Pricing & Reimbursement

2020

Third Edition

Contributing Editor:
Grant Castle

glg global legal group

Global Legal Insights
Pricing & Reimbursement

2020, Third Edition
Contributing Editor: Grant Castle
Published by Global Legal Group

GLOBAL LEGAL INSIGHTS – PRICING & REIMBURSEMENT

2020, THIRD 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 978-1-83918-062-0
ISSN 2517-6463

Printed and bound by TJ International, Trecerus Industrial Estate, Padstow, Cornwall, PL28 8RW
2020

CONTENTS

Preface	Grant Castle, *Covington & Burling LLP*	
General chapter	*Reimbursement and Funding of Hospital-Based Drug Therapies* Stephen Hull, Robert Reidy & Kaytlyn Oliver, *Hull Associates LLC*	1
Country chapters		
Australia	Greg Williams, Colin Loveday & Sheena McKie, *Clayton Utz*	16
Belgium	Pieter Wyckmans & Michiel D'herde, *Quinz*	31
Brazil	Rodrigo Augusto Oliveira Rocci, *Dannemann, Siemsen Advogados*	46
Canada	Teresa Reguly, Eileen McMahon & Manpreet Singh, *Torys LLP*	59
China	Nicolas Zhu, *CMS China*	72
France	Catherine Mateu, *Armengaud Guerlain*	80
Germany	Dr. Ulrich Reese & Carolin Kemmner, *Clifford Chance*	98
India	Archana Sahadeva, *Sahadeva Law Chambers*	113
Ireland	Marie Doyle-Rossi & Maree Gallagher, *Covington & Burling LLP*	125
Italy	Sonia Selletti & Mauro Putignano, *Astolfi e Associati, Studio Legale*	135
Japan	Kazuhiro Kobayashi, *Oh-Ebashi LPC & Partners*	150
Korea	Kyungsun Kyle Choi & Yunjoh Lee, *Kim & Chang*	161
Netherlands	Koosje van Lessen Kloeke, *Leijnse Artz*	167
Poland	Agata Zalewska-Gawrych & Marta Jagodzińska, *Food & Pharma Legal Wawrzyniak Zalewska Radcy Prawni sp.j.*	182
Spain	Jordi Faus, Lluís Alcover & Joan Carles Bailach, *Faus & Moliner*	188
Sweden	Camilla Appelgren, *Mannheimer Swartling Advokatbyrå* Odd Swarting, *Cirio Advokatbyrå*	207
Switzerland	Dr. Oliver Künzler, Dr. Carlo Conti & Dr. Martina Braun, *Wenger Plattner*	218
United Kingdom	Grant Castle, Brian Kelly & Raj Gathani, *Covington & Burling LLP*	227
USA	Rujul Desai, Anna Kraus & Kristie Gurley, *Covington & Burling LLP*	240

PREFACE

Welcome to the 2020 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 19 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, explain significant changes and key trends. Authors also discuss policy issues that affect pricing and reimbursement decisions, including 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 the 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 seek to market medicines and the payers that must allocate healthcare budgets and spend taxpayer money judiciously. Those budgets are becoming more and more limited, at a time when 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 the COVID-19 pandemic and the global recession that has already started.

From the innovative industry perspective, we have seen changes in the focus of its 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 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 simply 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, focussing 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 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.*, "*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
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Reimbursement and Funding of Hospital-Based Drug Therapies

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Hull Associates LLC

Abstract/synopsis

It has been well established that the growth of specialty pharmaceuticals, which today represent approximately 45% of the United States pharmaceutical market, has been accompanied by greater spending by hospitals on inpatient drugs (Healthcare Distribution Alliance, 2019) (NORC, 2019). In part, this shift may coincide with greater numbers of physician-administered therapies for rare and difficult-to-treat diseases. Analyses of US spending on inpatient drugs have found that annual spending increased almost 10% per hospital admission between 2015 and 2017 (NORC, 2019).

But are the systems of reimbursement for inpatient care designed to address these costs? Because many hospital environments are reimbursed via bundled payment methods, innovator companies selling to hospitals must address a completely different set of challenges from prescription pharmaceuticals – in particular previously determined, fixed payments for hospital stays, and in some international markets, capped annual budgets that limit overall spending on such products.

Globally, the most common scenario of payment in hospitals is the use of Diagnosis Related Groups (DRG) to pay a predetermined amount for an entire patient discharge, which reflect the primary diagnoses and procedures provided to the patient. But DRG systems create obvious disincentives for adoption of promising new therapies and diagnostics since hospitals often cannot cover their additional costs. Starting with the US in 2000, special pathways to address the high additive costs of new innovative drugs were developed in a number of DRG payment systems (106th Congress, 2000). England, Germany and France all subsequently implemented systems of add-on payment for certain inpatient innovations as part of their DRG type-systems.

Drugs that achieve supplemental payment are often indicated for rare or severe diseases. But different requirements and lack of transparency in health technology assessments (HTAs) for these products varies by country, which can lead to delays in reimbursement and patient access for new drugs (Akehurst, 2017). Variability may even be greater for hospital-based therapies.

This chapter describes the special pathways established for high-cost, specialty drug products in the United States, Germany, France, and England along with recent developments that directly impact the evidence portfolios that manufacturers need to anticipate to succeed in today's markets.

Country	Inpatient Reimbursement System	Mechanism for New Innovations
Germany	Inpatient: G-DRG System	"NUB" Innovation Clause, ZE Supplements
France	Inpatient: GHS System	*Liste en Sus*, add-on payment for drugs
England	Inpatient/Outpatient: HRGs	High Cost Drugs List, Cancer Drugs Fund
United States	Medicare: DRGs Commercial: DRGs, *Per Diem*, Discounted Charges	Medicare: New Technology Add-on Payment (NTAP) Commercial: Negotiated rates

USA reimbursement schemes – inpatient hospital setting

Medicare

In the United States, the cost of Medicare inpatient care is covered by a patient's DRG payment for each admission in over 3,000 hospitals nationwide (Centers for Medicare & Medicaid Services, 2020). Because DRGs pay for admissions with a pre-determined, bundled payment that is calculated from prior year data, there is a time lag in the update to payments for new innovations. Hence, new innovations may struggle to gain adoption until DRG payment rates for admissions reflect the added costs of the drug. For small volume therapies used in select patients, it is quite possible the DRG rates for large volume conditions will never adjust upward sufficiently to compensate their costs.

Section 533 of the Medicare, Medicaid, and SCHIP Benefits Improvement and Protection Act of 2000 (BIPA) mandated that Medicare implement an add-on payment to adequately cover the costs of new innovations introduced in the hospital setting (106th Congress, 2000). The core concept of the US legislation was to create a bridge for promising innovations to receive add-on payment to the DRG payment, while Medicare collected data on the overall costs of admissions so it could then make a permanent assignment to an appropriately paying DRG.

While the original statute required Medicare to pay additionally for qualified new drugs, it did not specify the exact criteria for eligibility. This was refined in 2001 when CMS used its authority under the statute to provide the process and criteria for new technology add-on payments (NTAP) (Centers for Medicare & Medicaid Services, 2001). Additional modifications to the statute were implemented under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) which amended the NTAP criteria (Medicare Modernization Act, 2003). The current eligibility criteria are:

(1) the drug or technology must be new;
(2) the drug, medical service or technology must be costly such that the DRG rate otherwise applicable to discharges involving the medical service or technology is determined to be inadequate; and
(3) the drug, service or technology must demonstrate a substantial clinical improvement over existing services or technologies (Centers for Medicare & Medicaid Services, 2019).

"New" under CMS rules means within two to three years following market introduction (Centers for Medicare & Medicaid Services, 2001). Drugs that are considered substantially similar to older technologies are not considered new (Centers for Medicare & Medicaid Services, 2010).

Demonstrating inadequate payment involves a formula for the applicable DRG payment groups, based on the lesser of 75% of the standardised amount increased to reflect the difference between costs and charges, or 75% of one standard deviation beyond the geometric mean standardised charge for all cases to which the new technology is assigned (Centers for Medicare

& Medicaid Services, 2019). Cost thresholds for each MS-DRG are published annually on the Data Files webpage of the CMS website under each year's Inpatient Prospective Payment System (IPPS) final rule (Centers for Medicare & Medicaid Services, 2019).

Determining substantial clinical improvement under the Medicare definition can be complex. Drugs are considered eligible if:

- the drug offers a treatment option for a patient population unresponsive to, or ineligible for, currently available treatments; or
- use of the drug significantly improves clinical outcomes for a patient population as compared to currently available treatments (Centers for Medicare & Medicaid Services, 2001).

Applicants must submit data to CMS verifying that the average charge per case exceeds the MS-DRG cost threshold. CMS makes add-on payments only for individual cases that are more costly. The payment caps for traditional NTAP approved drugs currently are the lesser of:

(1) 65% of the cost of the new drug; or
(2) 65% of the excess cost compared to the standard DRG payment (Centers for Medicare & Medicaid Services, 2019).

Recently, CMS established an alternative pathway for NTAP approval. This alternative pathway applies to a special class of anti-microbial drugs designated by the FDA as a Qualified Infectious Disease Product (QIDP) (Centers for Medicare & Medicaid Services, 2019).

QIDPs are antibacterial or antifungal drugs for human use intended to treat serious or life-threatening infections, including those caused by an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens, or any qualifying pathogens listed by the US Secretary of Health and Human Services (HHS) (United States House of Representatives, 2020).

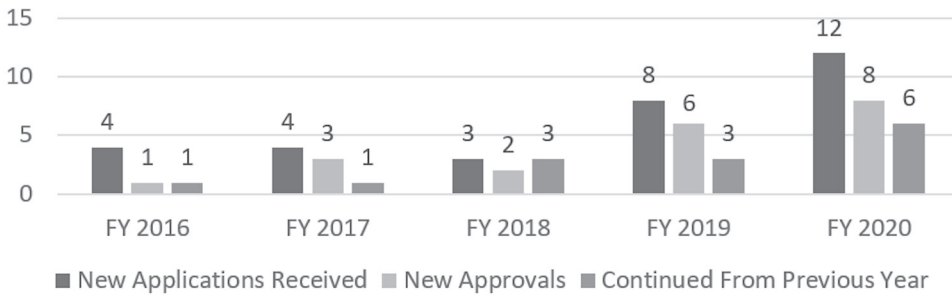
Under this new alternative NTAP pathway, such drug products given a QIDP designation by the FDA will be considered new and not substantially similar to an existing technology for purposes of NTAP payment under the IPPS, and will not need to meet the previously defined "newness" criterion that it represents an advance that substantially improves, relative to technologies previously available (Centers for Medicare & Medicaid Services, 2019).

