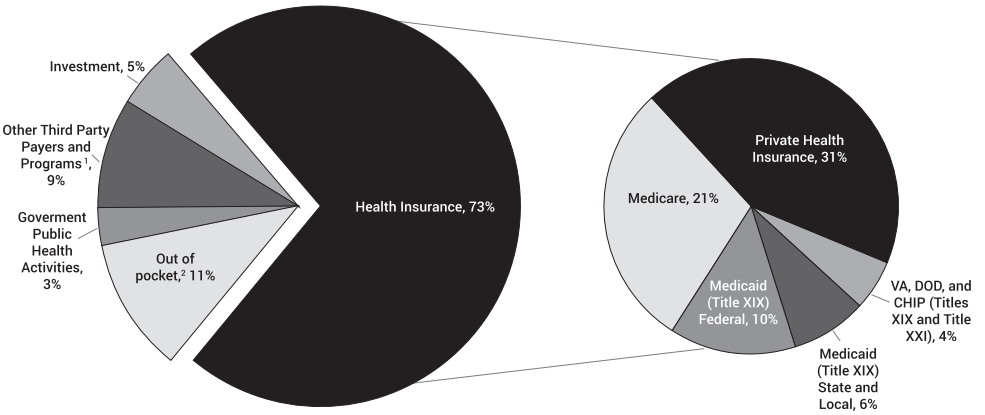
Although many developed nations choose to provide health care under a universal or single payer system, the U.S. has elected to use a multiple payer model combined with government- and privately run safety net programs and mandatory access to emergency care for all residents.[4] In addition to funding Medicaid and other programs aimed at vulnerable populations, the federal government requires drug manufacturers to provide outpatient drugs to health care providers that primarily serve low-income and uninsured individuals under a program known as the 340B Drug Pricing Program. Private charitable foundations also provide financial assistance or free product to eligible patients who struggle to afford expensive prescription drugs.

Health care spending

The U.S. has the highest health care spending *per capita* in the world.[5] *Per capita* spending has increased dramatically in recent decades, rising by 290% between 1980 and 2018.[6] In 2019, health care spending grew 4.6% and accounted for 17.7% of the Gross Domestic Product ("GDP").[7]

In 2019 alone, the U.S. spent approximately $3.8 trillion on health care.[8] Figures 1 and 2 show how health care spending breaks down across payers and services, as estimated by the Centers for Medicare & Medicaid Services ("CMS").

Figure 1: The nation's health dollar – where it came from[9]



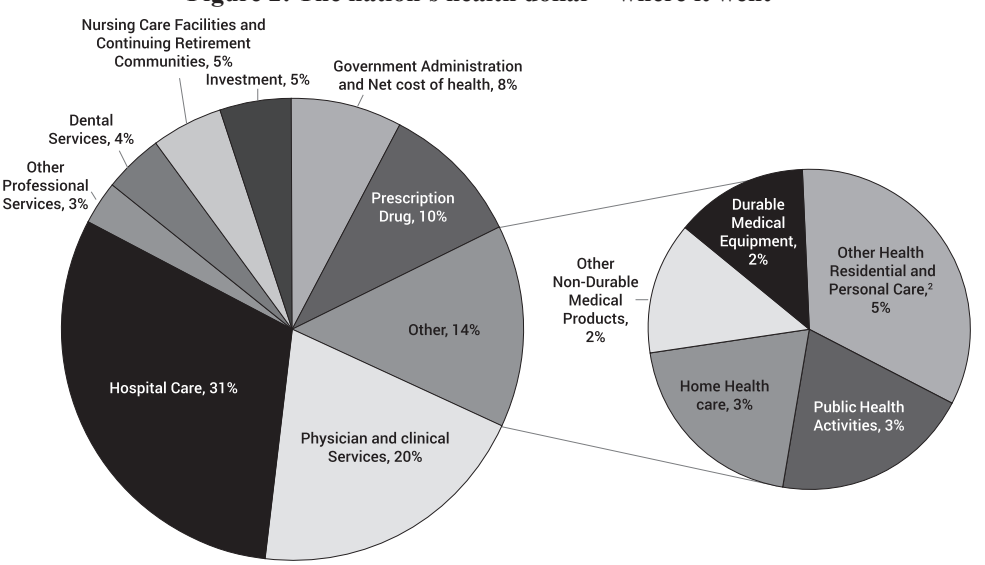
[1] Includes worksite health care, other private revenues, Indian Health Service, worker's compensation, general assistance, maternal and child health, vocational rehabilitation, Substance Abuse and Mental Health Services Administration, school health, and other federal and state local programs.

[2] Includes co-payments, deductibles, and any amounts not covered by health insurance.

Note: Sum of pieces may not equal 100% due to rounding.

SOURCE: Centers for Medicare & Medicaid Services, Office of Actuary, National Health Statistics Group.

Figure 2: The nation's health dollar – where it went[10]



[1] Includes Noncommercial Research and Structures and Equipment.

[2] Includes expenditures for residential care facilities, ambulance providers, medical care delivered in non-traditional settings (such as community centers, senior citizens centers, schools and military field stations), and expenditures for Home and Community Waiver programs under Medicaid.

Note: Sum of pieces may not equal 100% due to rounding.

SOURCE: Centers for Medicare & Medicaid Services, Office of the Actuary, National Health Statistics Group.

As shown in Figure 2, CMS estimates that prescription drugs account for approximately 9% of health care spending. CMS estimates that, in 2019, prescription drug spending increased 5.7% to $369.7 billion of the national health expenditures, faster than the 3.8% growth rate in 2018.[11] Some sources estimate that the percentage of spending on prescription drugs is actually closer to 15% of total spending, when accounting for non-retail drug sales as well as the gross profits of other parties in the drug supply chain, such as wholesalers, pharmacies, PBMs, providers, and payers.[12]

In part because of the federal dollars at stake, health care is the primary target of federal civil enforcement actions, including with respect to drug pricing and market access issues. In 2020, the federal government recovered more than $2.2 billion in settlements and judgments under the False Claims Act ("FCA"), which prohibits persons from making false claims (or causing false claims to be made) to the government – $1.8 billion related to health care cases, including those involving drug and medical device manufacturers, managed care providers, hospitals, pharmacies, hospice organizations, laboratories, and physicians.[13] Previously, 2019 was the tenth consecutive year in which civil health care fraud recoveries exceeded $2 billion.[14] Additionally, the federal government utilizes the Anti-Kickback Statute ("AKS") to combat activity that increases utilization and costs to federal programs, skews prescribing and other health care decisions, and creates an uneven competitor playing field.[15] Navigating this enforcement landscape requires a sophisticated understanding of the FCA, AKS, and government price reporting laws, as well as corresponding state laws.

The cost of prescription drugs

The high list price of prescription drugs in the U.S. is frequently discussed in the press and public discourse. Yet, the headlines often fail to capture both the types of drugs driving health care expenditures and the intricacies of the drug supply chain that create a significantly lower net price for a given drug product.

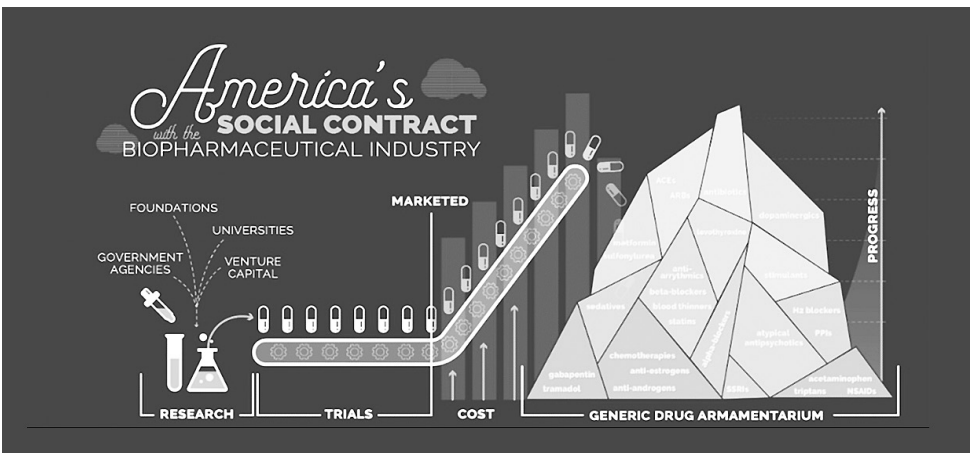
Branded versus generic drugs

Approximately 9 out of 10 prescriptions filled are for inexpensive generic drugs.[16] Prescription drug spending is primarily driven by the price of on-patent drugs. In general, after 10–15 years, these branded drugs lose patent protection, and inexpensive generic versions enter the market.

As illustrated in Figure 3, from Peter Kolchinsky's article entitled "American's Social Contract with the Biopharmaceutical Industry", the high price of branded drugs supports a "growing mountain" of highly utilized generic drugs.[17] Offering manufacturers higher prices for on-patent drugs for a limited period of time incentivizes innovation. The U.S. receives a return on its investment after the patent expires, at which point the drug rapidly declines in price. Payers encourage the utilization of generic drugs by implementing lower cost-sharing requirements.

See overleaf

Figure 3: America's Social Contract with the Biopharmaceutical Industry[18]



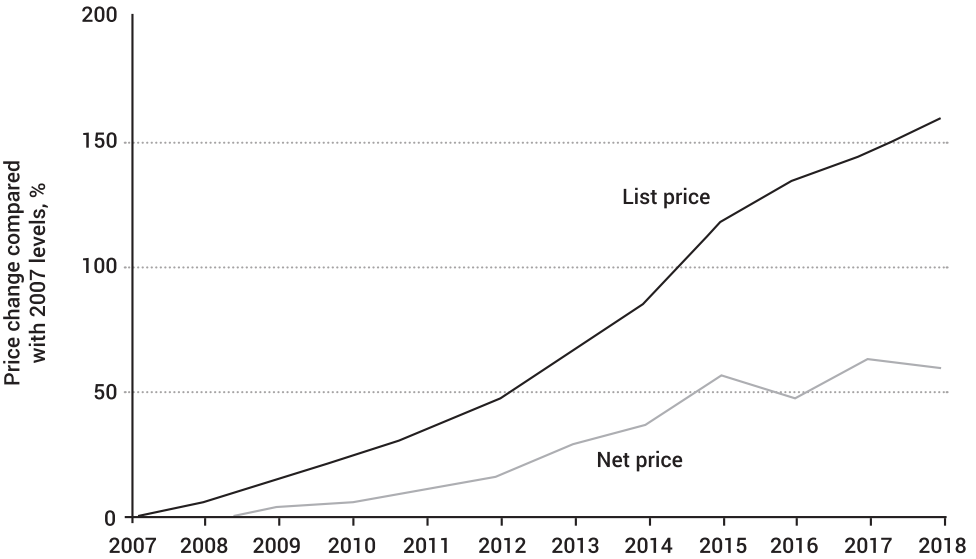
A small subset of branded drugs known as "specialty drugs" are a principal driver of prescription drug prices and expenditures. Medicare defines specialty drugs as pharmaceuticals costing $670 or more per month,[19] and other payers look at factors beyond price, designating products as specialty drugs if they (a) are novel therapies, (b) require special handling, monitoring, or administration, or (c) are used to treat rare conditions.[20] Specialty drugs account for approximately 2% of prescriptions but almost half of prescription drug spending.[21] Further, specialty share of net prescription drug spending increased from 26.2% in 2009 to 49.5% in 2018.[22] This trend is driven in part by innovation – specialty drugs represented the largest proportion of new drug products launched during this time period – and in part by patent expirations for traditional drug products.[23] In particular, cell and gene therapies represent the next frontier of specialty medications, with products such as chimeric antigen receptor T-cell ("CAR-T") therapy presenting tremendous promise to treat cancer on a highly personalized level. Many of these innovative treatments are priced – or are expected, once approved, to be priced – above $1 million for a course of treatment, but offer potential cures for otherwise fatal and/or debilitating conditions. Often, companion diagnostics and/or next generation sequencing tests are required as a prerequisite to accessing specialty drugs, and these tests have their own reimbursement and pricing dynamics.[24]

List price versus net price

Figure 4 illustrates that there is a significant gap between the list prices often cited in policy debates on drug pricing and the net prices actually reflecting the amount of money manufacturers receive.

See overleaf

Figure 4: List price *vs.* net price[25]



Changes from 2007 to 2018 in list and net prices for branded products that were available in January 2007 and for which U.S. sales were reported by publicly traded companies. Net prices are net of all concessions made by manufacturers including rebates, coupon cards, 340B discounts, prompt pay discounts, return provisions, and any other deductions captured in the reporting of net sales.

The gap between list price and net price reflects various price concessions, such as discounts and rebates, associated with the numerous transactions throughout the U.S. drug supply chain, including among entities such as manufacturers, wholesalers, pharmacies, PBMs, and payers. According to the Pew Charitable Trust, manufacturer rebates grew from $39.7 billion in 2012 to $89.5 billion in 2016, significantly offsetting increases to drug list prices.[26] The prevalence of additional fees, such as administrative and service fees required by PBMs, may also impact pricing considerations.

Global comparisons

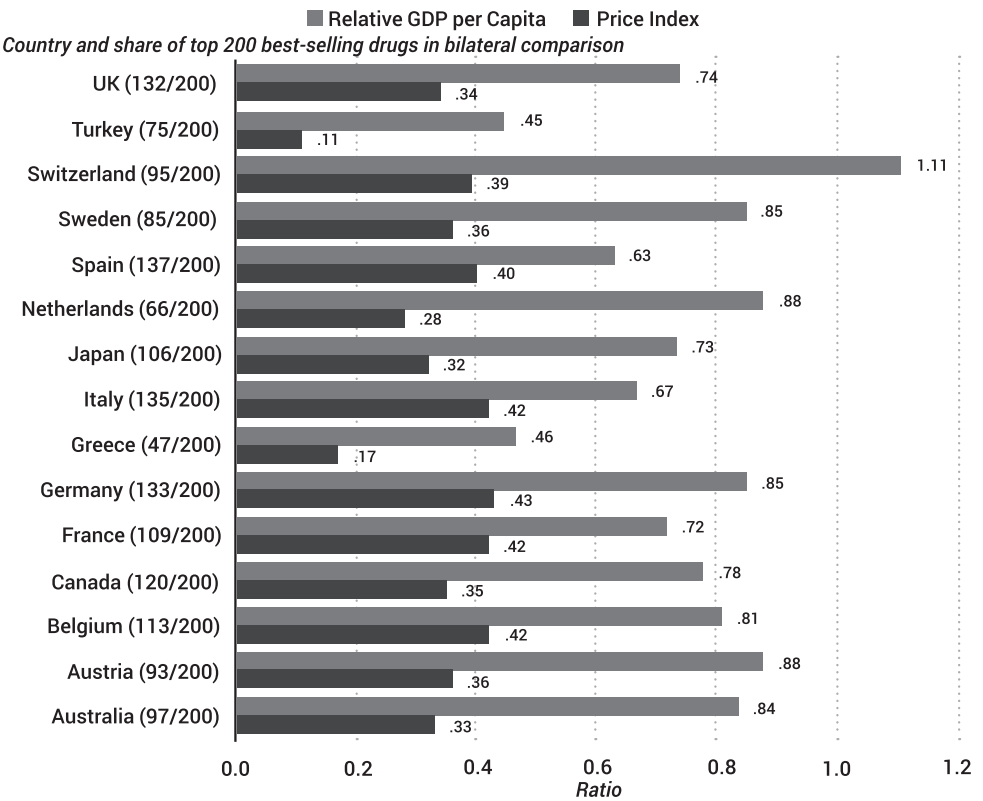
Health care spending in the U.S. far outpaces international averages. In 2019, national health care expenditures generated 17.7% of GDP (in comparison to the Organisation for Economic Co-operation and Development ("OECD") average of 8.8%), totaling about $11,582 *per capita* (in comparison to the OECD average of $4,223.5).[27]

Prices for prescription drugs are significantly higher in the U.S. in comparison to other industrialized nations. Figure 5, reproduced from a report by the Council of Economic Advisers ("CEA"), shows the U.S. Price Index for 200 top-selling prescriptions, as well as relative GDP *per capita*. As the chart demonstrates, observed patented drug prices are far higher in the U.S. than can be explained by differences in *per capita* income alone. A price index of 0.34, for instance, indicates that prices in the United Kingdom are 34% of those in the U.S., even though the GDP in the United Kingdom is 74% of that in the U.S.