Applicants seeking NTAP approval through the alternative QIDP pathway must submit data to CMS verifying that the average charge per case exceeds the MS-DRG cost threshold, and CMS will make add-on payments only for individual cases that are more costly. For FDA-designated QIDPs, the payment caps for alternative NTAP approved technologies are currently the lesser of:

(1) 75% of the cost of the new service or technology; or
(2) 75% of the excess cost compared to the standard DRG payment (Centers for Medicare & Medicaid Services, 2019).

As the NTAP legislation approaches the end of its second decade, there is debate as to whether it has had any true impact, with only a small volume of drug products deemed eligible. By September 30, 2007, 28 applications had been received, eight had been approved – and only one of these was a drug product, drotrecogin alpha (activated) protein for treatment of severe sepsis associated with acute organ dysfunction (Bockstedt, 2010). But now, in 2020, there are currently 14 newly approved or continually approved drugs that qualify for NTAP (Centers for Medicare & Medicaid Services, 2019) (Centers for Medicare & Medicaid Services, 2018). Two drugs designated as QIDPs are currently approved for NTAP: VABOMERE™ and ZEMDRI™ (Centers for Medicare & Medicaid Services, 2019).

Applications and approvals for new technology add-on payments (drugs only), United States FY 2016–FY 2020



The drugs newly approved for NTAP in FY 2020 are:

- AZEDRA® – a treatment for cancers known as heochromocytoma and paraganglioma.
- CABLIVI® – therapy for thrombotic thrombocytopenic purpura, a blood disorder.
- ELZONRIS™ – a drug used to treat blastic plasmacytoid dendritic cell neoplasm, a cancer of the blood and bone marrow.
- ERLEADA™ – a breakthrough treatment for prostate cancer.
- SPRAVATO® – a nasal spray medication for treatment resistant depression.
- XOSPATA® – medication used to treat acute myeloid leukemia that is resistant to other treatments.
- JAKAFI™ – treatment for bone marrow disorders.
- BALVERSA™ – second-line treatment for locally advanced or metastatic urothelial carcinoma.

Medicaid

Medicaid reimbursement of hospital care varies by state, with some states applying a bundled, DRG system known as the All Patient Refined – Diagnosis Related Groupings (APR-DRG) and others relying on a *per diem* or fee-for-service model (Henry J Kaiser Family Foundation, 2012). As of November 2018, 37 states rely on DRGs, eight established *per diem* rates, and one state uses a combination of the two methods for inpatient hospital services. The remaining five states use another approach, such as a per stay payment or cost-based reimbursement (MACPAC, 2018).

Each state government determines the amount of payment. Unlike commercial or Medicare plans, the payments are often considered to be below the cost of care (Reinhardt, 2009).

Alongside the system of reimbursement for hospitals is the outpatient 340b drug discounting programme, which provides hospitals access to discounted drugs for low income patients. This programme has been criticised as providing hospitals with undue financial margins, without any mandate to pass on savings to patients (US Government Accountability Office, 2011). Hence, it may help hospitals adjust to disproportionately low Medicaid payments, but it does not help support manufacturer introductions of innovations in that setting.

Private commercial payers

Under commercial plans, payment for inpatient pharmaceuticals can also be bundled with no separate payment, although generally commercial payment rates are higher than Medicare rates. Only 23% of payers, based on covered lives, are reimbursed based on the Medicare model, an 11-percentage point decline from the previous year (Magellan Rx Management, 2019).

The system of discounted charges has been criticised as providing hospitals with excessive margins for dispensing and prescribing drugs, both physician-administered and prescription. One recent study found average hospital mark-ups for 20 leading drugs to be 487% (Moran Company, 2017). When compared to the reported costs for those same cases, the authors found average hospital reimbursement by the commercial payers was 252% above costs.

Thus, the commercial payer methods of reimbursement may provide an avenue of payment that helps offset losses for the same drugs used for other patients whose DRG-based reimbursement shifts risk for the drug costs onto the hospital. The net impact of these two very different systems of payment regularly leads to the phenomena of "cost shifting" within hospitals, where the revenue for certain commercially insured patients helps to balance a hospital's books for capped reimbursement under DRG systems, both public and private.

Germany's NUB process and hospital therapies

With European Union or national drug regulatory approval, a drug can be adopted by German hospitals. In 2011, the Act on the Reform of the Market for Medical Products (*Arzneimittelmarkt-Neuordnungsgesetz*, AMNOG) mandated a G-BA (Joint Federal Committee) review prior to local Statutory Health Insurance (SHI) reimbursement for all new drugs. The G-BA is the highest authority in German healthcare and is the key decision-maker for assignment of premium drug pricing. Otherwise the new therapy is reimbursed at the level of the standard therapy.

Clinical evidence presented in the AMNOG dossier is usually the same evidence used for regulatory drug approval. The G-BA, with the support of the Institute for Quality and Efficiency in Health Care (IQWiG), subsequently analyses the potential additional patient benefit based on the following parameters:

- **Clinical**: mortality, morbidity, quality of life and side effects.
- **Economic**: duration of therapy, dosage and cost of drug/yearly therapy cost, if applicable, size of target patient group based on clear definition of indication, any additional/accompanying health services needed with the new therapy.

The AMNOG dossier evaluation and subsequent discussion in the G-BA, including hearings with experts from industry, physicians' and patients' associations, have a fixed timeframe of six months (Joint Federal Committe (G-BA), 2017).

Hospital adoption initially depends on clinicians, but long-term adoption depends on adequate reimbursement. Larger university hospitals may adopt new drugs before reimbursement is established to ensure the availability of an innovative therapy to patients in need. Long-term, all types of hospitals need to achieve cost-covering reimbursement via the German DRG system.

G-DRGs and NUB innovation payment

The German DRG system (G-DRG) for hospital payment was originally based primarily on the Australian Refined DRG system, with a number of modifications, including the possibility of both short-term and permanent supplemental add-on payments for certain therapies.

One G-DRG payment usually covers all costs of a patient's hospital stay, including treatment, drugs, and devices. As of 2020, nursing fees are excluded from this bundle and are paid separate daily fees. Hospitals must also follow annual hospital budgets, which are calculated according to annual case mix.

Permanent implementation of new (and higher) tariffs for innovative drugs into the DRG system takes at least three years. Temporary bridge funding is possible for new hospital

drugs under the NUB Innovation Clause (*Neue Untersuchungs- und Behandlungsmethoden*). NUB funding must be applied for each year, by each hospital using the new drug (Cornelia Henschke, 2013). To qualify, drugs must fulfil the following criteria (InEK Institute for Remuneration System in the Hospital, 2018 to 2020):

(1) not properly reimbursed via existing coding and fees;
(2) have been used for less than four years in German hospitals; and
(3) cause significant additional costs for the hospital stay.

InEK (*Institut für das Entgeltsystem Im Krankenhaus*), the agency that administers the German DRG system, has never published a threshold for determining "additional cost" but a commonly known unofficial threshold is €500 per case.

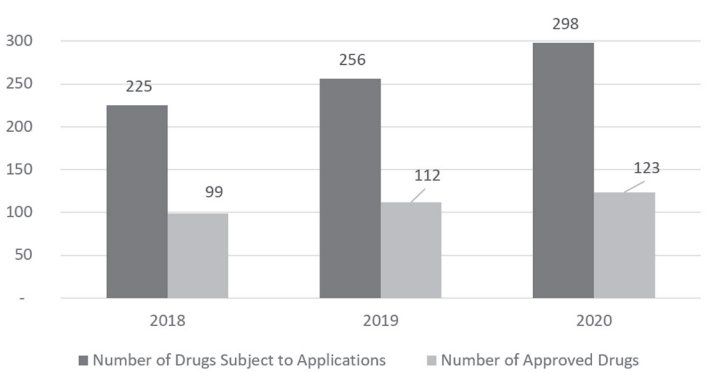
Hospitals apply individually for NUB funding through the InEK. Once approved, NUB status allows each hospital to negotiate one-year supplemental fees with local Statutory Health Insurance (SHI) funds (IGES, 2018). Each hospital must reapply for each NUB supplement, annually, and products are typically eligible for up to four years. Notably, there is no official time limitation on eligibility for NUB, and it can widely differ between products.

To date, oncologic drugs and antimycotics make up the majority of drugs approved for NUB. Severity of illness, demonstrated proven patient benefit and cost are the major success factors in obtaining NUB funding.

Following the NUB process, InEK then reviews data from "calculation" hospitals to determine the appropriate, long term integration into the G-DRG system based on the total cost of associated care. Hence, a drug may be integrated into the cost structure of identified G-DRGs or be assigned a permanent supplemental payment.

As the trend depicted below shows, drug-related NUB applications, as well as approvals, have increased annually. Overall, applications from 2018 to 2020 have experienced a 43% success rate.

Drug-related NUB applications and approvals, 2018–2020



(InEK Institute for Remuneration System in the Hospital, 2018 to 2020)

ZE permanent supplemental payments

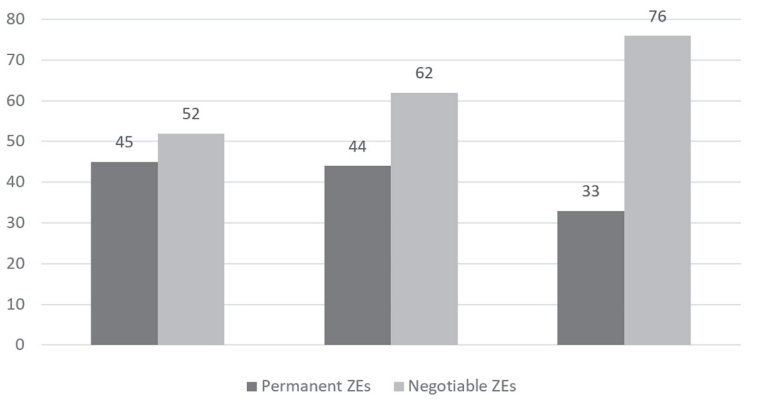
If drugs do not "fit" into the DRG structure, InEK may consider ZE (*Zusatzentgelt*) permanent supplemental payment. ZE payments are used for drugs with multiple DRG assignments.

ZE services are nationally designated but issued in two forms: one with a nationally fixed reimbursement price; and a second that is locally negotiated (similar to the NUB).

Eligibility requirements for a ZE are:
- clearly defined procedure (with OPS code);
- used with multiple DRGs without fixed association to any DRG; and
- relevant cost for the total DRG system, especially the hospitals rendering the service.

While permanent supplemental payments slightly decreased over the past few years, negotiable ZEs for drugs are increasing. Drug related ZEs often are published with a whole list of reimbursable amounts depending on dosage (if applicable) and are reviewed annually.

InEK ZE assignments for inpatient drugs, 2018–2020



(InEK Institute for Remuneration System in the Hospital, 2018 to 2020)

The French *Liste en Sus* and Hospital Funding

In France, the High Authority on Health (*Haute Autorite de Sante*, HAS) review pathway is mandatory for hospital use of all new drug products. Manufacturers must submit a clinical dossier to the HAS Transparency Committee, which analyses the severity of the pathology, the drug efficacy, the side effects, and positioning.

The HAS applies an evidence review process and assigns an appraisal of "Medical Services Rendered" (SMR) and "Improvement to Medical Services Rendered" (ASMR). The SMR takes into account the seriousness of the pathology for which the drug is indicated and data specific to the drug itself in a given indication (efficacy and adverse effects; positioning in the therapeutic strategy – particularly in relation to other available therapies – and existence of therapeutic alternatives; and public health relevance). The SMR can be important, moderate, low or insufficient. The ASMR corresponds to the therapeutic progress made by a drug. Depending on the assessment, several levels of ASMR have been defined on a five-point scale, where only products with an ASMR level III or better are eligible for *Liste en Sus* supplemental payment.

If expected drug sales are over €20 million, a health economic review will also likely be required.

If the HAS review is positive, the drug can either be listed on the list for community (*Homologation assurés sociaux*) and/or on the list for hospitals (*Homologation collectivité*).

The *Comité économique des produits de santé* (CEPS) will review the economic dossier provided by the manufacturer:
- The CEPS will negotiate the tariff with manufacturer. Budget impact models are critical.
- For ASMR I to III, drugs are eligible for a listing on the *Liste en Sus*, paid in addition to the GHS.

- In some cases, some hospital pharmacies can deliver drugs to ambulatory patients for home use. These drugs are listed on the "Retrocession list".
- Reimbursement rates will depend on the SMR level in the outpatient setting.

Each drug reviewed by the HAS CT receives an SMR and ASMR according to the clinical evidence submitted, which will determine the level of reimbursement.

- SMR (*Service Medical Rendu*) is written for drugs at the time of the review, which can be confirmed, upgraded or downgraded for old drugs according to available clinical studies. New drugs also receive a rating (major/important, moderate/low, insufficient).
- ASMR (*Amelioration de Service Medical Rendu*) reviews are written for drugs that are improvements on existing medications or variations on existing treatments (*HAS Haute Autorite De Sante*, 2014).

SMR and ASMR reviews must be sufficiently favourable for the new drug to be listed on the *Liste des Médicaments Remboursables* (Reimbursed Drugs List), which allows the drugs to be reimbursed.

Each French hospital reviews new drugs via internal technology appraisal committees and may take a few months following approval of reimbursement in France. These committees include physicians, pharmacists and finance managers. Medico-economic evidence is welcomed by finance managers in order to understand incomes and costs of standard *versus* new protocols.

Price negotiations are more substantial in public than in private hospitals. Typically, there is little price negotiation with private hospitals, where acquisition prices are close to the *Liste des Médicaments Remboursables* (Reimbursed Drugs List). Conversely, in public hospitals, there are significant negotiations for some of the drugs listed.

Hospital Inpatient Payment for Drugs

French inpatient or outpatient acute hospital services are financed through a payment-per-case prospective payment system, using two related groupings. Cases are assigned to a DRG-like type of classification among 700 *Groupes Homogènes de Malades* (GHM), which has severity adjustment for comorbidities. A nationally fixed tariff (*Groupe Homogène de Séjours*, GHS, Homogeneous Discharge Groups) is then applied to each GHM.

The GHS tariffs are used to pay public hospitals and a portion of costs in private hospitals. The GHS assignment of each patient discharge reflects a combination of diagnosis (ICD-10) and procedure (CCAM) codes.

A unique feature of the French system is the tendency to pay for a large number of drugs via add-on, supplemental payment. These drugs are listed on the *Liste en Sus*, which is published annually.

Unlike the US and German temporary add-on payments, the *Liste en Sus* technically does not have a time limitation, and some products can remain listed for years.

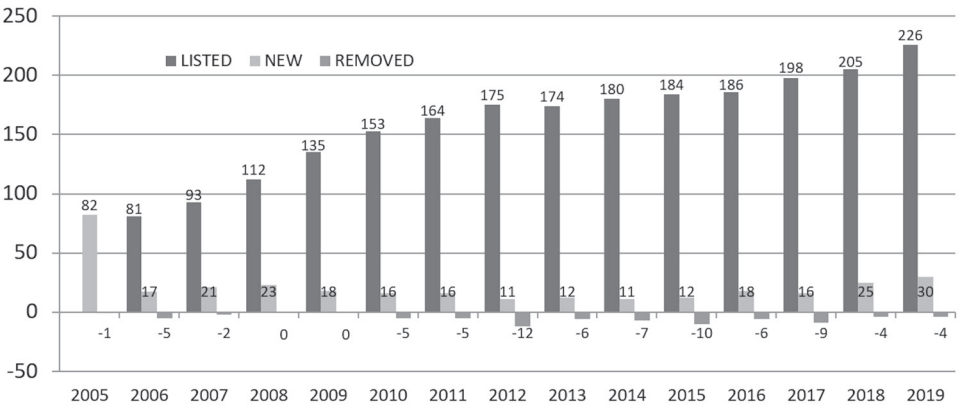
The *Liste en Sus* mostly includes anticancer, anti-inflammatory, auto-immune and immunoglobin drugs. It is reserved for drugs that are not used uniformly for all patients in a GHS, and where the cost is considered significantly higher than the applicable GHS payment. Nevertheless, drugs are reassessed every five years.

There are five conditions that the hospitalisation council sets out for inclusion on the *Liste en Sus*:

(1) expected usage of the drug;
(2) evidence level appraised for the drug (assuming an ASMR above III);
(3) frequency of the new drug prescriptions within the GHS is below 80%;
(4) cost is more than 30% of the GHS tariff; and
(5) cost is similar to that of comparable products (*Ministère des Affaires sociales et de la Santé*, 2018).

There has been a consistent increase in the number drugs listed on the *Liste en Sus*, and as of 2019, there are total of 256 products listed, 30 of which are newly listed. From 2011 to 2019, the number of listed drugs increased by over 42%.

Drugs listed on the *Liste en Sus*



(Liste en Sus, 2019)

Provision of high-cost drugs to the English NHS

In England, the Health Resource Groups (HRG) system is comprised of a case-mix payment system for all hospitals, both public and private. There is a national tariff of fixed prices for hospital admissions, reflective of averages nationwide. Each specific procedure is assigned a reference cost.

High cost drugs and devices account for around 25% of expenditures on specialised care in England. To ensure that providers and commissioners of health services can deliver the best value of care to patients, NHS England continues to implement measures introduced in recent years which are designed to reduce excess spending and maximise clinical benefit.

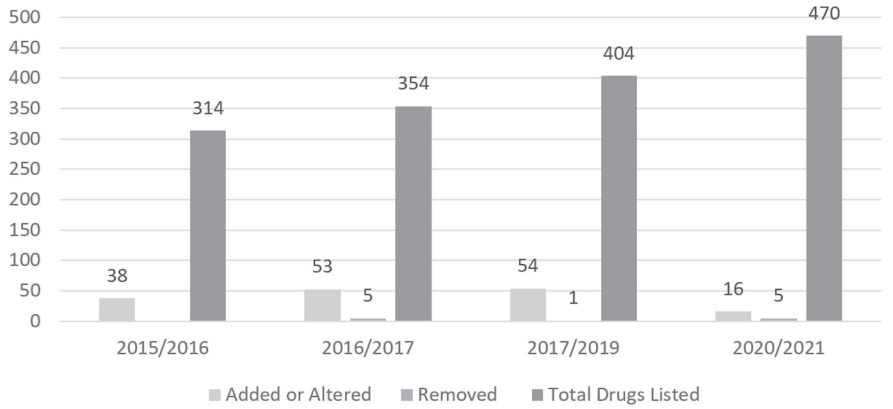
In England, drug add-on payments are negotiated locally with Clinical Commissioning Groups (CCGs) or designated nationally for specialised services. The High Cost Drug List in the NHS is intended for specialised products whose use is concentrated in a relatively small number of centers. The purpose of this list is to enable additional payment by NHS England to the hospital trust for inpatient or outpatient-dispensed, high-cost drugs (NHS England and NHS Improvement, 2016).

As in all markets, eligibility for separate payment depends on several requirements. Requirements for the High Cost Drug list have historically been:

(1) The drug and its expected associated costs of care are disproportionately high compared to the other expected costs of care within the HRG, which would affect fair reimbursement.
(2) There is, or is expected to be, more than £1.5 million spend or 600 cases in England *per annum*.

Drugs which no longer meet the criteria, and so will not lead to systematically incorrect reimbursement of providers will be considered for removal from the high cost list (Department of Health and Social Care, 2012).

High cost drug list, England, 2015/2016–2020/2021



- In the 2015/2016 time period, a total of 314 drugs were listed, 38 were added or altered (NHS England and Monitor, 2014).
- For the 2016/17 list, 53 were added or altered, and five were removed, leaving a total of 354 drugs listed (NHS England and Monitor, 2016).
- For 2017/2019, 54 drugs were newly added or altered to the inpatient High Cost Drug List. Only one drug was removed. There were 404 drugs listed (NHS England and Monitor, 2017).
- For 2020/2021, 16 drugs were proposed to be added to the inpatient High Cost Drug List. Five drugs were proposed to be removed. There are a total of 470 drugs listed (NHS England and Monitor, 2020).