On the other hand, as demonstrated in the parentheticals along the y-axis, many of the 200 top-selling drugs are not available for sale in the countries of comparison. For example, in the United Kingdom, only 132 of the 200 drugs showed evidence of significant sales. Put another way, certain prescription drugs, such as some of the most innovative treatments for

cancer, are more readily available in the U.S. than they are abroad. In its analysis, the CEA states that "[t]he absence of significant sales volume for these drug products might be the result of delayed regulatory approval, a decision by a public insurance program not to cover a drug based on health technology assessment criteria, or other factors".[28]

Figure 5: Foreign-U.S. Price Index for 200 top-selling prescriptions and relative GDP *per capita* for selected nations, 2017[29]



Pharmaceutical pricing and reimbursement

Marketing authorization

All drug products must be approved for use in the U.S. by the Food and Drug Administration ("FDA"), which is a government agency within the Department of Health and Human Services ("HHS"). FDA is charged with "protect[ing] the public health", including by ensuring that drugs are safe and effective, and "promot[ing] the public health" by efficiently reviewing and approving new drug products.[30] Currently, there are over 20,000 prescription drugs approved for marketing in the U.S., as well as 300 FDA-licensed biological products.[31]

FDA approves new drugs and new uses of approved drugs on the basis of safety and effectiveness. Innovative drug products are approved through New Drug Applications ("NDAs") and Biologics Licensing Applications ("BLAs").[32] Manufacturers must demonstrate substantial evidence of effectiveness (or, for biologics, evidence that the product is "safe, pure, and potent") based on adequate and well-controlled clinical investigations.[33] FDA may also approve generic versions of an approved drug product as well as biological products that are

biosimilar to a reference product.[34] Generic drug approval requires proof of bioequivalence, whereas a biosimilar must be highly similar to the reference product, with "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product".[35] In 2020, FDA approved 53 new drugs and biological products, 72 first-time generic drugs, and three biosimilar products.[36]

FDA's timeline for reviewing NDAs and BLAs is generally set by a commitment letter issued by the Agency under the Prescription Drug User Fee Act of 1992 ("PDUFA"). Following criticism of the slow pace at which FDA approved new drugs during the HIV/AIDS crisis in the 1980s, Congress passed PDUFA in 1992 to authorize the collection of user fees from drug manufacturers in order to help fund FDA's drug approval process.[37] Congress reauthorizes PDUFA every five years, most recently in 2017, and parallel user fee programs now exist for generic drugs ("GDUFA") and biosimilars ("BsUFAs"). In 2019, 45% of FDA's budget was paid for by user fees, with the remaining 55% provided by federal budget authorization.[38] Performance goals under PDUFA stipulate that FDA aims to review and act on 90% of standard NDA and BLA submissions within 10 months of either filing (for new molecular entity ("NME") drug products and original BLAs) or receipt (for non-NME drug products).[39] Certain drug products may also be eligible for priority review, under which FDA aims to review and act on 90% of NDA and BLA submissions within six months of either filing or receipt.[40]

An NDA or BLA can receive priority review if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.[41] In addition to priority review, other programs may be available to help expedite the development and review of drugs intended to address an unmet medical need in the treatment of serious or life-threatening diseases or conditions, including breakthrough therapy designation, fast track designation, and accelerated approval.[42]

In addition to approving new drugs, FDA also grants exclusive marketing rights to drugs approved under certain criteria. New chemical entities, meaning drugs that contain no active moiety that has been approved by FDA, benefit from five years of marketing exclusivity, running from the time of NDA approval.[43] During that time, FDA cannot accept for review any NDA or abbreviated NDA ("ANDA") or a drug containing the same active moiety.[44] FDA offers 12 years of exclusivity for biologics, seven years for orphan drugs (drugs designated and approved to treat diseases or conditions affecting fewer than 200,000 in the U.S., or more than 200,000 with no hope of recovering costs), three years for applications or supplements containing new clinical investigations, and six additional months of market protection where the sponsor has conducted and submitted pediatric studies.[45] Other incentives are also available, such as priority review vouchers for drugs treating neglected tropical diseases, rare pediatric diseases, and medical countermeasures.[46]

Unlike regulators in many other countries, FDA does not consider price or cost-effectiveness in approving prescription drug products through the use of health technology assessment ("HTA") bodies or otherwise regulate the prices charged by manufacturers or reimbursement offered by payers. As described in further detail below, however, both government and private payers view FDA approval as a precondition for reimbursement.

Coverage and reimbursement

Whether a drug product is covered, and at what price, is determined by each payer's coverage, coding, and payment criteria. This section provides key terminology applicable to coverage and reimbursement,[47] followed by a summary of criteria for reimbursement under the two largest government-sponsored plans, Medicare and Medicaid, as well as the 340B Program. This section also includes considerations for coverage and reimbursement under private plans.

Key terminology

Actual Acquisition Cost ("AAC"). A state Medicaid program's determination of a pharmacy's actual price paid to acquire a drug product marketed or sold by a manufacturer.[48]

Average Manufacturer Price ("AMP"). The average price paid to the manufacturer for a drug in the U.S. by (1) wholesalers for drugs distributed to retail community pharmacies, and (2) retail community pharmacies that purchase the drug directly from the manufacturer.[49]

Average Sales Price ("ASP"). The average price of a manufacturer's sales of a drug (by National Drug Code) to all purchasers in the U.S., as calculated by sales divided by the total units of the drug sold by the manufacturer in the same quarter.[50]

Average Wholesale Price ("AWP"). The list price of a drug from a wholesaler to a pharmacy, as calculated and published by certain price reporting compendia.[51]

Best Price. The lowest available price offered by the manufacturer to any wholesaler, retailer, or provider, excluding certain government programs.[52]

Wholesale Acquisition Cost ("WAC"). The list price of a drug from a manufacturer to wholesalers or direct purchasers, not including prompt pay or other discounts, rebates or reductions in price.[53]

Government-sponsored plans and programs

A. **Medicare**

Medicare was established in 1965 under Title XVIII of the Social Security Act as a federally funded program to provide health insurance to individuals aged 65 and older.[54] It has since been expanded to cover individuals with disabilities or end-stage renal disease ("ESRD"). CMS administers the Medicare program, along with Medicaid and certain other federal health care programs.

i. Benefit designs

Medicare benefits are defined by statute, and Medicare provides coverage only for an item or service that falls within the statutorily identified benefit categories. In addition, the Medicare statute expressly excludes from coverage certain items or services, such as cosmetic surgery and some dental services. For a drug product to be covered by Medicare, it must, among other things, be "reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member".[55] The Medicare program is divided into four parts that offer different benefits for beneficiaries:

- Part A provides hospital insurance that covers inpatient hospital services, as well as post-hospital skilled nursing facility services, hospice care, and some home health services. Inpatient hospital services include drug products and biologics.[56] Individuals aged 65 and older generally qualify for premium-free Part A benefits based on payroll taxes they or their spouses paid. Individuals under age 65 who have received disability benefits for at least 24 months also qualify for premium-free Part A benefits. Part A benefits are managed by Medicare Administrative Contractors ("MACs"), which are private health care insurers awarded geographic jurisdictions to process certain Medicare claims.[57] MACs make coverage determination on a case-by-case basis or as local coverage determinations ("LCDs") or pursuant to national coverage determinations ("NCDs").[58]
- Part B provides supplemental medical insurance for a range of outpatient services, including physicians' services, laboratory services, durable medical equipment ("DME"), and other medical services.[59] Part B also provides coverage of certain items and supplies, such as outpatient drug products that are not usually self-

administered and are furnished incident to a physician's services.[60] All individuals entitled to Part A may voluntarily enroll and obtain Part B benefits for a monthly premium.[61] Like Part A benefits, Part B benefits are managed by MACs, which determine coverage on a case-by-case basis or based on LCDs or pursuant to NCDs.[62] Parts A and B, together, constitute "original Medicare".[63]

- Part C Medicare Advantage ("MA"), formerly known as Medicare +Choice, provides an alternative method for beneficiaries to receive benefits. Instead of receiving benefits separately through Part A and Part B, beneficiaries may choose to enroll in a MA plan offering combined Part A and Part B benefits.[64] MA plans are administered by private health plans, such as health maintenance organizations ("HMOs"), preferred provider organizations ("PPOs"), private fee-for-service ("PFFS") plans, and special needs plans ("SNPs"). These private plans contract with CMS to provide all the required Part A and B benefits through a managed care system.[65] Plans may also offer alternative cost-sharing arrangements for beneficiaries or coverage for additional benefits not covered under original Medicare, such as over-the-counter ("OTC") drugs, vision care, or dental services.[66] All MA plans, except PFFS plans, must offer options that include coverage for prescription drugs ("MA-PDs").[67] MA-PDs generally must comply with Part D requirements, as discussed below.
- Part D was established by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA") and first implemented in 2006. Part D offers voluntary prescription drug coverage for beneficiaries entitled to Part A benefits or enrolled in Part B. Beneficiaries with original Medicare can enroll in a stand-alone prescription drug plan ("PDP") that is administered by a private health plan.[68] Part D plan sponsors create formularies identifying the prescription drugs that are covered by their plans. Formularies must meet federally specified criteria, including coverage of all therapeutic categories and classes and providing at least two drugs in each category or class.[69] Part D plans must be reviewed and approved by CMS.[70]

ii. Coverage and reimbursement methodology

As a preliminary matter, drug products generally must be approved by FDA in order to be reimbursed by Medicare. Parts A and B, however, cover only items or services that are "reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member".[71] Thus, drug products also must be considered "reasonable and necessary" based on available clinical and scientific evidence, which is a different standard from FDA approval. In addition, Part D covers only outpatient prescription drug products that are FDA-approved and used for a medically accepted indication.[72]

As indicated above, coverage determinations for drug products vary depending on which Part of Medicare is reimbursing. With respect to Medicare Parts A and B, most coverage determinations are made by MACs on a case-by-case basis or through LCDs to determine whether a given product will be covered in the MAC's jurisdiction. CMS also makes NCDs to determine coverage of a drug product nationwide.[73] MACs typically review new drug products upon submission of an LCD request, which triggers a 60-day review period to determine whether the request is complete, and then a lengthier review to evaluate the request itself, invite and incorporate public comment, and ultimately issue a final determination.[74]

Under Part D, the private plan sponsors administering the PDP and MA-PD benefits determine which prescription drug products are covered. The plan sponsors

developing formularies to identify which prescription drug products are covered, subject to the requirements above. Formularies usually include "tiers" setting forth different beneficiary cost-sharing requirements.[75] Part D formularies must be developed and reviewed by a pharmacy and therapeutics ("P&T") committee, which must "make a reasonable effort" to review new drug products within 90 days and make coverage determinations within 180 days of a drug's introduction to the market.[76] CMS reviews formularies to ensure that they are consistent with federal requirements related to formulary design. A plan must cover at least two drugs for a particular therapeutic class,[77] and must cover "substantially all" immunosuppressant (for prophylaxis of organ transplant rejection), antidepressants, antipsychotics, anticonvulsants, antiretrovirals, and antineoplastics.[78]

Part A reimbursement

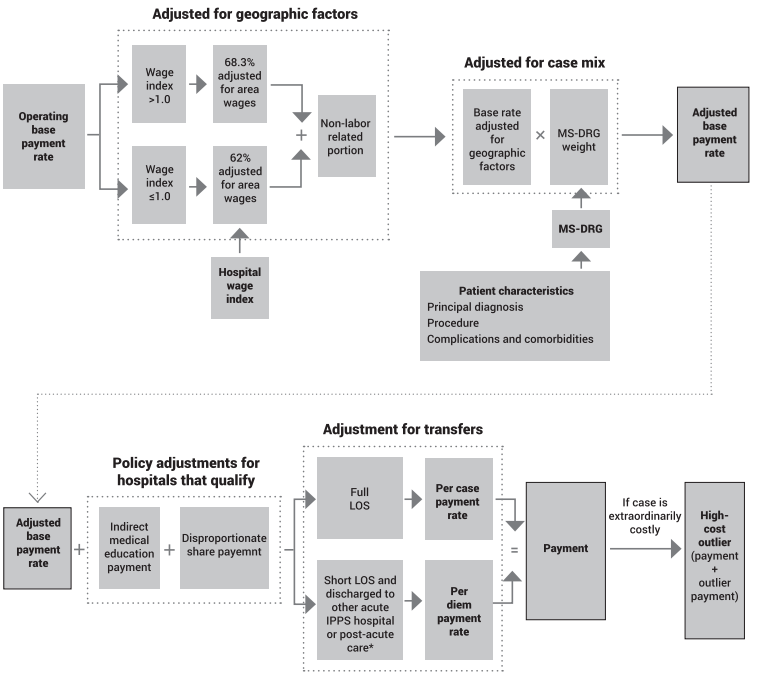
Reimbursement for most acute care hospital services under Part A is determined using the inpatient prospective payment system ("IPPS") based on diagnosis-related groups ("DRGs"). The IPPS was established by Congress through the Social Security Amendments of 1983.[79] Reimbursement under Part A is intended to cover all of the services and supplies provided during the beneficiary's spell of illness, including any drug products provided to the beneficiary; hospitals are statutorily prohibited from billing for items and services separately, or "unbundling" items and services.[80]

The IPPS formula contains two basic components. First, a base payment amount is prospectively determined by CMS to cover the operating and capital expenses per discharge, adjusted by a wage index for the geographic area in which the hospital is located.[81] Second, a weighting factor is associated with the DRG to which the beneficiary is assigned, to account for the resources required to treat the beneficiary.[82] The base payment amount, adjusted by the wage index, is multiplied by the weight of the beneficiary's DRG to determine the reimbursement payment amount. Medicare may also provide add-on payments, on top of the adjusted base payment, to cover costs associated with extraordinary treatment cases ("outliers"), teaching hospitals, or qualified new technologies. Disproportionate share hospitals ("DSHs") that treat a certain volume of low-income patients receive additional payments for operating and capital expenses.[83] Additionally, Medicare has established several quality incentive programs under which hospitals may receive incentive payments or penalties associated with quality of care criteria set by CMS.[84]

Certain hospitals, or hospital units, are exempted from the IPPS and receive reimbursement based on alternative methodologies. These include psychiatric hospitals or units, rehabilitation hospitals or units, children's hospitals, and long-term care hospitals.[85]

See overleaf

Figure 6: Acute inpatient prospective payment system for Fiscal Year 2021[86]



Note: MS–DRG (Medicare severity diagnosis related group), LOS (length of stay), IPPS (inpatient prospective payment system). Capital payments are determined by a similar system. In addition to the inpatient operating and inpatient capital payments per discharge, hospitals may receive additional payments, such as those related to direct graduate medical education, uncompensated care, and bad debts. Additional payments are also made for certain rural hospitals. Hospitals may receive penalties or additional payments based on their performance on quality standards.