Though it is encouraged, prior appraisal by the National Institute for Health and Care Excellence (NICE) is not a requirement for listing on the High Cost Drugs list.

NHS England recommends payments for high cost drugs excluded from National Tariff be made on the basis of a pass-through of the actual price charged to providers. A central repository of prices for excluded drugs, known as Pharmex, is currently being developed to provide robust data for effective procurement. Providers are mandated to provide Pharmex data.

An online clinical decision support tool (known as "Blueteq") was implemented in 2015/16 as NHS England's standard electronic contractual prior approval system and covers a range of high cost drugs excluded from tariff.

Starting in 2016/17, the scope of items covered by Blueteq has been extended to *all* high cost drugs excluded from tariff where NHS England Clinical Commissioning Policies or NICE Technology Appraisals exist, or where there is variation in uptake, or significant financial risk (NHS England, 2015).

Cancer Drugs Fund

The Cancer Drugs Fund (CDF) was initially established in 2011 as a temporary solution to enable access to cancer drugs that are not routinely available through the NHS. The budget for the CDF increased annually in the initial years, but actual spending continued to exceed its budget. The Fund was originally scheduled to conclude in 2014 but was later extended to the end of March 2016, and then taken over by NHS England and a new appraisals approach was enacted (NHS England, n.d.). The new process offers managed access arrangement to new treatments, while additional evidence is collected to address clinical uncertainty. The additional evidence is used to help NICE to decide if a new treatment should be routinely funded.

NICE appraises all new systemic anti-cancer therapy drug indications expected to receive a marketing authorisation. The process aims to publish draft guidance before a drug receives marketing authorisation, with final guidance published within 90 days of marketing authorisation. The appraisal process is based on the NICE Technology Appraisal, but with additional specific amendments for the Cancer Drug Fund (National Institute for Health and Care Excellence, 2014) (National Institute for Health and Care Excellence, 2016).

The process allows NICE to make one of three recommendations:

- recommended for routine commissioning – 'yes';
- not recommended for routine commissioning – 'no'; or
- recommended for use within the CDF (new).

"*Recommended for use within the CDF*" can be applied for drugs for which NICE considers there to be "plausible potential" to meet the criteria for routine commissioning, but there remains significant clinical uncertainty.

For those drugs that have received either a "yes" or a draft recommendation for use within the CDF, interim funding is available at the point of marketing authorisation. However, in order to receive this funding, pharmaceutical manufacturers must agree to the expenditure control mechanism (NHS England Cancer Drugs Fund Team, 2016).

Since the new approach to funding cancer drugs began in July 2016, approximately 41,000 patients have been registered to receive treatment with 79 drugs, treating 160 different cancer indications (NHS England Cancer Drugs Fund Activity Update, 2020). As of May 2020, 32 drugs covering 57 indications are listed (NHS England, 2020).

The CDF budget remains fixed at £340 million (NHS England Cancer Drugs Fund Activity Update, 2020). If this fixed budget is exceeded, the additional cost is paid back by companies who generate income from the CDF via a proportional rebate to NHS England and NHS Improvement. In December 2019, the UK government promised to extend the CDF into an 'Innovative Medicines Fund' which could add an additional £160 million. There are still questions about what drugs outside of cancer could qualify, with indications suggesting candidates may be from medicines selected for the Early Access to Medicines Fund (EAMS) – a pre-licensing indicator of promising innovation given by the Medicines and Healthcare products Regulatory Authority (MHRA).

Recent Decisions on CAR-T Therapies

Currently CAR-T is not routinely commissioned in the UK. It is only available through the CDF for a limited period of around two years, as further data is collected for reappraiasal. The CDF will only pay for the CAR-T drug; all other hospital-related costs are commissioned by NHS England Specialised Services, as in the case for allogeneic haematopoietic stem cell transplantation (i.e. the service specification sets out an approach to defining the pathway as commencing from decision to transplant [30 days] and ends 100 days following the transplantation procedure). After this, commissioning responsibility returns to CCGs (NHS England, 2018).

Conclusions

While there is growing attention to the costs of prescription pharmaceuticals, hospital dispensed specialty pharmaceuticals may face increasing challenges to justify premium prices under increasingly constrained methods of hospital payment. Notably, DRG payment systems are adding tighter controls on overall drug spending and may, in some markets, be very reluctant to provide supplemental add-on payment.

In the USA, hospitals help compensate under-reimbursement for some inpatient

pharmaceuticals via higher markups on other patients. But in single payer environments, such as Britain or Germany, no such cost shifting is possible.

Some systems have maintained special pathways to fund cancer drugs specifically, which has, to some extent, created a safe harbour in some markets. However, these pathways typically place limitations on drug prices.

In those markets in particular, manufacturers face a multi-tiered economic challenge and must prove therapeutic value from an economic standpoint at both societal and provider levels. Robust economic modelling, based on well-designed comparative clinical trials, has thus become a necessity for market success. In addition, for the newest generations of immune-oncology therapies, hospitals simply cannot afford acquisition of the product. In these cases, some manufacturers are obliged to negotiate direct payment agreements with insurers so that costs can be amortised over time, and in some instances, payments can be linked to therapeutic outcomes.

* * *

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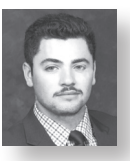

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Australia

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Abstract

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

Market introduction/overview

Australia is a nation with a population of approximately 25.5 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 2019, is approximately 37 years, compared to approximately 35 years in June 1999. The Australian population is also growing – the annual population growth rate for the year ending 30 June 2019 was 1.5%, roughly two-thirds of the population growth is attributable to immigration and one-third to natural increases.

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

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

worse health outcomes. The life expectancy of an Aboriginal or Torres Strait Islander person is approximately 10 years less than that of the average Australian.

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

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

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

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

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

The total Commonwealth budget for health, aged care and sport for 2019–2020 was approximately AU$104 billion (AU$435 billion over four years). Of the AU$435 billion provisioned for in the forward estimates (the next four years), the Government has provisioned AU$40 billion for over 5,000 life-saving and life-changing medicines products, including an additional AU$331 million for new and amended listings in the 2019–2020 budget. At an overall cost of approximately AU$11 billion, the PBS is the third-largest item in the health budget after Medicare (more than AU$24 billion, with a commitment to increasing Medicare spending by AU$6 billion to AU$30.7 billion in 2022–2023) and aged care (this year, with a commitment to record funding of AU$21.6 billion).[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. Those rebates, which are discussed in greater detail in section "Policy issues that affect pricing and reimbursement" below, are currently estimated to be worth AU$3 billion.[4]

Pharmaceutical pricing and reimbursement

Regulatory classification

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

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

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

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

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

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

A further separate programme is the Life Saving Drugs Program (**LSDP**), which is a programme through which the Government subsidises high-cost transformational therapies for rare diseases which do not meet the usual expectations of the PBS for cost-effectiveness. The LSDP sits outside the PBS and is managed through individual agreements between the sponsors of such products and the Commonwealth. There are currently 16 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 2020, is up to AU$41.00 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$4.60); and an additional fee for ready-prepared items (currently AU$1.25). Neither of these fees can be added to increase the amount payable by the patient above the co-payment amount.
- Some brands of medicines have a price premium or brand premium. This is an additional amount which represents the difference between the price at which the sponsor is prepared to sell and the price which the Government is prepared to subsidise. Government policy is to only allow such arrangements in limited circumstances, typically where an innovator medicine and one or more generic brands of the same drug are listed on the Schedule.

The legislation also provides for a "Safety Net". If a patient's prescriptions exceed the relevant Safety Net Threshold for a calendar year, general patients pay for further PBS prescriptions at the concessional co-payment rate, and concessional patients will receive PBS prescriptions at no additional charge for the remainder of the year. On 1 January 2020, the Safety Net Thresholds were lowered and current Safety Net thresholds (as at 1 January 2020) are AU$316.80 for concession card holders and AU$1,486.80 for general patients.

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

Registration/listing and decision-making

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

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

The Pharmaceutical Benefits Advisory Committee (**PBAC**) is established by the National Health Act to act as an advisor to the Department of Health and Minister for Health in relation

to the listing and pricing of pharmaceutical items on the PBS. The PBAC's functions include making recommendations to the Minister as to the drugs which it considers should be made available as pharmaceutical benefits on the PBS, as well as providing advice on issues relating to the administration of the PBS more generally.[15] The Minister may not list a pharmaceutical item on the Schedule unless the PBAC has recommended that the Minister do so.

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

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

(a) comparative health gain – including magnitude and clinical importance of effect;
(b) comparative cost-effectiveness – including on a cost-effectiveness or cost-minimisation basis; as well as a consideration of comparative costs including healthcare resources not limited to cost of the drug;
(c) patient affordability in the absence of PBS subsidy;
(d) predicted use in practice and financial implications for the PBS (projected annual net cost); and
(e) predicted use in practice and financial implications for the Australian Government health budget (projected annual net cost).

The Department of Health has also published a "Procedure guidance for listing medicines on the Pharmaceutical Benefits Scheme" (version 1.8, June 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, are bioequivalent or biosimilar, which are listed on the PBS, or if there

are no brands of pharmaceutical items having another listed drug in the same therapeutic group. Generally speaking, F1 drugs are "innovator" or "single brand" drugs, which are still on patent and for which there is no suitable alternative for patients. Drugs on F2 are drugs for which there are multiple brands; that is, drugs that are off patent and operating in a competitive market with generic or biosimilar brands available.

Appeals

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

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

(a) resubmission to the PBAC (where a sponsor intends to challenge a decision made by the PBAC);
(b) independent review (a form of merits review); or
(c) judicial review.