** Transfer policy for cases discharged to post-acute care settings applies for cases in 278 selected MS–DRGs.*

Part B reimbursement

Medicare reimburses certain drug products under Part B when they are administered "incident to" a physician's services, generally in the physician's office or other outpatient setting.[87] Part B drugs include, for example, drugs that are infused or injected. These drugs are reimbursed under the "buy and bill" model, through which providers first purchase drugs and then submit claims for reimbursement after the drugs have been administered to a beneficiary. In order to obtain reimbursement for Medicare Part B drugs, providers must submit claims to MACs using Healthcare Common Procedure Coding Systems ("HCPCS") codes.[88]

The current reimbursement methodology for most Part B drugs was established by the MMA.[89] Under this methodology, reimbursement payments for Part B drugs are generally calculated based on the ASP, which the manufacturer reports to CMS.[90] A drug's ASP is calculated by dividing the manufacturer's sales of the drug to all purchasers in the U.S. in a specific quarter (excluding nominal sales to certain entities and sales that are exempt from the determination of Medicaid best price) by the number of units of the drug sold by the manufacturer in the same quarter.[91]

Manufacturers report ASP on a quarterly basis. Certain manufacturers, such as those with Medicaid rebate agreements, are obligated to report ASP data,[92] while other manufacturers voluntarily report ASP data or WAC data.[93] Reimbursement rates are updated quarterly; however, the rates are calculated using the reported ASP from two quarters ago.[94]

Reimbursement for Part B drugs administered in the physician office setting is statutorily set at 106% of ASP, referred to as "ASP+6".[95] Beneficiaries are generally responsible for 20% of the cost of drug products under Part B.[96] ASP+6 is intended to account for variability in provider acquisition costs and to compensate providers for the additional costs associated with the complexity of Part B drugs, many of which are used to treat serious illnesses such as cancer, cerebral palsy, and multiple sclerosis. Specific Part B drugs, including newly launched drugs, certain preventative vaccines, compounded drugs, and certain radiopharmaceuticals, are reimbursed under alternative formulas, rather than at ASP+6.[97]

Under certain circumstances, reimbursement for Part B drugs is included, or "bundled", with the payment for other services. For example, payments for certain drugs administered in hospital outpatient departments are bundled with the payments for services under the hospital outpatient prospective payment system ("OPPS").[98] Other drug products, such as drugs with pass-through status, are reimbursed separately under OPPS. Reimbursement rates for such drugs vary from year to year and are currently set at ASP+6 for most drugs and ASP minus 22.5% for most drugs acquired through the federal 340B program, discussed below.[99]

Part C reimbursement

MA plans contract with CMS to provide all required Part A and Part B items and services to Medicare beneficiaries in exchange for a monthly capitated payment. MA contracts are awarded based on a competitive bidding process. Reimbursement payments are then calculated by comparing the plan's bid, which establishes the plan's estimated costs of providing Part A and Part B services to the average beneficiary, to the benchmark plan. If the plan's bid is lower than the benchmark, the reimbursement payment equals the bid amount, plus a rebate based on the difference between the bid and the benchmark that is passed on to the beneficiaries. However, if the bid is equal to or greater than the benchmark, the benchmark will be the reimbursement payment and beneficiaries are required to pay an additional premium based on the difference between the bid and the benchmark.[100]

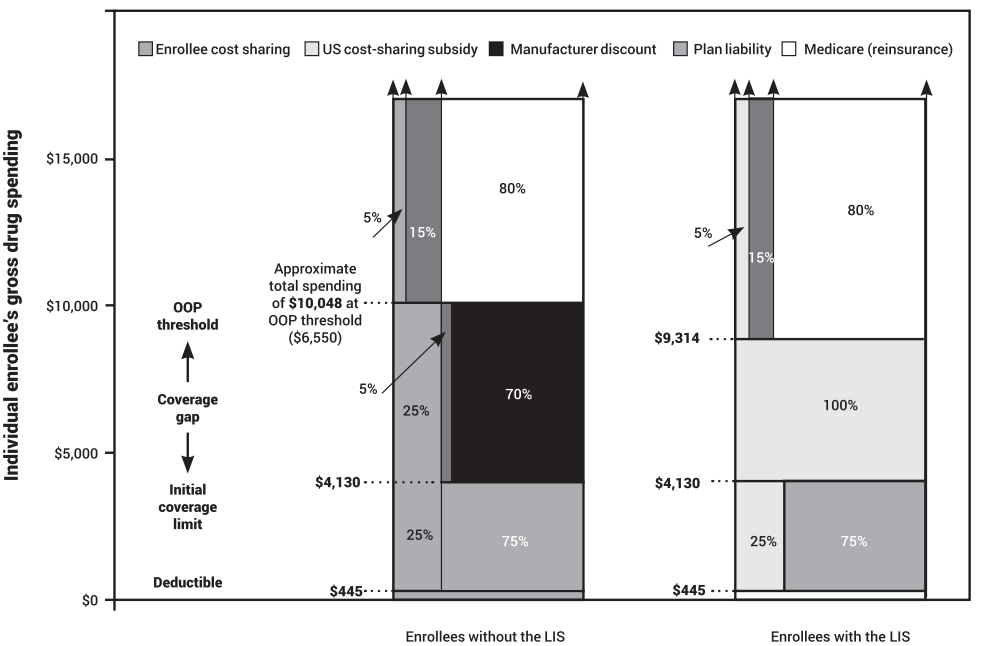
For MA-PD plans offering prescription drug coverage, a separate Part D bid must be submitted to CMS. Reimbursement for the prescription drug part of the MA plan is then calculated separately, in the same manner as stand-alone PDPs (discussed below).[101]

Part D reimbursement

Under Part D, stand-alone PDPs must provide standard prescription drug coverage, as set forth by statute, or alternative coverage that provides actuarially equivalent benefits.[102] In 2021, the standard benefit includes a $445 deductible and 25% coinsurance for the cost for both brand-name and generic drug products between $455 and $4,130. Beneficiaries then enter the coverage gap, also referred to as the "doughnut hole", until they reach the catastrophic limit and out-of-pocket threshold of $6,550. After reaching the catastrophic limit, beneficiaries pay the higher of either a 5% coinsurance or a set amount per prescription.[103] Under Part D as it was originally implemented in 2006, beneficiaries were responsible for all drug costs incurred while they were in the coverage gap. However, provisions of the Patient Protection and Affordable Care Act (often shortened to the Affordable Care Act or "ACA") slowly reduced cost-sharing requirements during the doughnut hole, including by phasing in larger Medicare subsidies and requiring manufacturers to provide discounts for brand-name during purchased by beneficiaries in the coverage gap.[104] As of 2020, the doughnut hole is closed, meaning beneficiaries are responsible for only the 25% coinsurance until they reach the catastrophic limit.[105] Different

cost-sharing obligations apply for qualifying beneficiaries who receive low-income subsidies ("LIS") under Part D, for which the federal government pays in full or in part the drug cost-sharing expenses.[106] Full LIS beneficiaries have a $0 deductible and subsidized coinsurance payments in the initial coverage (25%), coverage gap (25%), and catastrophic coverage (5%) phases, with a copayment of $9.85; partial LIS beneficiaries have a $99 deductible plus a coinsurance of 15% through the coverage gap phase and a $9.85 copayment in the catastrophic coverage phase.[107]

Figure 7: Part D 2021 standard defined benefit and LIS benefit structures[108]



Note: LIS (low-income subsidy), OOP (out of pocket). For beneficiaries without the LIS (left bar), the coverage gap is depicted as it would apply to brand-name drugs, which are eligible for a 70% manufacturer's discount in the coverage gap. There is no discount for generic prescriptions, and thus cost sharing in the coverage gap is 25% and plans are responsible for 75%. Because of this difference, total covered drug spending at the out-of-pocket ("OOP") threshold depends on the mix of brand and generic prescriptions each individual fills while in the coverage gap. The dollar amount shown ($10,048) was estimated by CMS for an individual with an average mix of drugs who does not receive Part D's LIS and has no other supplemental coverage. The bar depicting LIS enrollees (right) reflects full rather than partial LIS coverage. LIS enrollees do not receive brand discounts from manufacturers. For most LIS enrollees, Medicare's LIS pays for all cost sharing except nominal copayments, thereby including most spending in the coverage gap.

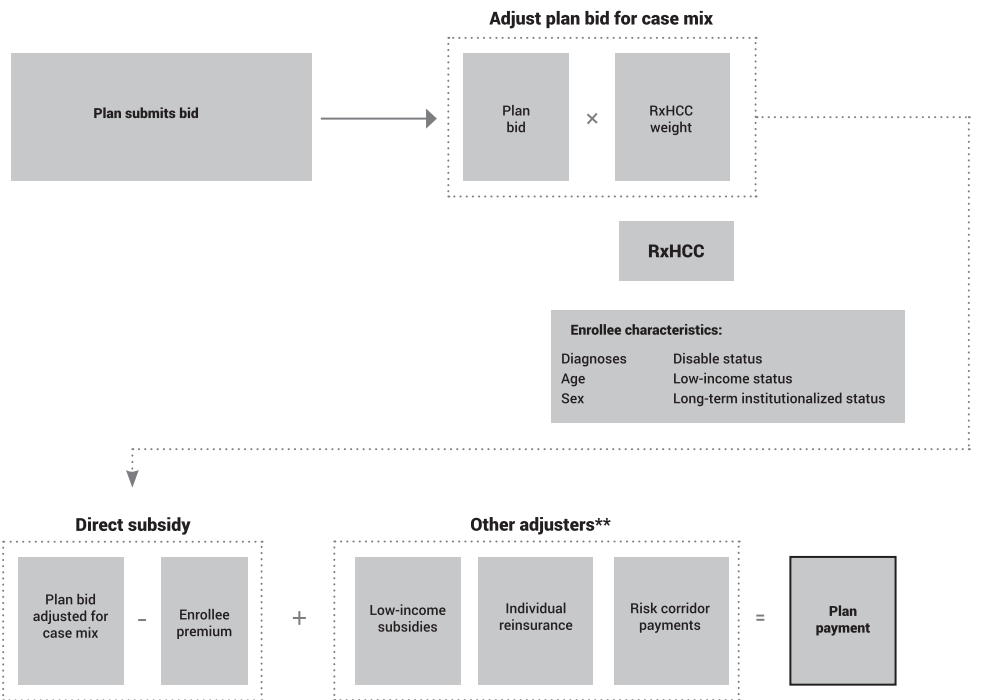
Source: MedPAC depiction of Part D benefit structure for 2021 as set by law.

Part D reimbursement payments made to PDPs and MA-PDs are based on a competitive bidding process. Plan sponsors determine their bids based on the expected costs of providing coverage for the average Medicare beneficiary. CMS provides monthly capitated payments to

plans to subsidize the standard benefit coverage.[109] As noted above, CMS also pays additional subsidies for LIS beneficiaries and reinsurance subsidies to cover the costs of beneficiaries with high prescription drug expenses.

Unlike reimbursement under Medicare Part A and Part B, the federal government does not play a role in determining the calculation for drug product reimbursement under Part D. Instead, plan sponsors usually contract with PBMs to negotiate prices with manufacturers. Plans also establish a network of pharmacies to provide access to covered drug products for its beneficiaries.[110] The Medicare statute prohibits the federal government from interfering with Part D price negotiations or establishing a required formulary or reimbursement formula for Part D drug products.[111]

Figure 8: Part D payment system[112]



Note: RxHCC (prescription drug hierarchical condition category). The RxHCC is the model that estimates the enrollee risk adjuster. Beginning in 2011, CMS replaced its single model of risk scores with five separate sets of model coefficients for: long-term institutionalized enrollees; aged low-income enrollees; aged non-low-income enrollees; disabled low-income enrollees; and disabled non-low-income enrollees. Prior to 2011, payments on behalf of beneficiaries with low-income and long-term institutionalized status were adjusted using multipliers intended to reflect those individuals' higher levels of drug spending.

** Figure 8 outlines the process for calculating enrollee premiums.*

*** Plans receive interim prospective payments for individuals' reinsurance and low-income subsidies that are later reconciled with CMS.*

B. Medicaid

Medicaid was established by the Social Security Act of 1965 to provide health care services to low-income individuals.[113] The program is funded jointly by federal and state governments. States are not required to participate in Medicaid, but all 50 states, Washington, D.C., and the U.S. territories have chosen to participate. The federal Medicaid statute establishes federal requirements that states must satisfy in order to receive matching federal funds. However, the statute also provides flexibility for states to design their programs within the federal guidelines.[114]

In order to receive Medicaid benefits, individuals must qualify through an eligibility pathway that provides coverage to identified populations. Some pathways are mandated by federal law, while others are optional pathways that states may choose to offer. States may also apply for a Medicaid waiver in order to offer coverage to populations beyond the mandatory and optional pathways. The federal Medicaid statute defines the categories of individuals who are covered by a certain pathway ("categorical eligibility") and whether there are any financial requirements ("financial eligibility"), as well as the extent to which a state can alter or adjust the pathway's requirements.[115]

i. Benefit designs

Medicaid coverage includes a range of benefit options, including primary care, preventative care, and long-term care services and support. Medicaid beneficiaries may receive benefits through a fee-for-service ("FFS") system or a managed care system, depending on which systems are offered by the state. Through the FFS system, states provide reimbursement to health care providers for each service they provide to beneficiaries. Through the managed care system, states pay managed care organizations ("MCOs") a monthly capitated fee to provide benefits to eligible individuals.[116]

An individual's benefits vary based on the eligibility pathway through which he or she obtains coverage. State programs may offer either traditional Medicaid benefits, which include a range of required and optional benefits specified by federal law, or alternative benefit plans ("ABPs"), which are based on a coverage benchmark but must include the essential health benefits ("EHBs") that private health plans are generally required to provide. States may also apply for a Medicaid waiver to provide additional services.[117] Under the traditional Medicaid benefit framework, prescription drug coverage is an optional benefit, but all states have chosen to offer it; for ABPs, prescription drug coverage is a mandatory benefit.[118] Further, some state Medicaid programs also provide coverage for OTC drug products.[119]