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

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

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

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

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

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

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

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

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

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

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

- automatic price reductions which apply on the 5th, 10th and 15th anniversary of listing for drugs on the F1 formulary (5%, 10% and 5%, respectively),[27] subject to a Ministerial discretion;
- statutory price reductions on the first listing of a bioequivalent or biosimilar brand of a pharmaceutical item (currently 25%, in place during the term of the Strategic Agreement with Medicines Australia, until June 2022), subject to a Ministerial discretion, as well as certain exemptions for new pharmaceutical items which are new presentations of existing medicines;[28] and
- for medicines on F2, price-disclosure-driven price reductions. These require sponsors to provide the Commonwealth with periodic data about the discounts and other benefits which they provide in association with the supply of the medicine. The Commonwealth

then uses a formula set out in regulations[29] to calculate the weighted average effective price for a medicine and the AEMP for each brand of that medicine is reduced accordingly. As a result, once a medicine is on F2, its AEMP reduces over time to the minimum price at which sponsors are prepared to sell it.

Issues that affect pricing

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

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

A pharmacist may supply another substitute benefit if:

(a) the prescriber did not indicate that only that benefit was to be supplied (in practice, by checking a box or writing "substitution not permitted" on the script);
(b) the Schedule of Pharmaceutical Benefits states that the specified benefit and the substitute benefit are equivalent;
(c) the substitute benefit is a listed brand of a pharmaceutical item; and
(d) the supply of the substitute benefit is not otherwise prohibited by State or Territory law.[31]

Products which the Department has determined are "Schedule equivalent" are marked on the Schedule of Pharmaceutical Benefits with what is colloquially known as an "a" flag. The "a" flag has been relatively uncontroversial in the context of generic (bioequivalent) medicines. However, in the newer area of biological (biosimilar) medicines, the use of the "a" flag has been a cause for some concern within the medical community and industry. It has led to the Department's Biosimilar Awareness Initiative, directed at prescribers, pharmacists and consumers. 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 of the administrative steps required to prescribe a particular medicine, to encourage biosimilar uptake.[32]

Policy issues that affect pricing and reimbursement

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

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

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

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

Within that framework, three policy issues which are 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 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] and an extension until 30 June 2020.[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.

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

Rebates

The last 20 years have seen dramatic growth in the use of risk-sharing agreements (described in section "Pharmaceutical Pricing and Reimbursement", "How are drug prices set? What is the relationship between pricing and reimbursement?" above) to create a difference between the published price of a medicine (the AEMP) and the effective price paid by the Commonwealth

for that medicine. Under these deeds, the difference between published price and effective price represents rebates paid by the sponsor to the Commonwealth. Almost all high-cost drugs are now listed on the Schedule with a confidential risk-sharing arrangement in place.

This has resulted in a dramatic growth in rebates over the last decade (see section "Market introduction/overview" above) to the extent that the size of the rebates is about 25% of the total PBS budget and close to half of the amount of that budget attributable to the price charged by sponsors for their products.

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.

In the meantime, the Government's approach to special pricing arrangements and the terms of agreement 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. There are recent suggestions that the Government will move to a streamlined rebate model whereby invoices are issued monthly, calculated on the basis of real time data.

Timely access to medicines

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

For example, in the Fourth Edition of its *Facts Book* (July 2015), Medicines Australia reported that the success rate for submissions to the PBAC has been declining and that it took on average 22 months for a new medicine to be listed on the Schedule, with the success

rate for initial submissions being just slightly more than 50%.[39] The PBAC's rigid meeting schedule exacerbates the problem because it means that if a submission is rejected by the PBAC it is usually a minimum of four months – and more commonly, eight months – before the medicine can return to the PBAC.

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

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.[40] 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.[41]

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.

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/australias-health/australias-health-2018/contents/table- of-contents. As at the date of this update, no report for "Australia's Health 2019" has been published online.
3. Health Portfolio Budget Statements 2019–2020, Budget Related Paper No 1.9, March 2019; https://www.health.gov.au/sites/default/files/health-portfolio-budget-statements-2019-20_0.pdf. See also Budget 2019–20 *Fact Sheet* – 'Improving Access to Medicines – Pharmaceutical Benefits Scheme – new and amended listings', April 2019: https://www.health.gov.au/sites/default/files/improving-access-to-medicines-pharmaceutical-benefits-scheme-new-and-amended-listings_0.pdf, and Budget 2019–20 *Fact Sheet* – Aged Care 'Supporting older Australians – Investing in safe and quality aged care': https://budget.gov.au/2019-20/content/factsheets/download/fact_sheet_aged_care.pdf.
4. 2018–2019 Medicines Australia Federal Budget Submission (https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/02/2018-2019-MA-Federal-Budget-Submission.pdf). 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).
5. http://www.pbs.gov.au/info/about-the-pbs.
6. Section 3, Therapeutic Goods Act 1989 (Cth) – "Medicine".
7. Sections 84 "PBS prescriber", 88–90 of the National Health Act. The Schedule of Pharmaceutical Benefits identifies which items are able to be prescribed by which type of PBS prescriber (e.g. dentists and optometrists cannot prescribe general PBS items but have access to a separate Dental Schedule or Optometrical Schedule (respectively)).
8. http://www.health.gov.au/LSDP.
9. https://www1.health.gov.au/internet/main/publishing.nsf/content/FD13E541FA14735CCA257BF0001B0AC0/$File/LSDP-compact-with-Medicines-Australia.pdf.
10. http://www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-applications.

11. Currently, Belgium, Finland, Ireland, Italy, Malta, the Netherlands, New Zealand, Norway, Slovenia, Sweden and the United Kingdom.
12. Includes medical treatment by a medical practitioner, dental treatment by a participating dental practitioner, optometrical treatment by an authorised optometrist, midwifery treatment by an authorised midwife or nurse practitioner treatment by an authorised nurse practitioner (section 86 of the National Health Act).
13. http://www.pbs.gov.au/info/about-the-pbs#What_are_the_current_patient_fees_and_charges.
14. Section 85 of the National Health Act.
15. Section 101 of the National Health Act sets out the functions of the PBAC.
16. Section 101(3A) of the National Health Act.
17. Section 101(3B) of the National Health Act. Section 100 of the National Health Act also empowers the Minister to make special arrangements for, or in relation to, providing that an adequate supply of pharmaceutical benefits will be available to persons living in isolated areas, who are receiving treatment in circumstances where pharmaceutical benefits are inadequate for that treatment or if the pharmaceutical benefits can be more conveniently or efficiently supplied under those arrangements. Examples include the Efficient Funding of Chemotherapy 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. http://www.pbs.gov.au/industry/listing/procedure-guidance/files/Procedure-Guidance-for-Listing-Medicines-on-the-PBS-v1.8.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://www1.health.gov.au/internet/main/publishing.nsf/Content/New-7th-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. As at the date of this update, no announcement has been made as to whether a new agreement has been reached.
37. https://medicinesaustralia.com.au/policy/strategic-agreement/.

38. http://www.pbs.gov.au/info/industry/pricing/improving-access-to-medicines-improved-payment-administration.
39. https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/11/MAFactsBook4_update2015.pdf.
40. https://www.pbs.gov.au/medicinestatus/home.html.
41. https://www.pbs.gov.au/info/news/2020/04/procedure-guidance-standardised-redactions-to-psds.

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Belgium

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Abstract

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

The Belgian legislator has adopted a positive reimbursement list system which entails that the compulsory health insurance shall only reimburse medicinal products that are included on the list of reimbursable 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, without taking into account additional expenses in the context of the COVID-19 pandemic, are forecast to reach €49.19 billion in 2021, putting pressure on the health budget. The Belgian government is also being pressured by the European Commission to make budget savings in order to meet its fiscal deficit target.[1] Cost-containment measures are therefore essential to keep expenditures within bounds. These cost-containment efforts inevitably have an impact on the reimbursement system.

Overview of the healthcare system in Belgium

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

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

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

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

Pharmaceutical pricing and reimbursement

Regulatory classification

Original medicinal products vs. generic medicinal products and biosimilars

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

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

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product. Similarity to the original medicinal product in terms of quality characteristics, biological activity, safety and efficacy, based on a comprehensive comparability exercise, 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" or "**OTC**" medicinal products) are not subject to a prescription and can be freely supplied by the pharmacist. The applicant for a marketing authorisation must indicate in its application the proposed classification of the medicinal product. However, the final classification decision is taken by the Minister of Social Affairs and Public Health. Once the product is classified as prescription-only, the product can be further divided into subcategories. For example, the Minister can decide that some prescription-only medicinal products may only be prescribed by certain groups of specialists, or, with respect to medicinal products intended exclusively for use in a hospital, that the supply of these medicinal products will be reserved for hospital pharmacists.[11]

Reimbursable vs. non-reimbursable medicinal products

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

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

Who is/are the payors?

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

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

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

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

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

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

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

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

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

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

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

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

Depending on the (sub-)class in which a medicinal product is ranked, different reimbursement procedures and timelines apply.[22] For example, for medicinal products ranked in sub-classes 2A or 3A, a simplified administrative reimbursement procedure exists which does not require the involvement of the CRM, and under which a reimbursement decision must be taken by the Minister within 60 calendar days.[23] As for medicinal products ranked in sub-classes 2C, 3B or 3C, the procedure may not take more than 90 calendar days.[24] For all other medicinal products, the standard period of 180 calendar days will apply.[25] It is to be noted that the RD Reimbursement includes specific procedures with respect to parallel imported medicinal products, orphan medicinal products and biosimilars.[26]

Moreover, depending on the (sub-)class in which the medicinal product is ranked, the CRM will evaluate different reimbursement criteria to formulate a (positive or negative) reimbursement proposal. For example, when a medicinal product is ranked in class 1, all reimbursement criteria included in Article 4 of the RD Reimbursement must be weighed to

formulate the reimbursement proposal. Otherwise, when a medicinal product is ranked in sub-class 2B, 2C, 3B or 3C only the reimbursement criteria (i)–(iv) as set out above must be evaluated.[27]

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

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

It is to be noted that in light of the COVID-19 pandemic, as of 13 March 2020, the Belgian government has introduced a general "clock-stop", as it has become increasingly difficult to respect the deadlines provided by the NIHDI Act and the RD Reimbursement. During this clock-stop, the binding deadlines in relation to the reimbursement procedure have been suspended indefinitely, until determined otherwise by a new Royal Decree depending on the further evolution of the COVID-19 pandemic in Belgium.[33] This clock-stop does not prevent pharmaceutical companies to file new reimbursement applications; however, it could affect the timelines of launching a medicinal product on the market (see also below under "Successful market access", "Pharmaceutical pricing and reimbursement").

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.[34]

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).[35] 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 above under section "Who is/are the payors?", "Pharmaceutical pricing and reimbursement", the patient contribution is determined and limited by law.

Category A and Fa include vital medicinal products, such as medicinal products for the treatment of cancer or diabetes. Medicinal products included in category A and Fa shall be fully reimbursed and represent up to 15% of public expenditure on medicinal products. Categories B and Fb cover therapeutic essential medicinal products, such as antihypertensives and account for approximately 80%–85% of public expenditure on medicinal products.

Medicinal products that are ranked in category B and Fb shall be reimbursed at 75%–85% of the reimbursement base for non-hospitalised patients and at 100% for hospitalised patients. Medicinal products intended for symptomatic treatment are ranked in category C, which corresponds with a general reimbursement rate of 50%. Category C covers, for example, the influenza vaccine, providing a general reimbursement rate of 40%. Category Cx includes contraceptives with a general reimbursement rate of 20%. Categories C, Cs and Cx represent a minor percentage of public expenditure on medicinal products. Non-reimbursed medicinal products, such as sleeping pills or tranquilisers, are included in the so-called "category D".[36]

These reimbursement rates must be applied on the reimbursement basis. The reimbursement basis shall in principle be equal to the public price (see below under section "How are drug prices set? What is the relationship between pricing and reimbursement?", "Pharmaceutical pricing and reimbursement").[37] However, for example, for medicinal products containing the same active substance, a reference reimbursement system applies which reduces the reimbursement basis of the original medicinal products from the moment a generic version is introduced. This reference reimbursement system is also referred to as the "patent cliff". After application of the patent cliff, the reimbursement basis shall be lower than the public price initially determined by the Minister of Economic Affairs (see below under section "How are drug prices set? What is the relationship between pricing and reimbursement?", "Pharmaceutical pricing and reimbursement").

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

Following the opening of a reference cluster, the reimbursement basis of the original product will automatically be reduced by a certain percentage. In principle, a reduction of 43.64% will occur. For medicinal products ranked in reimbursement category A, a reduction of 51.52% will occur. It should be noted that there are exceptions to the aforementioned percentages; for example, for injectable medicinal products, a reduction rate of 23.37% and 27.82% (if the medicinal product is ranked under reimbursement category A) will apply. This reduction rate shall be applied on the ex-factory price. 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.[38]

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.[39]

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

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

The main pricing rules are included in:

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

The prices of medicinal products are subject to a price control by the Price Department of the Federal Public Service ("**FPS**") for Economic Affairs.[40] 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.[41] 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).[42] The Minister of Economic Affairs determines the price on the basis of the scientific and economic information submitted by the applicant.

As mentioned above, the pricing procedure and the reimbursement procedure run in parallel. The pricing procedure differs depending on whether reimbursable or non-reimbursable medicinal products are involved.[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 these measures is the introduction of the reference reimbursement system or the patent cliff. As mentioned above under section "How is the reimbursement amount set? What methodology is used?", "Pharmaceutical pricing and reimbursement", once a generic version enters the market, a reference reimbursement system applies, pursuant to which the reimbursement basis and the public price of the original medicinal product will automatically be reduced.

The purpose of this reference system is twofold. On the one hand, the reference system is intended to stimulate competition by encouraging innovative pharmaceutical companies to lower their prices. If the original product becomes more expensive for the patient, innovative

pharmaceutical companies will be forced to lower the price of their product in order to stay competitive. On the other hand, the reference system is also an important means to keep expenditure on medicinal products within bounds, as its application results in a lower contribution by the health insurance. Physicians are also encouraged to prescribe products that are less expensive because of the need for budget control.[52] For example, 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.[53]

In addition, the Minister of Social Affairs and Public Health has recently introduced a new reimbursement system, pursuant to which an innovative medicinal product shall no longer be reimbursed if that product continues to be more expensive compared to "the least costly"[54] 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.[55] This new regime should encourage innovative pharmaceutical companies to lower their prices faster, and at the latest within 21 months after the application of the patent cliff. The new regime should also allow the health insurance to free up additional budget that can be invested in the reimbursement of innovative medicinal products.

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 (e.g. the old drugs cliff for active substances with a turnover of less than €1.5 million equal to 19.75%, for active substances with a turnover between €1.5 million and €10 million equal to 23.62%, etc. The maximum mandated price decrease under the old drugs cliff for non-biological drug products is 29.42%).[56] 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.[57] Importantly, the application of the biocliff because of 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. Moreover, the application of the old drugs cliff also causes the biocliff 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.[58] 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"). Additionally, the Belgian government has implemented various measures within the context of the COVID-19 pandemic.

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.[59] 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.[60] 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.[61] 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 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.[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]

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

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

Another important trend is the shift towards personalised healthcare solutions. Personalised or precision medicine allows for the development of healthcare solutions that are tailored to a specific (and smaller) sub patient population based on the patient's genetic profile and characteristics. Through personalised medicine, patients receive treatments that are adequate and effective for them, and as the European Parliament states in its briefing on personalised medicine of October 2015, "*the aim of personalised medicine is generally perceived to be the 'right treatment for the right person at the right time*"[64] 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.

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.

Successful market access

While obtaining marketing authorisation is a prerequisite and a necessity, it is not the only determinant of successful market access. Obtaining an official price and reimbursement for the medicinal product are also critical to ensure effective market access. Pharmaceutical companies must have a deep understanding of the market and develop a comprehensive market access strategy, which includes a pricing and reimbursement strategy.

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

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

Endnotes

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6. Article 6*bis* of the Law of 25 March 1964 concerning the medicinal products (the "**Medicines Act**").
7. EMA – Guideline on similar biological medicinal products (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf).
8. EMA – Biosimilars in the EU: Information guide for healthcare professionals (http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC50022 6648.pdf).
9. Article 6*bis* of the Medicines Act.
10. EMA – Biosimilars in the EU: Information guide for healthcare professionals (http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC50022 6648.pdf).
11. Article 6, §1*bis* of the Medicines Act.
12. https://economie.fgov.be/nl/themas/verkoop/prijsbeleid/gereguleerde-prijzen/geneesmiddelen-voor-menselijk.
13. Article 2 of the Royal Decree of 7 May 1991 on the establishment of the patient contribution.
14. On 15 March 2018, the new RD Reimbursement was published in the *Belgian State Gazette*. The RD Reimbursement repeals the Royal Decree of 2001 and applies to all reimbursement applications submitted as from 1 April 2018. For applications submitted prior to 1 April 2018, the procedures and timelines included in the text of the Royal Decree of 2001, will apply. This contribution sets out the rules and procedures included in the new RD Reimbursement as applicable to applications submitted as from 1 April 2018.
15. Article 6 of the Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems (the "**Transparency Directive**"); Article 35*bis* of the NIHDI Act and Article 2 of the RD Reimbursement; the positive list is included in an appendix to the RD Reimbursement.
16. Article 10 of the RD Reimbursement.
17. Article 3, §1 of the RD Reimbursement; note that for some medicinal products a simplified administrative procedure exists which does not require the involvement of the CRM (see Articles 50–54 of the RD Reimbursement).
18. Article 10 of the RD Reimbursement.
19. Article 15, §1, third paragraph of the RD Reimbursement.
20. Article 35*bis*, §2 of the NIHDI Act; Article 4 of the RD Reimbursement.
21. Article 35*bis*, §2 of the NIHDI Act; Article 5 of the RD Reimbursement.
22. Procedure class 1 medicinal products: see Articles 16–22 of the RD Reimbursement; Procedure class 2B medicinal products: see Articles 23–29 of the RD Reimbursement; Procedure class 2C medicinal products: see Articles 30–36 of the RD Reimbursement; 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.
23. Article 15, §1, first paragraph of the RD Reimbursement.
24. Article 15, §1, second paragraph of the RD Reimbursement.
25. Article 15, §1, third paragraph of the RD Reimbursement.
26. Procedure parallel imported medicinal products: see Articles 43–49 of the RD Reimbursement; procedure orphan medicinal products: see Article 55 of the RD Reimbursement; and procedure biosimilars: see Articles 56–58 of the RD Reimbursement.
27. Article 6 of the RD Reimbursement.
28. Note that medicinal products with similar reimbursement conditions are included in the same reimbursement group. For example, cardiovascular medicinal products are included in reimbursement group I. Some medicinal products reimbursement shall only be reimbursed upon certain conditions. These conditions can, for example, relate to the need for diagnostic examination, the maximum dosage, the age of the patients, etc.
29. Articles 20, 27, 34 and 40 of the RD Reimbursement.
30. Articles 20, 27, 34 and 40 of the RD Reimbursement.
31. Articles 3, §1 of the RD Reimbursement; see http://www.riziv.fgov.be.
32. Articles 22, 29, 36, 42 and 54 of the RD Reimbursement.
33. Article 1 of the Royal Decree nr. 20 of 3 May 2020 regarding temporary measures to combat the COVID-19 pandemic and to ensure the continuity of care under the compulsory insurance for medical care.
34. Articles 59–89 of the RD Reimbursement.
35. Article 2, §1 of the Royal Decree of 7 May 1991 on the establishment of the patient contribution.
36. Article 2, §1 of the Royal Decree of 7 May 1991 on the establishment of the patient contribution; Belgium Pharmaceuticals & Healthcare Report Q4 2017.
37. Article 35*bis*, §2*bis* of the NIHDI Act.
38. Article 35*ter*, §3 of the NIHDI Act.
39. Article 5 of the Act of 1 April 2019 containing provisions on the reimbursement of pharmaceutical specialties and the administrative costs, efficiency and transparency of the insurance institutions
40. Article 3, §1 of the RD Pricing.
41. Article V.10, §1 of the Code of Economic Law.
42. Article 3, §2 of the RD Pricing.
43. As specified in the RD Pricing.
44. Article 3, §6 of the RD Pricing.
45. Article 3, §9 and §10 of the RD Pricing.
46. Article 4 of the RD Pricing.
47. Article 3, §7 of the RD Pricing.
48. Article 35*octies*, §1 of the NIHDI Act.
49. As specified in the MD Pricing.
50. http://ec.europa.eu/competition/sectors/pharmaceuticals/antitrust_en.html.
51. Belgium Pharmaceuticals & Healthcare Report Q4 2017.
52. Articles 73 and 146*bis* of the NIHDI Act.
53. The pilot project was installed pursuant to the national convention 2018–2019 of the National Commission Physicians-Health Insurance Funds, see https://www.inami.fgov.be/SiteCollectionDocuments/akkoord_artsen_ziekenfondsen_2018_2019.pdf.
54. For the qualification of "least costly" see Article 73, §2 of the NIHDI Act.
55. Article 35*ter*/1 of the NIHDI Act.