Individuals who are eligible for both full Medicaid benefits and Medicare, known as "dual eligibles", generally must obtain prescription drug coverage through a Medicare Part D plan. State Medicaid agencies are statutorily prohibited from providing reimbursement for drug products covered by Part D for dual eligibles, but agencies may provide reimbursement for drug products that are expressly excluded from the definition of a covered Part D drug.[120]

ii. Coverage and reimbursement methodology

Pursuant to the Medicaid Drug Rebate Program ("MDRP"),[121] state Medicaid programs must maintain an "open formulary" covering all drugs by a participating manufacturer. In exchange, manufacturers agree to make rebate payments intended to ensure that Medicaid pays the "best price" for drug products.[122] Many states also have developed preferred drug lists ("PDLs"), which include drugs for which manufacturers offer supplemental rebates beyond those offered by the MDRP. Providers are encouraged to prescribe drugs on the state PDL to Medicaid

beneficiaries; the drugs on the PDL are generally subject to fewer utilization management controls. Additionally, the federal Medicaid statute allows state programs to exclude certain drugs, classes of drugs, or drug uses from coverage.[123]

State Medicaid programs usually reimburse community retail pharmacies for drug products dispensed to Medicaid beneficiaries. In addition, some states may require Medicaid beneficiaries to pay a nominal copayment for outpatient prescription drug products.[124]

FFS Medicaid reimbursement payments to pharmacies are generally based on the drug product's ingredient cost and the pharmacist's dispensing fee. In 2016, CMS issued a final rule requiring states to use the AAC to determine ingredient cost.[125] However, federal regulations permit states to choose how they calculate AAC by using either a survey of pharmacy providers, the AMP, or the National Average Drug Acquisition Cost ("NADAC").[126] The drug's ingredient cost is combined with a professional dispensing fee, which is usually a fixed amount intended to cover the pharmacy's costs for obtaining, storing, and dispensing the drug.[127]

Medicaid managed care plans also reimburse pharmacies for drug products dispensed to beneficiaries. Like payments made by FFS Medicaid, managed care reimbursement rates are based on the drug's ingredient costs and dispensing fees. To calculate ingredient costs, MCOs are not required to use the AAC but must make payments sufficient to ensure appropriate access for their beneficiaries.[128] MCOs negotiate reimbursement terms with pharmacies rather than creating a generally applicable payment formula. They also may negotiate their own rebates and other discounts from manufacturers.[129]

Many states contract with PBMs, which serve as intermediaries between the state Medicaid agencies, pharmacies, manufacturers, and beneficiaries. States may use PBMs for Medicaid programs administered on a FFS basis or through a managed care system to perform multiple administrative and financial functions. PBMs working on behalf of MCOs may negotiate drug prices with pharmacies; conversely, PBMs working with Medicaid programs must comply with federal and state requirements for drug reimbursement.[130] Concerns regarding the lack of transparency for PBMs have led some states to consider disclosure requirements for PBMs.[131]

To control the cost of prescription drugs, federal and state governments have implemented policies to create certain payment limitations for Medicaid reimbursements. The federal upper limit ("FUL") is a payment limitation that caps the reimbursement payment for ingredient costs of certain multiple source drugs.[132] Currently, CMS has set the FUL at 175% of the weighted average of the most recently reported AMP for the specific form and strength of a drug.[133] In addition, most states have created a maximum allowable cost ("MAC") program to limit reimbursements for certain multiple source drugs. State MAC programs operate similarly to the FUL cap; however, states have discretion to decide which drugs are included in the program and how the reimbursement limitation for those drugs is calculated. As of 2014, 45 states had established MAC programs.[134] Finally, for single source drugs and drugs not subject to FUL or MAC limitations, reimbursement – in the aggregate – may be determined by the lower of either (1) the AAC and dispensing fee, or (2) the providers' usual and customary charges to the general public.[135]

Pursuant to the MDRP, as discussed above, a drug product is covered by Medicaid only if the manufacturer enters into a Medicaid rebate agreement.[136] The agreement

requires the manufacturer to provide a rebate to the state's Medicaid agency, which is then shared between the federal and state governments in order to reduce federal and state expenditures. For single source and innovator multiple source drugs, Medicaid's basic rebate formula requires a payment in the amount of the greater of either the difference between a drug's quarterly AMP and the best price for the same period, or a flat percentage (23.1%) of the drug's quarterly AMP.[137] Drug manufacturers owe an additional rebate when their AMPs for individual products increased faster than inflation. For other drug products, separate rebate structures would apply, as demonstrated in Figure 9.

Figure 9: Medicaid drug rebate formulas[138]

Drug Category	Basic Rebate	Additional Rebate
Single Source	The greater of either 23.1% of AMPa per unit or AMP minus best priceb per unit	Required when prices rise faster than the inflation rates – difference between the products' per unit current AMP and the base period AMP adjusted by CPI-Uc for each quarter since launch
Innovator Multiple Source Drugs	The greater of either 23.1% of AMP or AMP minus best price per unit	Required when prices rise faster than the inflation rates – difference between the products' per unit current AMP and the base period AMP adjusted by CPI-U for each quarter since launch
Line Extension Productsd	The greater of (1) the basic and additional rebate for the new drug, or (2) the product of the line extension drug's AMP and the highest additional rebate for any strength of the original brand drug and the number of units of each dosage form and strength of the line extension drug	
Blood Clotting Factorse	The greater of 17.1% of AMP per unit or AMP minus best price per unit	Required when prices rise faster than the inflation rates – difference between the products' per unit current AMP and the base period AMP adjusted by CPI-U for each quarter since launch
FDA Approved Pediatric Indicationf	The greater of 17.1% of AMP per unit or AMP minus best price per unit	Required when prices rise faster than the inflation rates – difference between the products' per unit current AMP and the base period AMP adjusted by CPI-U for each quarter since launch
Non-innovator Multiple Source and Other Drugs	13% of AMP	Not applicable

Source: Congressional Research Service ("CRS") review of the SSA §1927. Payment for Covered Outpatient Drugs, and 42 CFR §447.502. Definitions.

a. AMP is the average manufacturer price, or the average U.S. price manufacturers received for their product when sold to retail community pharmacies.

b. Best price (single source and innovator multiple source) is the drug manufacturer's lowest U.S. price during the reporting period (see the glossary in Appendix E).

c. CPI-U is the consumer price index for all urban consumers as updated by the U.S. Department of Labor (http://www.bls.gov/cpi/).

d. A line extension is an oral solid dose (generally a pill or capsule) of a single source or multiple source innovator drug that is a new formulation of an existing drug, such as an extended release formulation (SSA §1927(c)(2)(C). CMS proposes to use the FDA regulation 21 CFR §206.3, which is defined solid oral dosage form as capsules, tablets, or similar drug products intended for oral use (77 Federal Register 5324, February 2, 2012).

e. Clotting factor drugs receive a separate payment under SSA §1842(o)(5) and are

included on a regularly updated list maintained by the Secretary (SSA §1927(c)(I)(B)(iii)(II)(aa)).

f. FDA approved pediatric drugs are those approved for marketing by the FDA for pediatric indications (SSA §1927(c)(I)(B)(iii)(II)(bb)).

C. 340B drug pricing program

The federal 340B program requires manufacturers to provide outpatient prescription drugs to certain providers that serve low-income and uninsured individuals (frequently referred to as "safety net providers").[139] Established in 1992, the 340B program was conceived to address an unintended consequence of the MDRP – the requirement to report the best price resulted in manufacturers no longer offering voluntary discounts to safety net providers.[140] Under the 340B program, any manufacturer that participates in the MDRP must: (1) offer the 340B price if the drug is made available to any other purchaser at any price; (2) offer to covered entities (defined by Section 340B of the Public Health Service Act to include federally qualified health centers, various disease-specific programs, and publicly owned hospitals treating a disproportionate number of low-income patients); (3) cover outpatient drugs (defined by statute to include all outpatient drugs, including infusion therapies, provided they are not associated with an inpatient stay); and (4) set the 340B price at no more than a statutorily defined ceiling (the "ceiling price").[141]

The ceiling price is calculated quarterly using MDRP figures (AMP minus the Unit Rebate Amount ("URA")) from two quarters prior, except that 340B pricing is estimated for new drugs until the MDRP figures become available. Manufacturers may voluntarily offer lower "sub-ceiling" pricing to covered entities. After purchasing the drug at the ceiling price, the covered entity generally seeks reimbursement from the patient's insurance (commercial or government) or potentially the patient. The statute prohibits covered entities from obtaining duplicate discounts under 340B and MDRP, and bans them from diverting discounted drugs to anyone but their own patients. The mandatory discounts required under the 340B Program are exempt from best price (and related) calculations. Consequently, critiques of the program include that discounts are sometimes not passed onto the uninsured or underinsured patients and covered entities do not use the proceeds from the difference between the 340B price and the reimbursed amount to provide charity care.[142]

In 2010, the ACA expanded 340B eligibility to include additional categories of hospitals, and draft guidance from the Health Resources and Services Administration ("HRSA") removed the restriction on 340B entities' use of only one contract pharmacy, leading to growth in the number of 340B prescriptions.[143] In addition, hospital acquisition of oncology practices has driven increased 340B profitability for hospitals.[144] 340B spending has increased significantly in recent years, rising from $5.3 billion in 2010 to $24.3 billion in 2018.[145]

In 2018, HHS reduced Medicare Part B reimbursement rates for certain drugs acquired under the 340B program from ASP+6 to ASP minus 22.5%, so as to "better, and more appropriately, reflect the resources and acquisition costs that these hospitals incur."[146] In litigation challenging this change in reimbursement, a U.S. District Court ruled that HHS exceeded its statutory authority by reducing the reimbursement rate in this manner.[147] In 2020, a U.S. Court of Appeals reversed the district court's decision and determined that HHS had reasonably interpreted the Medicare statute and acted within its authority in implementing the rate cut of ASP minus 22.5% for drugs purchased under the 340B program.[148] In February 2021, the American Hospital Association ("AHA"), the Association of American Medical Colleges ("AAMC"), and America's Essential Hospitals ("AEH") asked the U.S. Supreme Court to review the case. The petition for review is still pending as of June 2021.[149]

In 2020, several manufacturers sought to prevent duplicate discounts and ineligible rebates in the 340B Program by limiting distribution of 340B covered outpatient drugs via contract pharmacies. The 340B statute does not reference contract pharmacies; however, HRSA guidance in 2010 suggested that covered entities may create ship-to arrangements with an unlimited number of contract pharmacies.[150] In response to the manufacturers' limited distribution approach, HRSA sent individual manufacturers letters stating that their new contract pharmacy policies violate the 340B statute and that any overcharges must be refunded to impacted entities.[151]

D. **Private plans**

Over two-thirds of Americans are covered by private insurance. The vast majority of those with private insurance have employment-based coverage – in 2018, 178.4 million Americans had coverage through an employer.[152] The ACA requires large employers to provide full-time employees and their dependents with coverage, and plans must meet minimum standards for affordability and coverage.[153] Employers generally pay most of the insurance premium on behalf of employees and their dependents, while employees are responsible for the remainder of the premium and cost-sharing requirements. On average, employers pay 82% of the premium for single coverage and 71% for family coverage.[154] Americans can also purchase insurance directly through state-based and multi-state Affordable Health Insurance Exchanges (also known as "Health Insurance Marketplaces"), where subsidies are available to individuals with incomes between 100% and 400% of the federal poverty level ("FPL").[155] Additionally, individual and group plans are also available for purchase outside of the Health Insurance Marketplaces.[156]

Private plans typically include medical and pharmacy benefits. Drugs used with durable medical equipment ("DME") are often covered under the pharmacy benefit. Physician-administered drugs, regardless of formulation, are typically covered and paid under the medical benefit. FDA approval is typically a prerequisite for coverage, but private plans have greater flexibility than public plans in defining the benefit category and placement of drugs on formularies, as well as adopting utilization controls, as discussed below.

Medicare rates frequently serve as a floor for payments under private plans. However, unlike Medicare's Part A and B benefits, private payers can and do negotiate prices and payments, often through negotiated aggregate rebates with drug manufacturers facilitated by PBMs. Drug payment rates vary depending on contracts with providers, manufacturers, vendors, and employers. Private payers often consider cost or cost-effectiveness in the coverage process, with many utilizing complex formularies to determine patient cost-sharing responsibilities, as discussed below.

Additional issues that affect pricing and reimbursement

Other parties in the drug supply chain

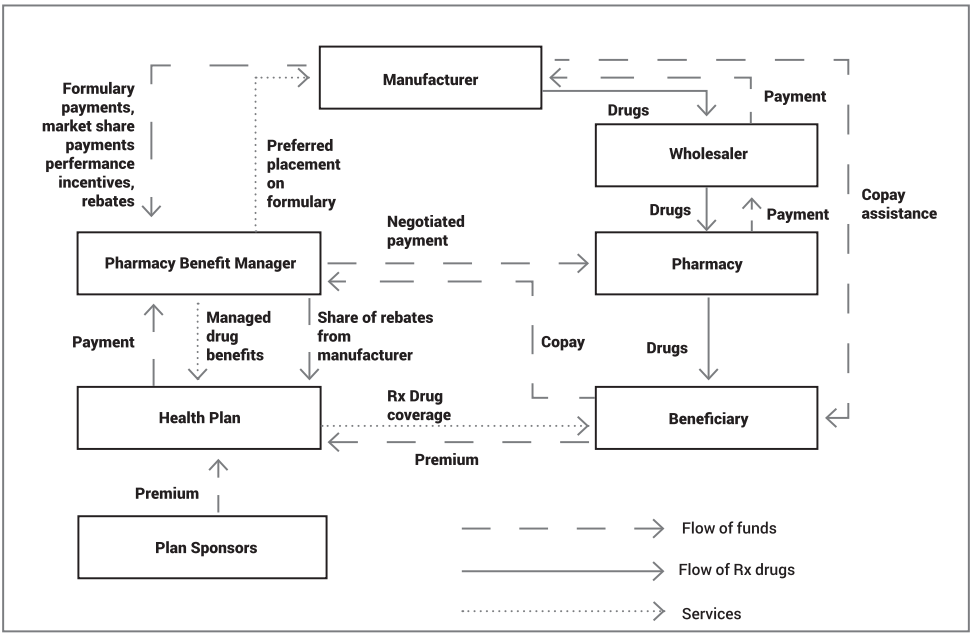
Understanding the pharmaceutical supply chain is key to understanding the cost of prescription drugs in the U.S., particularly in the private market. Manufacturers rarely receive the WAC or list price set by manufacturers because products are frequently discounted throughout the distribution system and are subject to various forms of service fees. These discounts flow through wholesale distributors, pharmacies, payers, and PBMs and are often paid retrospectively by the manufacturer in the form of rebates.

Wholesale distributors buy drugs from manufacturers and distribute them to pharmacies, hospitals, and other medical facilities. Pharmacies negotiate with wholesalers to purchase prescription drugs for their inventory, and, in turn, wholesalers negotiate with manufacturers to obtain drugs to distribute to pharmacies and other purchasers. Wholesalers also facilitate charge-backs for manufacturers to effectuate negotiated prices for their customers.