56. Article 69 of the Act of 27 April 2005 regarding the containment of the healthcare budget and containing various provisions relating health.
57. Article 30 of the Act of 30 July 2013 containing various provisions.
58. Article 69 of the Act of 27 April 2005 regarding the containment of the healthcare budget and containing various provisions relating health; Article 30 of the Act of 30 July 2013 containing various provisions.
59. http://www.deblock.belgium.be/nl/de-tijd-duur-medicijn-niet-altijd-meer-terugbetaald.
60. Article 116 of the RD Reimbursement.
61. KCE Report 288 – "How to improve the Belgian process for managed entry agreements? an analysis of the Belgian and international experience" (https://kce.fgov.be/sites/default/files/atoms/files/KCE_288_Improve_Belgian_process_managed_entry_agreements_Report.pdf).
62. KCE Report 288 – "How to improve the Belgian process for managed entry agreements? an analysis of the Belgian and international experience" (https://kce.fgov.be/sites/default/files/atoms/files/KCE_288_Improve_Belgian_process_managed_entry_agreements_Report.pdf).
63. Article 11 of the Act of 1 April 2019 (as amended by the Act of 4 May 2020) containing provisions on the reimbursement of pharmaceutical specialties and the administrative costs, efficiency and transparency of the insurance institutions.
64. http://www.europarl.europa.eu/RegData/etudes/BRIE/2015/569009/EPRS_BRI(2015)569009_EN.pdf.

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General considerations

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

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

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

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

Regulatory submission of drug application

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

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

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

Legal framework

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

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

A branded generic drug is that which "contains the same active ingredient(s), has the same

concentration, dosage form, administration route, dosage administration and therapeutic recommendation, it is equivalent to the drug registered with the federal authority responsible for the health surveillance, and it may differ only in characteristics relative to the product size and form, expiration term, packaging, labelling, excipients and vehicles, and it must always be identified by trade name or brand".[4]

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

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

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

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

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

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

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

Reference drugs

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

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

Generic drugs (branded and non-branded)

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

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

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

Biological products

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

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

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

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

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

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

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

As to the evidence of safety and efficacy, for *new biological* drugs, the applicant must

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

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

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

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

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

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

Simplified procedure for marketing approval

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

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

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

Regulatory pathway for conducting clinical trials in Brazil

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

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

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

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

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

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

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

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

Expedited pathway for drugs for rare diseases

On December 28, 2017, ANVISA issued Resolution RDC 205/2017, establishing expedited pathways for rare diseases drugs, defined as those destined to treat diseases with prevalence of 65/1000 patients, in relation to clinical trials, Good Manufacture Practice Certificates and marketing approval.

According to Resolution RDC 205/2017, ANVISA can consent to clinical trials without the

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

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

In order to submit a marketing approval application through the expedited pathway established by Resolution RDC 205/2017, applicants must submit at the same time the requirement for pricing approval and must commercialise the approved drug within one year as of the date of approval.

Pricing

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

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

New drugs

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

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

i. greater efficacy in relation to the existing drugs for the same therapeutic indication;
ii. same efficacy with a significant decrease in the adverse effects; or
iii. same efficacy with a significant reduction in the global cost of treatment.

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

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

New presentations

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

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

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

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

i. a drug considered new on the list of the ones marketed by the company, except if it meets the requirements to be classified into Category V; or
ii. a drug already marketed by the company, in a new pharmaceutical form.

Category V comprises drugs fitting one of the following situations:

i. a new pharmaceutical form in the country; or
ii. a new association of active ingredients already existing in the country.

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

Requirements for price approval

The drug manufacturers that intend to market new products and new presentations submit an Informative Document to the CMED applying for one of the Categories mentioned above and providing CMED with the following information.

Category I

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

i. brand name of a drug in Brazil and the other brand names for the same drug, used in the countries mentioned in item VII of this paragraph and in the manufacturer's origin country;
ii. drug approval number and EAN code, both comprising 13 digits;
iii. substances from which the drug is formulated;
iv. a copy of the package leaflet;
v. a presentation form in which the drug will be marketed;
vi. the price at which the company intends to market each presentation, with the discrimination of taxes and marketing margins;
vii. the manufacturer's price, accompanied by the due source proof, traded in Australia, Canada, Spain, United States of America, France, Greece, Italy, New Zealand, Portugal, and the manufacturer's price in the product's country of origin, excluding taxes;
viii. the manufacturer's name and the manufacturing site of the active ingredient and the finished drug;
ix. the potential number of patients to be treated with the drug, with the indication of the corresponding period;
x. a cost-efficacy comparative analysis between the drug and the existing therapeutic alternatives;
xi. presentation of the following information on the product's patent: (a) number of the first international patent application, date of application, and the country where it was done; (b) number of patent application at INPI; and (c) innovation presented by the product which the patent application was based on;
xii. when available, presentation of economic assessment studies published;
xiii. phase III clinical trials conducted, which are relevant for the comparison between the new drug and those existing in the country for the same therapeutic indication, if any; and
xiv. new therapeutic indications for the same drug – in a trial, in phase of approval, or approved in other countries, if any.

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

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

appreciation or depreciation. In case of appeal against the CMED's decision, the average exchange rate published by the Brazilian Central Bank (BACEN) will be applied, calculated for the period of 60 business days previous to the date of the decision, with the purpose of conversion of the expressed price from foreign currency to Real.

Categories II and V

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

i. the brand name of the drug in Brazil and the other brand names for the same drug, used in the countries mentioned in item VII of this paragraph and in the manufacturer's origin country;
ii. the drug approval number and EAN code, both comprising of 13 digits;
iii. substances from which the drug is formulated;
iv. a copy of the package leaflet;
v. the presentation form in which the drug will be marketed;
vi. the price at which the company intends to market each presentation, with the discrimination of taxes and marketing margins;
vii. the manufacturer's price, accompanied by the due source proof, traded in Australia, Canada, Spain, United States of America, France, Greece, Italy, New Zealand, Portugal, and the manufacturer's price in the product's country of origin, excluding taxes;
viii. the manufacturer's name and the manufacturing site of the active ingredient and the finished drug;
ix. phase III clinical trials conducted, which are relevant for the comparison between the new drug and those existing in the country for the same therapeutic indication, if any; and
x. new therapeutic indications for the same drug – in trial, in phase of approval, or approved in other countries, if any.

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

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

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

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

i. In case of new associations in the country, (a) if the drugs that compose the association are commercialised separately, the association's price must not be higher than the sum of the monodrugs' prices, observing the strength proportion of active ingredients and the number of units, as long as the price does not incur a higher cost of treatment than other treatment(s) already existing, and (b) if the new association replaces, with confirmed advantages, the treatment with the monodrugs already commercialised taken separately, the company may present a justification for the proposed price, the relevance of which shall be assessed by the Technical-Executive Committee of the CMED.
ii. In case of new pharmaceutical forms, the price will be defined based on the cost of treatment with the drugs existing in Brazil for the same therapeutic indication, and it must not be, in any case, higher than the lowest price applied among the countries listed in item (vii) above.

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

Categories III, IV and VI

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

i. the brand name of the drug in Brazil and the other brand names for the same drug, used in the countries mentioned in item VII of this paragraph and in the manufacturer's origin country;
ii. the drug approval number and EAN code, both comprising of 13 digits;
iii. substances from which the drug is formulated;
iv. a copy of the package leaflet;
v. the presentation form in which the drug will be marketed; and
vi. the price at which the company intends to market each presentation, with the discrimination of taxes and marketing margins.

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

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

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

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

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

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

Price Adequacy Coefficient – PAC

According to CMED Resolution No. 02/2004, a compulsory discount for sales directed towards Governmental Entities, called Price Adequacy Coefficient – PAC, must be applied

to the FP of products listed in further regulations issued by the CMED. The value of PAC shall be updated every year by the CMED.

The value of PAC currently in force in Brazil is 20.09% off the FP, as per CMED Ordinance No. 11, of December 19, 2019, and it must be applied to products listed on Annex I of CMED Ordinance No. 3, of May 21, 2020.

Access to drugs

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

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

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

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

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

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

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

The vast majority of judicial precedents regarding this matter is favourable to patients. There are judicial decisions ordering the Government or the health insurance companies to provide patients even with drugs with no marketing approval granted by ANVISA. However, the National Council of Justice recommended the judges not to issue decisions granting access to products not approved by ANVISA, except in cases in which there is scientific evidence and urgent necessity of the product.

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

1. The Government may not be required to supply experimental drugs.
2. The lack of registration with ANVISA prevents, as a rule, the supply of drugs by judicial decision.

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

The Special Appeal No. 566471, which discussed the obligation of the Government to supply high cost drugs to patients, was ruled on March 2020 and, in summary, the Supreme Court decided that the drugs that are not included in CONITEC's CPRG should not be supplied to patients by the Government.

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

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

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

1. a reduction of the drug price;
2. a description of the disease and eligibility criteria of subgroups of patients benefitting from the risk-sharing agreement;
3. the definition of expected health outcome criteria and clinical effectiveness parameters;
4. the maximum number of patients per year who will receive the drug from the Ministry of Health, based on epidemiological criteria and/or estimate of demand, being established that, beyond such maximum number, the owner of the drug will bear the cost of the drug for the other patients;
5. the definition of the criteria for interrupting the supply of the drug to patients who do not present the expected health outcomes, within a defined timeframe, according to the best scientific evidence available; and
6. the definition of the periodicity of evaluation of the parameters of clinical effectiveness, according to the best scientific evidence available.