PBMs represent payers and employers in the selection, purchase, and distribution of prescription drug benefits, and often serve as a broker, without fiduciary obligations, between individual employers, payers, drug manufacturers, and pharmacies.[157] PBMs play several roles throughout the supply chain. These include:

- **Developing and maintaining prescription drug formularies for insurance plans.** PBMs maintain a national formulary, as well as custom client formularies, to provide tiered coverage for branded and generic prescription drugs.
- **Negotiating discounts from manufacturers.** PBMs negotiate discounts from manufacturers on behalf of insurers, in exchange for preferred formulary placement. Discounts generally come in the form of rebates. PBMs retain these rebates and pass along some portion of the manufacturer price concession under a blended effective rate for an employer's or plan's branded drug spend. Rebate agreements between PBMs and manufacturers often contain price protection provisions that require the manufacturer to pay additional concessions to the payer or PBM in the form of a penalty if the list price of the product increases above a predefined threshold year over year, on a cumulative multi-year basis, or both. Some larger payers negotiate directly with manufacturers for rebates and use the PBM for other administrative services such as Drug Utilization Review ("DUR") and claims processing. Rebates are not passed down to plan beneficiaries, but they may help reduce beneficiaries' overall insurance premium costs. Of note, rebates paid to PBMs have come under criticism as a key driver of drug costs[158] and have been the subject of recent rulemaking. Specifically, on November 20, 2020, the HHS Office of Inspector General ("OIG") promulgated a final rule amending the AKS safe harbor for discounts to eliminate protections for rebates or other price reductions from manufacturers to plan sponsors under Medicare Part D or PBMs acting on their behalf (commonly referred to as the "rebate rule"); the regulations simultaneously establish two new safe harbors that protect discounts offered by manufacturers on prescription drugs at the point-of-sale, allowing for a portion of the rebate to be passed through to the patient, and fixed-fee service arrangements between manufacturers and PBMs.[159] Implementation of the rebate rule has been delayed to January 2023, pursuant to litigation filed by the Pharmaceutical Care Management Association ("PCMA") against HHS.[160] It is unclear whether OIG will ultimately withdraw or modify the rebate rule prior to the January 2023 effective date. Additionally, the Federal Trade Commission ("FTC") continues to monitor PBM practices and impacts of PBM industry consolidation. FTC also recently established a working group to contemplate rulemaking, including competition rules with respect to rebates between manufacturers and third-party payers, such as PBMs.[161]
- **Creating pharmacy networks and negotiating lower dispensing fees.** PBMs create networks of pharmacies that agree to dispense prescription drugs under agreed-upon terms. PBMs negotiate a reimbursement rate for each drug product, as well as a dispensing fee. When a plan beneficiary pays for a prescription, the pharmacy generally passes the copayment or coinsurance to a PBM, which then pays the pharmacy the negotiated reimbursement and dispensing fee. This arrangement allows the PBM to create spread-pricing profits and impose penalty fees on pharmacies that do not achieve contracted performance goals such as rate of generic dispensing. PBMs also may operate pharmacies themselves, including mail-order and specialty pharmacies. When payers and PBMs operate and drive utilization to their own pharmacies through narrow networks, they can negotiate additional bulk purchase discounts from manufacturers that are retained by the payer or PBM pharmacy.

Figure 10: The flow of funds in the pharmaceutical distribution system[162]



Various entities across the drug supply chain are increasingly contracting and consolidating both horizontally and vertically. For example, three PBMs – Express Scripts, CVS Caremark, and OptumRx – control the majority of the market, together totaling an estimated 71% of Medicaid and Medicare Part D beneficiaries and 86% of the private market.[163] This demonstrates a high level of horizontal consolidation in the PBM industry. Further, these PBMs have some form of common ownership with large retail chains and/or specialty pharmacies, as well as payers, demonstrating an increasing level of vertical integration: CVS Caremark is affiliated with CVS and Aetna; Express Scripts is affiliated with Accredo and Cigna; and OptumRx is affiliated with BriovaRx and UnitedHealthcare.

While PBMs generally consider vertical integration to be to the benefit of patients,[164] there are concerns that extensive consolidation has reduced transparency in the financial relationships among payers and other participants in the drug supply chain and may adversely impact patient access due to significant bargaining power of the consolidated entities. On the other hand, PBMs generally have demonstrated success in keeping payers' net prices low and increasing the overall rate of price concessions achieved from manufacturers, providing a benefit to plans and payers. For example, a survey by the Pew Charitable Trust found that 91% of rebates were passed through to plans in 2016 (up from 78% in 2012).[165] PBMs retained roughly the same volume of rebates despite the higher rates of rebate pass-through due to an overall growth in rebate volume, including an estimated increase of manufacturer rebates from $39.7 billion in 2012 to $89.5 billion in 2016,[166] reflecting in part the impact of PBM bargaining power and negotiations.

Efforts to manage costs

Payers and PBMs have various tools at their disposal with which to control spending on prescription drugs. These tactics include:

- **Requiring greater cost sharing for high-cost products.** As indicated above, PBMs and payers have wide discretion to design formularies that determine how drugs are

reimbursed, as well as the rate of patient cost sharing for drug products (although, for Medicare Part D plans, these formulary designs must adhere to federal requirements and be approved by CMS). Tiered formularies are used to steer patients toward generics and branded drugs for which there exists no generic equivalent by requiring lower cost sharing for these drugs. Within a given formulary, tier 1 generally includes covered generic drugs (also called "preferred drugs"), and tier 2 generally includes preferred branded drugs for which there is no generic equivalent. Traditionally, PBMs used a three-tier structure, placing non-preferred drugs in tier 3. Today, many PBMs utilize a four-tier or five-tier structure, reserving the highest tiers (tiers 3, 4, or 5) for high-cost specialty drugs. PBMs shift a significant portion of the cost for non-preferred drugs to the patient, in the form of higher copayments (fixed dollar amounts) or co-insurance (a percentage of the cost of the drug). Negotiations with manufacturers typically involve the use of bidding tables where each manufacturer offers varying levels of rebates for exclusive, preferred, or parity formulary placement within competitive therapeutic classes (i.e., diabetes) where multiple clinically effective treatments are available for prescribing. Manufacturer bidding for government payer lives are typically separated from bidding activity for commercial payer lives due to the different coverage and reimbursement dynamics of each market. A developing trend is to show physicians the relative formulary status of a treatment option within their electronic health records at the time of prescribing, in order to better align the physician's decisions with the lowest cost option for the patient, employer, or health system.[167]

- **Utilization controls.** PBMs and insurance plans frequently require patients to obtain prior authorization before covering expensive medications. PBMs and insurance plans also may require a patient to try a preferred product (usually a lower cost generic) before agreeing to reimburse a more expensive product, a process known as "step therapy" or "fail first". Additionally, plans and PBMs may block coverage of certain drugs altogether, or utilize narrow pharmacy networks to limit patient access.
- **Mandatory substitution of generics.** Most state Medicaid plans require pharmacies to dispense a generic version of a drug product, if available, unless the patient's prescriber specifies that the branded version is medically necessary. Payers and PBMs also may encourage or require generic substitution, state law permitting. Multiple states require pharmacists to replace brand-name drugs with generics, unless a prescriber affirmatively blocks pharmacist substitution.[168] At least one state, Oklahoma, prohibits pharmacists from substituting pharmaceutical products without the consent of both the prescriber and the patient.[169]
- **Cost-sharing/copayment accumulators and maximizers.** PBMs and insurance plans have increasingly utilized benefit designs such as accumulators and maximizers to minimize and/or capture the effect of drug manufacturer copayment assistance. Under accumulator programs, the plan does not allow the value of manufacturer copayment assistance to count toward the beneficiary's deductible or out-of-pocket maximum. Thus, once the copayment assistance is exhausted, the beneficiary must pay the entire amount of his or her deductible before plan benefits are available. Under a maximizer program, the plan aligns the beneficiary's copayment obligation with available copayment assistance from manufacturers (i.e., by dividing the annual maximum benefit to set monthly copayment amounts for beneficiaries). Manufacturer assistance applies to the beneficiary's copayment obligation but not toward the beneficiary's deductible or out-of-pocket maximum. Accumulator and maximizer programs are subject to ongoing policy activity.
    - Recent federal rulemaking clarifies that accumulator programs (and, by extension, any accumulator elements included in maximizer programs) are expressly permitted

for health plans sold on the Affordable Health Insurance Exchanges, as well as most other plans, to the extent permitted by state law.[170] Additionally, in December 2020, CMS revised the methodology for calculating AMP and best price as part of the Medicaid Value-Based Purchasing Final Rule to require, beginning in 2023, that manufacturers "ensure" the full value of the copayment assistance is passed on to the patient and is not subject to accumulator programs in order to exclude such assistance from AMP and best price calculations.[171]

- Certain states have proposed and/or enacted legislation to address copayment accumulators and maximizers. In 2019, Arizona, Illinois, Virginia, and West Virginia enacted provisions that effectively prohibit accumulator programs by requiring health care plans to apply any third-party payments, such as copayment assistance from manufacturers, toward a patient's cost-sharing obligations.[172] Between 2020 and 2021, over a dozen states enacted some form of cost-sharing or coupon legislation,[173] such as Virginia and West Virginia legislation requiring insurers to account for any payments made on an insured's behalf in addition to the payments made by the insured when calculating the overall out-of-pocket cost sharing.[174] In 2021, Kentucky enacted legislation preventing insurers and PBMs from excluding any copayment assistance provided to beneficiaries when calculating cost-sharing requirements.[175] This is a rapidly evolving area with significant variation at both the state and federal policy levels.

- **Value-based contracts.** Manufacturers and payers are increasingly negotiating agreements to link the purchase price to clinical outcomes or financial measures, especially for high-cost specialty drugs. These arrangements are sometimes referred to as value-based contracts ("VBCs"), outcomes-based contracts ("OBCs"), or performance based risk sharing agreements ("PBRSAs").[176] A number of legal and regulatory requirements may be implicated by these arrangements. For example, the federal 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 health care program.[177] Statutory and regulatory safe harbors protect certain arrangements from AKS liability, including qualifying discount and warranty arrangements,[178] but there is some uncertainty with respect to how these safe harbors apply to VBC arrangements. In November 2020, HHS OIG issued a rule establishing three new safe harbors under the AKS for VBCs. However, these new safe harbor protections do not generally apply to manufacturers and other drug supply chain entities,[179] with a narrow exception for in-kind digital tools provided by manufacturers in care coordination. VBCs may also raise risks related to price reporting obligations, as the terms of such agreements can lead to significant variance in pricing at the per-patient level and potentially drop unit prices for certain patients below the "best price" traditionally offered for the drug product. In December 2020, CMS finalized regulations to facilitate value-based purchasing ("VBP") arrangements by allowing manufacturers to report VBPs under one of two methodologies: (1) under a bundled sales approach, which has been traditionally employed by manufacturers to distribute any VBP discount proportionally to the total dollar value of all units sold as part of the bundled arrangement; or (2) under a "multiple best prices" approach, to report multiple best price points for a single dosage form and strength to reflect the discounts or prices available under the VBP.[180] VBCs may also raise issues related to off-label promotion; for instance, if there is a need to share data on potential outcomes that are helpful to identify value but are not otherwise included in product labeling. FDA guidance expressly permitting the communication of health care

economic information ("HCEI") related to approved labeling lowers the risk related to such communications, and FDA has stated explicitly that it does not regulate terms for VBCs.[181]

- **Cost-effectiveness assessments.** PBMs and payers make coverage determinations based on certain cost-effectiveness information, including, where available, formal assessments conducted by the Institute for Clinical and Economic Review ("ICER"). ICER is a non-governmental entity that, similar to HTAs in other countries such as the National Institute for Health and Care Excellence ("NICE"), produces reports analyzing evidence on the effectiveness and value of drugs and other medical services in the U.S.[182] ICER's assessments evaluate two concepts: long-term value for money; and short-term affordability.[183] The assessments utilize the Quality-Adjusted-Life-Year ("QALY") to compare incremental cost-effectiveness of care options, with a health-benefit price benchmark of $100,000 to $150,000 per additional QALY.[184] Notably, the ACA's provisions for the Patient-Centered Outcomes Research Institute ("PCORI") prohibit the use of QALYs as a means for cost-effectiveness assessments at the federal-level.[185] Although ICER cannot directly control coverage decisions, ICER has become increasingly important in payer and PBM coverage and utilization determinations. For example, CVS Caremark has initiated a program allowing clients to exclude drugs from coverage if they are launched at a price exceeding $100,000 per QALY in analyses carried out by ICER.[186] Furthermore, certain states, such as New York, have relied on ICER reports to guide Medicaid drug review board decisions for certain covered outpatient drugs.[187] On a federal-level, the Department of Veteran's Affairs ("VA") has utilized ICER reports to help develop its drug formularies.[188] ICER has repeatedly received criticism for failing to include all evidence supporting clinical and economic benefits, lack of transparency in its assessments, and failing to incorporate enough of a patient-centered perspective, among other concerns.[189]

Efforts to facilitate access

A. Manufacturer financial assistance

Manufacturers frequently provide financial assistance or free product to patients to facilitate access. Such assistance may include manufacturer-sponsored patient assistance programs ("PAPs") (i.e. free drugs or diagnostic services), commercial copayment assistance (i.e. copayment coupons), and assistance provided by independent, third-party charitable entities (often referred to as "independent charity PAPs"). Eligibility for these types of programs may depend on income level, insurance status, and type of insurance. Additionally, manufacturers often provide other support services, such as assistance with navigating insurance coverage for specialty drugs.

Financial assistance to patients is highly regulated, particularly where this assistance is provided by drug manufacturers. The AKS limits the ability of manufacturers to provide coupons or discounts to patients enrolled in government health care programs, prohibiting manufacturers from providing direct subsidies to offset their out-of-pocket expenses for copayments and deductibles.[190] Although free drug programs for financially needy patients have historically not raised extensive concerns under anti-kickback laws, the HHS OIG, which is tasked with identifying and combating waste, fraud, and abuse within HHS, has articulated concerns with PAPs related to Medicare Part D.[191] For example, PAPs and copayment coupons may increase costs to the federal government under Medicare Part D because cost-sharing subsidies for Part D-covered drugs that count toward patients' true out-of-pocket expenses ("TrOOP") will increase the number of beneficiaries who qualify for catastrophic benefit in any given coverage year and the point during the year at which they reach the catastrophic benefit.[192] PAPs may

also have the effect of locking beneficiaries into the manufacturer's products, even if there are other equally effective, less costly alternatives, and patients may transition from a PAP to a government program such as Medicare Part D at some point in time.[193] OIG reiterated its position against manufacturer assistance related to Medicare Part D as recently as 2020, finding a proposal to provide copay assistance to Part D beneficiaries would be "highly suspect" under the AKS.[194] The OIG has also scrutinized charitable organizations that are not truly independent from manufacturer donors.[195] For example, OIG is concerned about independent charity PAPs defining disease-specific funds so narrowly that a donor earmarking funds for a given disease fund effectively results in subsidization of the donor's own products.[196] In 2021 and 2020, OIG issued favorable advisory opinions regarding financial support for high-cost, potentially curative gene and cell therapies, where the programs provide assistance ranging from covering administration of one-time treatment to providing wrap-around services, such as transportation and housing during treatment.[197]

B. Coverage of off-label use

In general, drug products must have FDA approval to be reimbursed by public or private payers. Coverage for "off-label" use of approved products – drugs used for a different disease or medical condition, given in a different way, or given in a different dose than specified in the approved label[198] – may be available in certain circumstances. For example, Medicare Part D covers drugs prescribed for off-label use if the drugs are listed in CMS-recognized compendia for determining medically accepted indications.[199] Under Part B, reimbursement for off-label use is permitted if the MAC determines the use to be medically accepted, taking into account the major drug compendia, authoritative medical literature, and/or accepted standards of medical practice.[200] State Medicaid programs mandate coverage of off-label uses where the drug is listed in CMS-recognized compendia.[201] Additionally, many states also currently require Medicaid programs and private payers to cover off-label use of drugs that meet certain criteria, with some requiring off-label coverage only for certain disease states such as cancer or other life-threatening or chronic and seriously debilitating conditions, and others mandating off-label coverage more broadly.[202] Off-label use is particularly widespread in oncology, where payers often use independent National Comprehensive Cancer Network Drugs and Biologics Compendium ("NCCN") guidelines to cover off-label treatments.

Off-label use remains controversial. On the one hand, off-label use may represent a physician's determination regarding which treatment would be medically appropriate for a given patient and is an important aspect of the physician-patient relationship. On the other hand, many off-label uses are being prescribed without strong evidence of their safety or efficacy in treating the off-label indication, raising patient safety concerns.[203] In any case, communications regarding off-label use outside of the physician-patient relationship are highly regulated, and manufacturers are prohibited from promoting drug products for any off-label use (although certain communications with payers or other communications consistent with labeling may be permissible).[204]

C. Expanded access and right to try

Even if reimbursement for unapproved drugs is not available, patients may gain access to investigational drug products through FDA's expanded access or "compassionate use" program. Expanded access allows patients with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

There are three types of expanded access INDs: individual patient expanded access INDs,

including for emergency use;[205] intermediate-size patient population expanded access INDs;[206] and treatment INDs for widespread use.[207] In all cases of expanded access use, FDA must determine that: (1) the patient(s) to be treated "have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy"; (2) the potential patient benefit justifies the potential risks, and the risks are reasonable given the disease or condition to be treated; and (3) granting the expanded access "will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use".[208] Additional criteria apply to each type of expanded access.

As a separate pathway, federal and state "right to try" laws permit patients with life-threatening diseases to access certain unapproved therapies without going through the FDA expanded access process. Following recent enactment of state-level laws in a significant majority of states,[209] the federal Right to Try Act was signed into law in 2018 to permit access to investigational drugs.[210] Under the federal Act, eligible patients must be diagnosed with a life-threatening disease or condition, have exhausted approved treatment options and be unable to participate in a clinical trial involving the eligible investigational drug, and have provided written informed consent.[211] Manufacturers have discretion over whether to make their products available to patients who qualify for access under the law.

D. Digital health solutions

Manufacturers are also increasingly looking toward digital health tools to facilitate access to prescription drugs and improve communications and outcomes across the care continuum. Digital health solutions encompass a wide range of items and services, ranging from telehealth services to phone applications ("apps") to wearables (i.e., Fitbit) to prescription digital therapeutics. Manufacturers may utilize digital health for real-time data generation as well as personalizing products and services for patients. Where appropriate, certain digital health tools may qualify in and of themselves for coverage and reimbursement (e.g., prescription digital therapeutics).

Policy issues that affect pricing and reimbursement

Cost of innovation, U.S. drug pricing, and "Foreign Underpricing"

Amidst global controversy over the high prices of innovative drug products, there is increasing debate regarding whether drug prices reflect the cost of innovation and, if so, whether this cost is appropriately distributed. The anticipated cost of developing a new drug, inclusive of capital costs and money spent on candidate drugs that fail to reach the market, has been estimated to range from less than $1 billion to more than $2 billion, and only about 12% of drugs succeed in the clinical trial process.[212] According to one study, the cost to develop a new prescription drug that gains marketing approval is estimated to be $2.6 billion as of 2013.[213] This is a significant increase from $802 million in 2003 (approximately $1 billion in 2013 dollars), representing a 145% increase in the 10-year time period between studies. Accounting for post-approval R&D, the cost of total development increases to nearly $2.9 billion.[214] Key drivers of this significant price tag include high failure rates for potential clinical drug candidates (an estimated seven out of eight compounds that enter the clinical testing pipeline fail in development) as well as high out-of-pocket clinical costs for drug trials, including increased complexity or clinical trial design and larger trials, higher cost of inputs, increased focus on targeting chronic and degenerative diseases, changes in protocol design to include efforts to gather HTA information, and testing on comparator drugs to accommodate payer demands for comparative effectiveness data.[215]

The cost of innovation appears to fall disproportionately on the U.S., where drug prices far outpace prices in other countries. In 2020, the CEA issued a report evaluating how the costs and benefits of medical innovation are distributed across developed nations. According to the CEA, while "[t]he U.S. Government and the biopharmaceutical industry have been critical to improving health worldwide by leading the way in the [R&D]", "foreign countries often do not make equal investments in the R&D that is necessary to fuel innovation and ensure the economic viability of biopharmaceutical products".[216] The report found that foreign "free-riding" has increased over the past 15 years, with patented drug prices in European countries falling from 51% of U.S. prices in 2003 to about 32% of U.S. prices in 2017.[217] The CEA concluded that "[f]oreign governments have implemented stricter price controls, enabling these products to be sold below fair market value, with Americans picking up the tab for making the availability of such products feasible in the first place", leading to a "slower pace of innovation" and "fewer potential new life-saving therapies for patients in all countries".[218] By contrast, "[r]educing foreign price controls would increase profits and innovation, thereby leading to greater competition and lower prices for U.S. patients".[219]

Addressing U.S. drug prices has been the subject of significant debate. Reform proposals range from addressing payment and reimbursement of drug prices in the U.S., to exercising trade policy tools to combat drug pricing practices in foreign markets.[220] Additionally, states are actively considering proposals that would address drug pricing practices by a variety of mechanisms. These issues are explored in more detail in the following section on emerging trends.

Emerging trends

Tying U.S. drug prices to international prices

Given disparities between U.S. and ex-U.S. drug prices, a number of proposals seek to require drug prices for certain U.S. payers to be based on prices in international markets, a practice referred to as "reference pricing". For example, the Trump administration issued an interim final rule, commonly referred to as the Most Favored Nation Final Rule ("MFN Rule"), which would have tied Medicare Part B payments for certain drugs to the lowest price paid in other economically advanced countries.[221] The MFN Rule was set to take effect on January 1, 2021; however, several courts enjoined the rule. Although CMS contended that it had good cause to proceed without notice-and-comment rulemaking, the courts determined that CMS' omission of notice and comment likely violated the Administrative Procedure Act ("APA").[222]

Reference pricing has also been contemplated in legislative proposals. For example, the Elijah E. Cummings Lower Drug Costs Now Act, passed by the U.S. House of Representatives in December 2019 and reintroduced to Congress in April 2021, is a Democratic proposal with several significant provisions related to drug pricing. In Title I, the bill gives HHS authority to directly negotiate prices for up to 250 drugs posing the greatest total cost to Medicare and the U.S. health system, and the maximum price set for such negotiations would be 1.2 times the average price of the drug in six foreign countries (Australia, Canada, France, Germany, Japan, and the United Kingdom) (or 85% of the AMP, where reference prices are not available).[223] Such pricing would apply to Medicare and other federal programs, as well as non-federal government plans. The Act includes steep penalties for drug companies that do not participate in the negotiation process or abide by the agreed-on price.[224]

Drug importation

In addition to relying on drug prices used abroad, the U.S. has also adopted new policies permitting importation of drugs. In fall 2020, the Trump administration issued a final rule

and FDA guidance for industry creating two new pathways for the importation of drugs from Canada and other countries. The final rule enables states and Indian tribes to develop importation programs for approval by FDA, in which wholesalers and pharmacists may import prescription drugs from Canada. The final rule also necessitates that importation sponsors demonstrate how their programs will reduce covered prescription drug costs in the United States.[225] FDA guidance creates a second pathway whereby manufacturers could import certain FDA-approved drugs that they sell abroad that are the same as U.S. versions. Under this pathway, manufacturers may utilize a new NDC for the imported products, which was intended to provide an avenue to lower the imported drugs' price compared to what the manufacturer's current distribution contracts necessitate.[226]

The importation rule was effective November 30, 2020; however, the Pharmaceutical Research and Manufacturers of America ("PhRMA") challenged the rule based on safety and other concerns. PhRMA's complaint alleges that the certification and final rule provide insufficient justification and evidence to meet the certification criteria specified in the Federal Food, Drug, and Cosmetic Act that the importation of drugs will "pose no additional risk to the public's health and safety" and will "result in a significant reduction in the cost" of the drugs for the American consumer. The complaint also alleges that the drug-tracing provisions of the final rule will create administrative and operational issues that undermine public health and safety.[227] The final rule has also been met with resistance from Canadian officials, who have issued an interim order barring exportation of certain drugs if doing so would lead to or exacerbate a shortage in Canada.[228] President Biden supported drug importation during his campaign, and the government moved to dismiss the complaint on standing and ripeness grounds on May 28, 2021.[229]

Additional proposals related to drug pricing reform in the U.S.

Federal and state policymakers have considered a number of additional proposals related to drug pricing reform. For example, in addition to setting forth Medicare negotiation provisions that cap negotiated prices at international reference prices, the Lower Drug Costs Now Act includes separate reform proposals, such as an out-of-pocket cap for Medicare Part D drugs, redesigning the Part D benefit and manufacturer discounts under the program, and limiting price increases to the inflation rate.[230] Separate legislative proposals, such as the Prescription Drug Pricing Reduction Act ("PDPRA"), would similarly include limits on price increases above inflation and out-of-pocket caps, as well as other proposals related to Part B payments (reducing payment for new single-source drugs from 106% to 103% of WAC, among other changes), and information disclosure, among other proposals.[231]

The Biden administration, as of June 2021, has yet to introduce significant drug pricing policies and did not include specific proposals in the "human infrastructure plan".[232] During the campaign, President Biden's platform included a number of proposals consistent with the Lower Drug Costs Now Act, such as a Part D out-of-pocket drug costs cap, Part D negotiation provisions, and limiting price increases to the inflation rate. The Biden campaign also put forward a proposal to establish drug pricing via an independent review board, which could include foreign reference pricing as a back stop, based on the German model for setting drug prices through negotiations between manufacturers and insurers.[233] Additionally, President Biden has committed to maintaining or expanding coverage and protections under the ACA,[234] which was the most significant regulatory overhaul and expansion of coverage since the creation of Medicare and Medicaid in 1965. The ACA has been repeatedly challenged in various court cases including before the Supreme Court, and in the most recent case (decided in June 2021), the Supreme Court held that the individual plaintiffs and states lacked standing to challenge the constitutionality of the ACA.[235]

States have also been active with respect to drug pricing reform proposals. Most notably, a significant number of states have proposed and enacted transparency laws that require manufacturers, PBMs, insurers, and other entities to report certain drug pricing information to state agencies.[236] While reporting requirements vary by state, these laws generally require manufacturers to report information regarding drug prices and drug price increases above a certain threshold. For example, California requires manufacturers to report price increases exceeding 16% of WAC.[237] Several states also require reporting upon the introduction of new prescription drugs to market with a WAC that exceeds the Medicare Part D specialty drug threshold.[238] States have adopted other mechanisms for price reporting, such as authorizing an independent board to compile a list of drugs on which the state spends significant dollars and/or for which the WAC has increased significantly over a period of time.[239] States are also considering and adopting proposals related to international reference pricing, generic manufacturing, drug importation, anti-price gouging and price increase penalties. Although state laws related to drug pricing are proliferating, a number of these laws have been subject to legal challenges or struck down by the courts.[240]

Impact of COVID-19 on pharmaceutical pricing and reimbursement

The COVID-19 pandemic has wide-ranging implications for the life sciences industry. The pandemic highlighted the need for manufacturers of finished medical products and suppliers of raw materials, components, and critical services to fortify supply chains, develop surge capacity, and implement other measures to prevent drug shortages. The pandemic also gave new insights into the need to navigate expedited development programs, unique access pathways (in particular, emergency use authorization), and related coverage pathways outside of the traditional routes of reimbursement and insurance coverage. In addition, the expansion of telehealth and digital prescribing during the pandemic may lead to the development of new policies enabling reimbursement for such services.[241]

In the context of COVID-19, the U.S. government has been acquiring medical products, including vaccines and therapeutics, directly from manufacturers. In the future, there may be an expansion of the U.S. government's procurement of innovative medical products (e.g., novel gene and cell therapies and new vaccine technologies) to enhance the government's ability to respond to epidemics and pandemics.[242] Manufacturers should monitor how changes necessitated by the pandemic may affect traditional market access pathways during and after the public health emergency.

Successful market access

As demonstrated by this chapter, the drug pricing and reimbursement infrastructure in the U.S. consists of a complex patchwork of policies and institutions. Successful market access requires navigating this infrastructure in a way that ensures drug products are available to patients, reimbursable by patients' health care plans, and appropriately valued. These efforts must be compliant with various overlapping regulatory requirements and minimize enforcement risk under the AKS, FCA and other federal and state laws.[243]

Accordingly, drug manufacturers and investors funding development of drug products should consider the following in designing both U.S. and global market access strategies:

- **Access.** Manufacturers should evaluate the criteria for favorable coverage under various private and public plans and coordinate appropriate engagement with PBMs facilitating coverage with these payers, as well as the relative use by patients who are covered under government *versus* private payers and the likely settings of care for one time or chronic use of the product. Successful market access strategies will include plans for patient

assistance and patient support services, pharmacy and wholesaler distribution networks, and other key features facilitating access to drug products.

- **Pricing.** Manufacturers should investigate the coverage, coding, and payment structures that will apply to their drug products for each payer type in the U.S. Pricing strategies should include conducting a reimbursement assessment, including comprehensive coding and payment analysis across all relevant settings of care, and developing rebate bidding and contracting strategies, preparing payer budget impact moles, conducting payer market research, and using HCEI to support the proposed pricing structure. Manufacturer list and net pricing scenarios for new products must account for all supply chain concessions over a multi-year time horizon with growing limitations on ability to increase pricing year over year, as well as model impacts based on government price reporting obligations (e.g., best price, AMP, and ASP) and mandatory rebate liabilities (e.g., MDRP).
- **Value.** Manufacturers should develop appropriate evidence, including real world evidence, and messaging to communicate the value proposition for their drug products, including by developing a thorough understanding of the prescribing pathway, comparator treatments, quality measures, patient need, and direct and indirect costs of treatment with the new drug. Manufacturers should prepare to demonstrate the cost-effectiveness of drug products, in the event of a potential ICER assessment or requests for such information from payers more generally. Consideration should be given to potential value-based pricing structures that link the purchase price to patient outcomes and product warranties, as well as provide more predictable cost outlays for both government and private payers.

If possible, manufacturers should develop U.S. market access strategies at least two years before approval and launch in the U.S. and integrate these strategies with global market access efforts. When appropriately structured, market access strategies can inform clinical development and clinical trial outputs, help guide positioning during the drug approval process, and facilitate market entry upon approval. Market access strategies also should include frequent review and updates based on changes in the U.S. reimbursement framework. The payers and programs involved in drug coverage and reimbursement are constantly evolving, and current or future proposals for reform and growing government enforcement activity focused on market access could significantly impact drug pricing in the U.S.

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21. IQVIA Inst. for Hum. Data Science, *Medicine Use and Spending in the U.S.: A Review of 2018 and Outlook to 2023* 5–6, 21 (May 2019), https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us---a-review-of-2018-outlook-to-2023.pdf?_=1587760606847; Express Scripts, *2019 Drug Trend Report*, https://www.express-scripts.com/corporate/drug-trend-report#2019-in-review (last visited May 13, 2020); *see also* Robert King, *Costly Specialty Drugs Make up 40% of 2018 Employer Drug Spending Despite Few Prescriptions*, FierceHealthcare (Aug. 21, 2019, 2:42 PM), https://www.fiercehealthcare.com/payer/costly-specialty-drugs-make-up-40-2018-employer-drug-spending-despite-few-prescriptions.
22. IQVIA Inst. for Hum. Data Science, *Medicine Use and Spending in the U.S.: A Review of 2018 and Outlook to 2023* 21 (May 2019), https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us---a-review-of-2018-outlook-to-2023.pdf?_=1587760606847.
23. *Id.*
24. This chapter focuses on the pricing and reimbursement of prescription drugs and does not address medical devices, diagnostic testing, or related topics.
25. Inmaculada Hernandez *et al.*, *Changes in List Prices, Net Prices, and Discounts for Branded Drugs in the US, 2007–2018*, 323 J. Am. Med. Assoc. 854, 857 (Mar. 3, 2020).
26. *The Prescription Drug Landscape, Explored*, Pew Charitable Trust (Mar. 8, 2019), https://www.pewtrusts. org/en/research-and-analysis/reports/2019/03/08/the-prescription-drug-landscape-explored.
27. *Health Expenditure and Financing*, OECD Health Statistics 2020, https://www.oecd.org/els/health-systems/health-data.htm (last visited Apr. 13, 2021) (capturing data from 2018 and estimating 2019); *NHE Fact Sheet*, Ctrs. Medicare & Medicaid Servs., https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NHE-Fact-Sheet (last visited May 24, 2021).
28. Council of Econ. Advisers, *Funding the Global Benefits to Biopharmaceutical Innovation* 11 (Feb. 2020), https://www.whitehouse.gov/wp-content/uploads/2020/02/Funding-the-Global-Benefits-to-Biopharmaceutical-Innovation.pdf.
29. *Id.*
30. 21 U.S.C. § 393(b)(1)–(2). FDA initially was established as the Bureau of Chemistry within the Department of Agriculture with the 1906 Pure Food and Drugs Act. Pub. L. No. 59-384, 34 Stat. 768, (1906). The 1906 Act banned interstate traffic in adulterated and mislabeled products, provided criminal penalties for violations, and authorized the seizure of offending products, but did not authorize the FDA to require premarket testing or approval for new drug products. The agency assumed its current gatekeeper role through the 1938 Federal Food, Drug, and Cosmetics Act ("FDCA"). Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended in scattered sections of 21 U.S.C.). The original FDCA required manufacturers to notify the agency and submit evidence of safety before marketing new drugs to the public. The subsequent 1962 Amendments transformed this premarket *notification* system in a premarket *approval* system, under which the agency must affirmatively approve new drugs on the basis of safety *and* efficacy. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962); *see also, e.g.*, Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 Va. L. Rev. 1753, 1764–65 (1996).
31. *Fact Sheet: FDA at a Glance*, U.S. Food & Drug Admin. (Nov. 2020), https://www.fda.gov/media/143704/download.
32. 21 U.S.C. § 355 (NDAs); 42 U.S.C. § 262 (BLAs).

33. 21 U.S.C. § 355(d) (NDAs); 42 U.S.C. § 262(a)(2)(C) (BLAs).
34. 21 U.S.C. § 355(j) (ANDAs); 42 U.S.C. § 262(k) (biosimilar applications).
35. 21 U.S.C. § 355(j)(8)(B) (ANDAs); 42 U.S.C. § 262(i)(2)(B) (biosimilar applications).
36. *Novel Drug Approvals for 2020*, U.S. Food & Drug Admin., https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020 (content current as of Jan. 13, 2021) (noting approval of 53 drug and biological products by the Center for Drug Evaluation and Research, and excluding from this list vaccines, allergenic products, blood and blood products, plasma derivatives, cellular and gene therapy products, or other products approved by the Center for Biologics Evaluation and Research); *2020 Biological License Application Approvals*, U.S. Food & Drug Admin., https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/2020-biological-license-application-approvals (content current as of Aug. 20, 2020) (noting approval of 8 biological products); *2020 First Generic Drug Approval*s, U.S. Food & Drug Admin., https://www.fda.gov/drugs/first-generic-drug-approvals/2020-first-generic-drug-approvals (content current as of Feb. 23, 2021) (defining "first generics" as the first approval by FDA which permits a manufacturer to market a generic product in the United States); *Biosimilar Product Information*, U.S. Food & Drug Admin., https://www.fda.gov/drugs/biosimilars/biosimilar-product-information (content current as of Dec. 17, 2020).
37. Pub. L. No. 102–571, 106 Stat. 4491 (1992).
38. *Fact Sheet: FDA at a Glance*, U.S. Food & Drug Admin., https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance (content current as of Nov. 20, 2020).
39. U.S. Food & Drug Admin., PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022 6, https://www.fda.gov/media/99140/download (last visited May 13, 2020).
40. *Id.*
41. Priority review is also available to manufacturers that have a priority review voucher or where other criteria are met. *See, e.g.*, *Guidance for Industry, Expedited Programs for Serious Conditions—Drugs and Biologics*, U.S. Food & Drug Admin., 24–25 (May 2014), https://www.fda.gov/media/86377/download.
42. 21 U.S.C. §§ 356(a) (breakthrough therapy designation), 356(b) (fast track designation), 356(c) (accelerated approval); *see also* 21 C.F.R. part 314, subpart H; 21 C.F.R. part 601, subpart E; U.S. Food & Drug Admin. *Guidance for Industry, Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014), https://www.fda.gov/media/86377/download. Additional pathways and designations may also be available. *See, e.g.*, 21 U.S.C. §§ 356(g) (Regenerative Advanced Therapy designation), 356(h) (Limited Population Pathway for Antibacterial and Antifungal Drugs), 355f(d) (Qualified Infectious Disease Product designation).
43. 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii); 21 C.F.R. § 314.108.
44. 21 C.F.R. § 314.108(b)(2). An NDA or ANDA can be submitted after four years if it contains a certification of patent invalidity or noninfringement.
45. 21 U.S.C. §§ 355(c)(3)(E)(iii), 355a(b), 360cc(a); 42 U.S.C. § 262(k)(7); 21 C.F.R. §§ 314.108, 316.31.
46. 21 U.S.C. §§ 360n, 360ff, 360bbb-4a.
47. In many cases, the definitions provided herein are summaries of statutory or regulatory definitions.
48. 42 C.F.R. § 447.502.
49. 42 U.S.C. § 1396r-8(k)(1).

50. *Id.* § 1395w-3a(c)(1).
51. *Pricing Policy Update: Important Information About AWP Data*, Wolters Kluwer, https://www.wolterskluwer.com/en/solutions/medi-span/about/pricing-policy-update (last visited June 2, 2021).
52. 42 U.S.C. § 1396r-8(c)(1)(C).
53. *Id.* § 1395w-3a(c)(6)(B).
54. Social Security Amendments of 1965, Pub. L. No. 89-97, tit. XVIII, 79 Stat. 286, 291–343 (1965).
55. 42 U.S.C. § 1395y(a)(1)(A).
56. *Id.* § 1395c *et seq*.
57. *Id.* § 1395kk-1.
58. *Id.* §§ 1395ff(f)(1)(B), 1395ff(f)(2)(B); *see also* Ctrs. for Medicare & Medicare Servs., *Medicare Program Integrity Manual*, ch. 13, § 13.1.1, https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/pim83c13.pdf (last updated Feb. 12, 2019).
59. 42 U.S.C. § 1395j *et seq.*
60. *Id.* § 1395k(a).
61. Some low-income beneficiaries may qualify for premium and cost-sharing assistance, either by qualifying for full Medicaid benefits or Medicare Savings Programs. *Id.* § 1396u-3.
62. *Id.* § 1395kk-1.
63. *Id.* §§ 1395j-1395w-6.
64. *Id.* § 1395w-21. MA plans are either local plans that serve a particular area, or regional plans that contract with CMS to provide services to one or more defined regions. Beneficiaries may choose to enroll in MA if there is a plan offered in their area. *Id.* § 1395w-28(4)–(5).
65. *Id.* § 1395w-22(a).
66. *Id.* § 1395w-22(a)(3); 42 C.F.R. § 422.100(c).
67. 42 U.S.C. § 1395w-131.
68. *Id.* § 1395w-101.
69. *Id.* § 1395w-104(b)(3)(C); *see also id.* § 1395w-104(b)(3)(G) (setting forth specified categories for which plans must include all covered Part D drugs). CMS automatically approves formulary classification systems that are consistent with the U.S. Pharmacopeia ("USP") category and class system. Alternative classification systems must be reviewed by CMS to determine if they are sufficiently similar to the USP or other common systems, such as the American Hospital Formulary Service classification system. *See* Ctrs. for Medicare & Medicaid Servs., *Medicare Prescription Drug Benefit Manual*, ch. 6 § 30.2.1, https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Part-D-Benefits-Manual-Chapter-6.pdf (last updated Jan. 1, 2016).
70. 42 C.F.R. § 423.272(b)(2); *see generally* Cong. Research Serv., R40611, Medicare Part D Prescription Drug Benefit (2018).
71. 42 U.S.C. § 1395y(a)(1)(A); 42 C.F.R. § 411.15(k).
72. 42 U.S.C. § 1395w-102(e); 42 C.F.R § 423.100.
73. 42 U.S.C. § 1395ff.
74. Ctrs. for Medicare & Medicaid Servs., *Medicare Program Integrity Manual*, ch. 13, § 13.2.2.3, https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/pim83c13.pdf (last updated Feb. 12, 2019).

75. Ctrs. for Medicare & Medicaid Servs., *Medicare Prescription Drug Manual*, ch. 6, § 30, https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Part-D-Benefits-Manual-Chapter-6.pdf (last updated Jan. 15, 2016); *see also* Ctrs. for Medicare & Medicaid Servs., *Medicare Managed Care Manual*, ch. 4, § 10.1, https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/mc86c04.pdf (last updated Apr. 22, 2016) (referring to the "Medicare Prescription Drug Manual" for requirements prescription drug coverage).
76. 42 U.S.C. § 1395w-104(b)(3)(A); 42 C.F.R. § 423.120(b)(1); *see also* Ctrs. for Medicare & Medicaid Servs., *Medicare Prescription Drug Benefit Manual*, ch. 6, § 30.1.5, https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Part-D-Benefits-Manual-Chapter-6.pdf (last updated Jan. 15, 2016).
77. 42 C.F.R. § 423.120(b)(2)(i).
78. 42 U.S.C. § 1395w-104(b)(3)(G)(iv). These classes of drugs are often referred to as "protected classes".
79. Social Security Amendments of 1983, Pub. L. No. 98-21, 97 Stat. 65 (1983).
80. 42 U.S.C. § 1395cc(a)(1)(H).
81. 42 C.F.R. § 412.2.
82. *Id.* § 412.60.
83. *Id.* § 412.2(f).
84. *Id.* §§ 412.150-412.172.
85. *Id.* § 412.22.
86. Medicare Payment Advisory Comm'n, *Hospital Acute Inpatient Services Payment System* 2 (Oct. 2019), http://www.medpac.gov/docs/default-source/payment-basics/medpac_payment _basics_19_ hospital _final_v2_sec.pdf?sfvrsn=0.
87. *See* 42 U.S.C. §§ 1395k(a)(1) (providing for coverage of medical or other health services), 1395x(s)(2) (defining medical and other health services to include drugs not usually self-administered).
88. 42. C.F.R. § 419.2(a).
89. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003).
90. 42 U.S.C. § 1395w-3a(b). For certain drug products that lack ASP data, reimbursement payments may be calculated using the WAC. *Id.* § 1395w-3a(c)(4). WAC may also be used if lower than the ASP. *Id.* § 1395w-3a(b)(4).
91. *Id.* § 1395w-3a(c)(1).
92. *Id.* § 1396r-8(b)(3).
93. For example, manufacturers of products paid as drugs under Part B but considered devices by Medicaid (and FDA) often do not have rebate agreements and thus would not be required to report ASPs. *See, e.g.*, Office of Inspector General, *Limitations in Manufacturer Reporting of Average Sales Price Data for Part B Drugs*, OEI-12-13-00040, 8 n.24 (July 2014), https://oig.hhs.gov/oei/reports/oei-12-13-00040.asp.
94. Ctrs. for Medicare & Medicaid Servs., *Medicare Claims Processing Manual*, ch. 17, § 20.1.2, https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c17.pdf (updated Aug. 30, 2019).
95. 42 U.S.C. § 1395w-3a(b); 42 C.F.R. § 414.904. The Budget Control Act of 2011 included sequestration requirements that reduced the payment rate for Part B to 4.3%. *See* Pub. L. No. 112-25, § 302, 125 Stat. 240, 256, 258-59 (2011). Additionally, for new drug products reporting WAC instead of ASP, the statutory reimbursement rate for these drugs is WAC plus 3%. 42 U.S.C. § 1395w-3a(c)(4) (amended from WAC plus 6% pursuant to Sustaining Excellence in Medicaid Act of 2019, Pub. L. No. 116-39, § 6, 133 Stat. 1062 (2019), following CMS rulemaking that had previously reduced this amount).

96. 42 U.S.C. § 1395*l*(a)(1).
97. 42 C.F.R. § 419.2(b); Ctrs. for Medicare & Medicaid Servs., *Medicare Claims Processing Manual*, ch. 17, § 20.1.3, https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c17.pdf (last updated Aug. 30, 2019).
98. Ctrs. for Medicare & Medicaid Servs., *Medicare Claims Processing Manual*, ch. 17, § 10, https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c17.pdf (last updated Aug. 30, 2019).
99. 42 U.S.C. § 1395u(o)(1)(C); 84 Fed. Reg. 61,142, 61,145 (Nov. 12, 2019). The reimbursement rate of ASP minus 22.5% for 340B-acquired Part B drugs is currently being challenged in federal court. *See American Hosp. Ass'n v. Azar*, 385 F. Supp. 3d. 1 (D.D.C. 2019).
100. 42 U.S.C. § 1395w-23; 42 C.F.R. § 422.304.
101. 42 C.F.R. § 422.304(b).
102. 42 U.S.C. § 1395w-102(a).
103. 42 C.F.R. § 423.104.
104. The Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 3301-3315, 124 Stat. 119, 461-80 (2010).
105. For brand-name drug products purchased by beneficiaries in the coverage gap, manufacturers provide a 70% discount and Medicare pays an additional 5%. For generic drug products, Medicare pays 75% of the cost. Ctrs. for Medicare & Medicaid Servs., *2020 Medicare Advantage and Part D Advance Notice Part 2 and Draft Call Letter* (Jan. 30, 2019), https://www.cms.gov/Medicare/Health-Plans/MedicareAdvtgSpecRateStats/Downloads/Advance2020Part2.pdf.
106. 42 U.S.C. § 1395w-114.
107. *See* Ctrs. for Medicare & Medicaid Servs., *Announcement of Calendar Year (CY) 2022 Medicare Advantage (MA) Capitation Rates and Part C and Part D Payment Policies* (Jan. 15, 2021), https://www.cms.gov/files/document/2022-announcement.pdf.
108. Medicare Payment Advisory Comm'n, *Report to Congress: Medicare Payment Policy* 413 (March 2021), http://medpac.gov/docs/default-source/reports/mar21_medpac_report_to_the_congress_sec.pdf.
109. 42 U.S.C. § 1395w-115.
110. Cong. Research Serv., R40611, Medicare Part D Prescription Drug Benefit (2018).
111. 42 U.S.C. § 1395w-111(i).
112. Medicare Payment Advisory Comm'n, *Part D Payment System* 3 (2019), http://www.medpac.gov/docs/default-source/payment-basics/medpac_payment_basics _19_partd_final_sec.pdf?sfvrsn=0.
113. Social Security Amendments of 1965, Pub. L. No. 89-97, tit. XIX, 79 Stat. 286, 343–53 (1965).
114. 42 U.S.C. § 1396a.
115. *Id.* § 1396a(a)(10). Other statutes and regulations promulgated by CMS also defined eligibility pathways. *See, e.g.*, *id.* § 1396v; 42 C.F.R. Part 435.
116. 42 U.S.C. §§ 1396b(m), 1395mm(a)(1).
117. *Id.* §§ 1396a, 1396u-7.
118. *Id.* §§ 1396a(a)(54), 1396u-7(b)(2)(A).
119. *See Medicaid Benefits: Over-the-Counter Products*, Kaiser Family Found., https://www.kff.org/other/state-indicator/medicaid-benefits-over-the-counter-products/?currentTimeframe=0&sort Model=%7B%22 colId%22:%22Location%22,%22sort%22:%22asc%22%7D (last visited May 14, 2020).

120. 42 U.S.C. § 1396u-5(d)(1).
121. *See generally id.* § 1396r-8.
122. *Id.* § 1396r-8(a)-(b).
123. *Id.* § 1396r-8(d)(2).
124. 42 C.F.R. § 447.53.
125. Medicaid Program: Covered Outpatient Drugs, 81 Fed. Reg. 5,169, 5,174-76, 5,347 (Feb. 1, 2016) (codified at 42 C.F.R. § 447.502) (replacing the estimated acquisition cost ("EAC") with AAC).
126. *Id*. at 5176.
127. 42 C.F.R. § 447.502.
128. 42 U.S.C. § 1396a(a)(30)(A).
129. Medicaid & CHIP Payment & Access Comm'n, *Medicaid Payment for Outpatient Prescription Drugs* 6 (May 2018), https://www.macpac.gov/wp-content/uploads/2015/09/Medicaid-Payment-for-Outpatient-Prescription-Drugs.pdf.
130. Rachel Dolan, *Understanding the Medicaid Prescription Drug Rebate Program*, Kaiser Family Found. (Nov. 12, 2019), https://www.kff.org/medicaid/issue-brief/understanding-the-medicaid-prescription-drug-rebate-program/.
131. For example, the Ohio state auditor released a report finding that state PBMs collected $208 million in fees for generic Medicaid prescriptions paid my managed care plans between April 1, 2017 and March 31, 2018. *See* Ohio Auditor of State, *Ohio's Medicaid Managed Care Pharmacy Services* 2 (Aug. 16, 2018), https://ohioauditor.gov/auditsearch/Reports/2018/Medicaid_Pharmacy_Services_2018_Franklin.pdf.
132. *See* 42 U.S.C. § 1396r-8(e)(4).
133. *See id.* § 1396r-8(e)(5); 42 C.F.R. § 447.514. If the FUL is less than the average AAC for retail community pharmacies, FUL is calculated using a higher multiplier to reflect average retail community pharmacies' acquisition costs. 42 C.F.R. § 447.514.
134. Cong. Research Serv., R43778, Medicaid Prescription Drug Pricing and Policy 13 (2014).
135. 42 C.F.R. § 447.512(b).
136. 42 U.S.C. § 1396r-8(b).
137. *Id.* § 1396r-8(c).
138. *See*, Cong. Research Serv., R43778, *supra* note 134, at 17.
139. The 340B program was established in 1992 through section 340B of the Public Health Services Act. *See* Veterans Health Care Act of 1992, Pub. L. No. 102-585, § 602, 106 Stat. 4943, 4967-71 (1992) (enacting Section 340B of the Public Health Service Act). 340B is administered by Health Resources and Services Administration ("HRSA"), an agency within HHS, through HRSA's Office of Pharmacy Affairs ("OPA"), and effectuated through the Pharmaceutical Pricing Agreement and addendum (collectively "PPA").
140. Mike McCaughan, *The 340B Drug Discount Program*, Health Affairs (Sept. 14, 2017), https://www.healthaffairs.org/do/10.1377/hpb20171024.663441/full/.
141. 42 U.S.C. § 256b.
142. *See*, *e.g.*, Rena M. Conti & Peter B. Bach, *The 340B Drug Discount Program: Hospitals Generate Profits By Expanding To Reach More Affluent Communities*, Health Affairs (Oct. 2014), https://www.healthaffairs.org/doi/10.1377/hlthaff.2014.0540.
143. Pub. L. No. 111-148, § 7101, 124 Stat. 119, 821-22 (2010); Notice Regarding 340B Drug Pricing Program—Contract Pharmacy Services, 75 Fed. Reg. 10,272 (Mar. 5, 2010); Stephen Barlas, *Health Care Reform Bill Expands Access to Section 340B Discounted Drugs for Hospitals*, 35 Pharmacy & Therapeutics 632, 632–34 (2010).

144. Avalere, *Hospital Acquisitions of Physician Practices and the 340B Program* 4 (June 2015), https://avalere.com/insights/avalere-white-paper-hospital-acquisitions-of-physician-practices-and-the-340b-program.
145. Adam J. Fine, *Exclusive: 340B Program Purchases Reach $24.3 Billion—7%+ of the Pharma Market—As Hospital Charity Care Flatlines*, Drug Channels (May 14, 2019), https://www.drugchannels.net/2019/05/exclusive-340b-program-purchases-reach.html; Adam J. Fine, *Exclusive: 340B Program Hits $16.2 Billion in 2016; Now 5% of U.S. Drug Market*, Drug Channels (May 18, 2017), https://www.drugchannels.net/2017/05/exclusive-340b-program-hits-162-billion.html.
146. Medicare Program: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems and Quality Reporting Programs, 82 Fed. Reg. 52,356, 52,362 (Nov. 13, 2017) (effective Jan. 1, 2018).
147. *American Hosp. Ass'n v. Azar*, 385 F. Supp. 3d. 1 (D.D.C. 2019).
148. Michelle M. Stein, *Hospitals Ask Supreme Court To Take Up 340B*, *Site Neutral Pay Cuts*, InsideHealthPolicy (Feb. 11, 2021; 12:57 PM ET), https://insidehealthpolicy.com/inside-drug-pricing-daily-news/hospitals-ask-supreme-court-take-340b-site-neutral-pay-cuts.
149. *American Hosp. Ass'n v. Azar*, 967 F.3d 818 (D.C. Cir. 2020), *petition for cert. filed* Feb. 12, 2021 (No. 20-1114).
150. Tom Mirga, *HRSA Says its 340B Contract Pharmacy Guidance Is Not Legally Enforceable*, 340B Report (Jul. 9, 2020); Notice Regarding Section 602 of the Veterans Health Care Act of 1992; Contract Pharmacy Services, 61 Fed. Reg. 43,549, 43,550 (Aug. 23, 1996); Notice Regarding 340B Drug Pricing Program-Contract Pharmacy Services, 75 Fed. Reg. 10,272 (Mar. 5, 2010).
151. Hailey Mensik, *HHS Orders 6 Drugmakers to Repay Providers for Violating 340B*, HealthcareDive (May 18, 2021), https://www.healthcaredive.com/news/hhs-orders-6-drugmakers-to-repay-providers-for-violating-340b/600353/. *See generally* Court Order to Dismiss, *American Hosp. Ass'n v. Azar*, No. 4:20-cv-08806-YGR (C.D. Cal. 2021); American Hosp. Ass'n Motion to Intervene, *Astrazeneca Pharm. v. Azar*, C.A. No. 21-00027-LPS (D. Del. 2021).
152. Edward R. Berchick *et al.*, *Health Coverage in the United States: 2018*, U.S. Census Bureau 3 (Nov. 2019), https://www.census.gov/content/dam/Census/library/publications/2019/demo/p60-267.pdf.
153. Pub. L. No. 111-148, § 1511, 124 Stat. 119, 252 (2010); *Minimum Value and Affordability*, Internal Revenue Serv., https://www.irs.gov/affordable-care-act/employers/minimum-value-and-affordability (last visited May 15, 2020).
154. Karen Pollitz *et al.*, *What's The Role of Private Health Insurance Today and Under Medicare-for-all and Other Public Option Proposals?*, Kaiser Family Found. (Jul. 30, 2019), https://www.kff.org/health-reform/issue-brief/whats-the-role-of-private-health-insurance-today-and-under-medicare-for-all-and-other-public-option-proposals/.
155. The Health Insurance Marketplaces were created under the ACA. *See* Pub. L. No. 111–148, 124 Stat. 119 (2010).
156. Many of those covered by government programs have some form of coverage through a private health insurer. This includes Medicaid enrollees covered by MCOs, which contract with MCOs, Medicare enrollees in Medicare Advantage Plans, and traditional Medicare enrollees who have supplemental private coverage, including Medicare Part D stand-alone prescription drug plans.
157. Cole Werble, *Health Policy Brief Series: Pharmacy Benefit Managers*, Health Affairs 1 (Sept. 2017), https://www.healthaffairs.org/do/10.1377/hpb20171409.000178/full/healthpolicybrief_178.pdf.

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Acknowledgments

The authors would like to acknowledge the significant contributions of Stefanie Doebler, Jennifer Plitsch, Beth Braiterman, Tara Carrier, Caitlin Koury, and Kassandra Maldonado.

Stefanie Doebler is co-chair of the firm's Health Care Practice Group, and a member of the Food, Drug, and Device Practice Group. Her practice focuses on health care compliance matters for pharmaceutical, biotech, and medical device clients. She provides advice related to advertising and promotion, fraud and abuse, transparency requirements, state law compliance and reporting regulations, interactions with health care professionals, Medicaid price reporting, and other aspects of federal and state regulation of pharmaceuticals, biologics, and medical devices. Ms. Doebler also advises on the development and implementation of health care compliance programs.
Tel: +1 202 662 5271 / Email: sdoebler@cov.com.

Jennifer Plitsch is co-chair of the firm's Government Contracts Practice Group, where her practice includes a wide range of contracting issues for large and small businesses in both defense and civilian contracting. Her practice involves advising clients on contract proposal, performance, and compliance questions as well as litigation, transactional, and legislative issues. She has particular expertise in advising clients on navigating 340B, Veteran Affairs, and Department of Defense pricing issues.
Tel: +1 202 662 5611 / Email: jplitsch@cov.com.

Beth Braiterman is an associate in Covington's Washington, D.C. office, where she is a member of the Health Care and Food, Drug and Device Practice Groups. Ms. Braiterman provides advice to pharmaceutical, biotech, and medical device clients on matters related to market access, pricing, reimbursement, value-based contracting, and advertising and promotion.
Tel: +1 202 662 5864 / Email: bbraiterman@cov.com.

Tara Carrier is an associate in Covington's Washington, D.C. office and a member of the Health Care and Data Privacy and Cybersecurity Practice Groups. Her practice focuses on a variety of health care compliance matters, including health information privacy and security, fraud and abuse, pricing and reimbursement, market access, and state law compliance.
Tel: +1 202 662 5019 / Email: tcarrier@cov.com.

Caitlin Koury is an associate in Covington's Washington, D.C. office and a member of the Health Care and Food, Drug and Device Practice Groups. Ms. Koury provides advice to life sciences companies on a variety of matters, including pricing and reimbursement, advertising and promotion, health information privacy and security, fraud and abuse, and market access.
Tel: +1 202 662 5649 / Email: ckoury@cov.com.

Kassandra Maldonado is an associate in Covington's Washington, D.C. office and a member of the Pharmaceutical Litigation & Investigations and White Collar groups. Ms. Maldonado provides advice to life sciences companies in a variety of matters including government pricing programs, the Bayh-Dole Act and 28 U.S.C. 1498, fraud and abuse, and congressional and regulatory pricing inquiries.
Tel: +1 202 662 5092 / Email: kmaldonado@cov.com.

Rujul Desai
Tel: +1 202 662 5427 / Email: rdesai@cov.com

Rujul Desai advises clients on drug pricing, market access, reimbursement, strategic contracting, and regulatory solutions for drugs, biologicals, devices, and diagnostics. He brings deep experience with biopharma, specialty pharmacy, and pharmacy benefit management ("PBM") companies.

Mr. Desai leads Covington client engagements across a wide range of U.S. and global market access and reimbursement issues, including optimizing new product launches, pricing, PBM and payer formulary access, value-based contracting, distribution network design, patient access and hub services, affordability programs, e-prescribing, digital health, and the use of health economic data and modeling.

Anna Kraus
Tel: +1 202 662 5320 / Email: akraus@cov.com

Anna Kraus advises on issues relating to the complex array of laws governing the health care industry. Her background as Deputy General Counsel to the U.S. Department of Health and Human Services ("HHS") gives her broad experience with, and valuable insight into, the programs and issues within the purview of HHS, including Medicare, Medicaid, fraud and abuse, and HIPAA privacy and security. Ms. Kraus is co-chair of Covington's Health Care Industry practice group.

Ms. Kraus regularly advises clients on Medicare reimbursement matters, particularly those arising under Part B and the Part D prescription drug benefit. She also has extensive experience with the Medicaid Drug Rebate program. She is a trusted adviser on health information privacy, security and breach notification issues, including those arising under the Health Insurance Portability and Accountability Act ("HIPAA") and the Health Information Technology for Economic and Clinical Health ("HITECH") Act.

Kristie Gurley
Tel: +1 202 662 5454 / Email: kgurley@cov.com

Kristie Gurley advises pharmaceutical and biotechnology companies on marketing authorization and market access issues, including with respect to product development, product approval and launch, pricing and reimbursement activities, advertising and promotion, payer communications, value-based contracting, and related areas. Ms. Gurley routinely advises on regulatory compliance and enforcement risk, commercial transactions, and administrative and legislative policy opportunities.

Covington & Burling LLP

One CityCenter, 850 Tenth St NW, Washington 20001-4956, USA
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