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

* * *

Endnotes

1. This requirement is pursuant to ANVISA Bylaw No. 9.782/99.
2. Act No. 6.360/76.
3. Act No. 9.787/99.
4. *Id.*

5. *Id.*
6. ANVISA Resolution RDC 200/2017.
7. *Id.*
8. According to Law No. 9.787 – XXV – bioavailability indicates the velocity and extension of an active ingredient absorption in a dosage form, from its concentration/time curve in the systemic circulation or its excretion in the urine.
9. ANVISA Resolution RDC 55/2010.
10. *Id.*
11. See Law No. 9.787/99 (generic drugs).
12. ANVISA Resolution RDC 55/2010.
13. *Id*.
14. Annex I is a form submitted for both the mother drug and the clone drug requesting marketing authorisation for the clone under the clone procedure.
15. The documentation refers to the translated dossier, including the protocol, investigator brochure, informed consent form, and sponsor and institutional declarations, which are sent to each site's institutional ethics committee (CEP) for review.
16. The Special Communicate is the official approval document.

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Canada

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Abstract

Canada is subject to a patchwork of laws and policies relating to the pricing and reimbursement of drug products. The price of Canadian drugs through the supply chain from manufacturer to wholesaler to pharmacy, and at the retail level, is subject to complex regulations under both federal and provincial laws. Prescription drugs are subject to both public and private reimbursement in Canada, and the price negotiated between manufacturers and payors will depend on the specifics of the drug in question. A drug's price and reimbursement can differ within jurisdictions of Canada and may change over the life cycle of the drug. The proximity of Canada's market to the US creates another area of complexity, relating to the impact of pricing of Canadian drugs and the potential availability of those drugs for the US market. Success in the Canadian market requires a deep understanding of the complexities of the healthcare system, the laws affecting the pricing of those drugs and the channels through which drugs are made available.

Market introduction/overview

Role of the Federal and Provincial Governments in Canadian healthcare

Canada's healthcare system, unlike that of the United States, is mostly publicly funded and is typically "free" at the point-of-use for Canadian residents. It is "free" in the sense that taxpayers do not receive bills for the healthcare services that they receive in a hospital or a physician clinic, but revenues to support Canada's healthcare system are obtained from Canadian taxpayers. Canadian residents may supplement the services and products available via Canada's healthcare system with insurance (obtained individually or through employers).

The Canadian federal government provides funding to the provinces to finance the delivery of healthcare, and the provinces, in turn, are responsible for delivering services, and managing and administering their individual healthcare insurance plans. The Canada Health Act specifies the minimum conditions that the individual provinces must implement to receive federal healthcare funding. For example, the provinces must provide coverage for certain essential physician services, surgical-dental services and hospital services. Each province manages its own public health insurance plan, and develops its own system of public health insurance, following the minimum standards sets out in the Canada Health Act. In addition, the provinces offer additional benefits, such as prescription drug plans for eligible patients, under their respective health insurance plans, funded and delivered on the provinces' own terms and conditions.

Physician services performed in a hospital and drugs administered in a hospital are paid out of the hospital's operating budget managed by the hospital, with funds received from the

provincial ministry of health in accordance with the minimum requirements of the federal Canada Health Act. For these drugs and services, there are no out-of-pocket expenses for provincial residents. Physician services performed outside of a hospital setting are also generally covered by the provincial ministries of health for provincial residents.

Role of the Provincial Governments in public prescription drug reimbursement

The cost of drugs that are administered to a patient in a hospital setting are covered by the public healthcare system, while the cost of a drug that is prescribed outside of a hospital setting is covered by either a public (government) drug plan, a private drug plan or "out of pocket" by the patient.

For prescription drugs that are used out of a hospital, each province maintains a public drug plan formulary, which lists the drugs and conditions for which the province will reimburse prescription drugs for an eligible insured person under the public plan.

Each province maintains legislation that governs payments and reimbursements under the public provincial drug plans. Each province has different eligibility requirements for inclusion in the public plan, but generally, publicly insured persons include persons 65 years of age or older, or persons who meet other criteria established by the province (e.g., low income or residents of long-term care homes or homes for special care). Some provinces also have specific medication assistance programmes for patients whose drug costs are high relative to their income.

Therefore, only a subset of the Canadian population receives government funded prescription drug coverage outside the hospital setting. The remainder of the population either pays for their prescription drugs out of their own pocket, or through private drug plans – for example, drug plans funded by their employers. It is estimated that approximately 60% of Canadians are enrolled in a private drug plan (primarily employer-sponsored), and that these plans cover about 36% of total healthcare system-wide spending on prescription drugs.[1]

Pharmaceutical pricing and reimbursement

Regulatory classification

Health Canada and provincial regulators

Pharmaceuticals are regulated federally by Canada's Food and Drugs Act (F&DA), Food and Drug Regulations (FDR), and various other legislation, by Health Canada (the equivalent of the United States Food and Drug Administration). The FDA and FDR govern all aspects of the manufacturing, importing, labelling, distribution and sale of drug products in Canada and include general prohibitions on false and misleading advertising.

Provincial governments have oversight for the professional practice of pharmacy and the operation of pharmacies. There is also a professional college of pharmacists in each province responsible for licensing, pharmacist disciplinary actions, standards of practice, codes of ethics and other policies and guidelines. No person can operate a pharmacy without a pharmacy licence, and no person can practise the profession of pharmacy without being accredited as a licensed pharmacist with the provincial college of pharmacists.

Prescription pharmaceuticals include medicinal ingredients listed on the Prescription Drug List under the F&DA or Controlled Drugs and Substances Act (CDSA) Schedules, maintained by Health Canada. In addition to Health Canada classification, the National Association of Pharmacy Regulatory Authorities (NAPRA) implements additional guidelines relating to location of sale of pharmaceuticals in pharmacies. The NAPRA administers the National Drug Schedules programme that consists of four categories of pharmaceuticals:

(i) pharmaceuticals that require a prescription for sale; (ii) pharmaceuticals that require pharmacist intervention at point of sale; (iii) pharmaceuticals that are sold in a self-selection area operated under a pharmacist's direct supervision; and (iv) pharmaceuticals that can be sold without professional supervision. In general, each pharmacy regulatory authority has adopted the National Drug Schedules into its legislation.

Marketing approval and process

A marketing authorisation for a prescription drug in Canada is known as a Notice of Compliance (NOC) and is issued in accordance with the requirements of the FDR. In order to obtain an authorisation for sale of a drug in Canada, a drug manufacturer files a New Drug Submission (NDS) with Health Canada. An NDS contains both preclinical and clinical results to support the safety, efficacy, and quality of the pharmaceutical, as well as details of its production, packaging, and labelling. It typically takes one to two years for an NDS to be reviewed and a NOC issued, although there are regulatory mechanisms that allow for fast-tracking/expediated approval of drugs in various contexts.

If a manufacturer wishes to include a new indication in the label of a drug or to change the strength or format/dosage form of the drug, then the manufacturer must file a Supplemental New Drug Submission (SNDS) seeking approval for this change. A new NOC is issued each time that an SNDS is reviewed and approved by Health Canada.

Generic drugs are approved via an Abbreviated New Drug Submission (ANDS) where the ANDS references data previously submitted to Health Canada by an innovator drug (known as the "reference drug") under an NDS. Any line extensions/new indications for a generic drug are approved via a Supplemental Abbreviated New Drug Submission (SANDS). Each ANDS and SANDS receives a NOC once reviewed and approved by Health Canada.

Biosimilar products are approved via the NDS pathway, but the NDS submitted for a biosimilar is condensed as a biosimilar manufacturer can provide evidence of similarity to a previously approved biologic in order to reduce the necessary data requirements for approval.

Along with a NOC, a Drug Identification Number (DIN) is also issued for each a drug. A DIN is an eight-digit number and uniquely identifies each pharmaceutical product sold in Canada. The DIN must appear on the label of each pharmaceutical. The DIN is issued to or held in the name of the "regulatory" manufacturer – i.e., the name of the entity identified on the drug label.

Over-the-counter (OTC) drugs are approved for sale following the review of a DIN submission – this is a less robust submission given the nature of the product. Vitamins, probiotics, supplements and homeopathic medicines are regulated as natural health products (NHP) in Canada, and also require approval from Health Canada prior to sale. The data requirements for these product submissions are less robust than for an NDS. A review of product labelling is included in the DIN submission and NHP application process.

Who is/who are the payer(s)?

The cost of a drug in Canada may be covered by a public (government) insurer, private health insurer or may be subject to self-pay, depending on the drug and the individual patient.

As noted above, drugs administered to patients in Canadian hospitals are provided at no cost to the patient and costs are covered from the hospital operating budget.

Outside of the hospital setting, provincial governments are responsible for the administration of their own publicly-funded drug plans. Each province maintains legislation that governs payments and reimbursement under the public provincial drug plans. In addition to the provinces, the federal government, through various programmes, provides prescription drug

coverage for Canadians who are members of eligible groups (e.g. First Nations and Inuit, federal armed forces and veterans).

The public drug plans determine what prescriptions drugs are listed and under what conditions for their eligible recipients. Each public plan has a list of pharmaceutical products for which it will reimburse pharmacists for dispensing to eligible plan members. This list is known as the public formulary. The public payer will often enter into agreements with pharmaceutical manufacturers where the public payer negotiates rebates on the list price of the pharmaceutical drug.

Many Canadians have private insurance that covers the cost of prescription drugs,[2] typically as part of the group health benefits provided by their employers. Employers purchase these plans from insurance companies and determine the terms of the plans – for example, what drugs are covered and how much of the cost of the drug the plan will cover. Outside of the province of Québec, there is no legislation which requires a private drug plan to cover any particular drug product.

Very few non-prescription drugs are covered by public drug plans; patients would typically pay out of pocket for OTC drugs and NHPs.

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

Because public drug plans are legislated and administered at a provincial level (or for federal public plans, through federal reimbursement policies), each public drug plan will enter into an independent agreement with a drug manufacturer for listing of a drug product on the provincial drug plan formulary (a product listing agreement or PLA). Product listing agreements generally include volume discounts and other cost containment measures (market caps, per patient caps, etc.).

Recognising the inefficiencies of having multiple parallel negotiations for the same drug product in each province, the public plans have developed several initiatives over the years to streamline negotiations, and to pool collective resources and increase the provinces' negotiating power.

In 1989, the federal and provincial governments created the Canadian Agency for Drugs and Technologies in Health (CADTH) to provide a single point for review, analysis, and recommendations for drugs and health technologies to each public drug plan. Under the Common Drug Review (CDR) initiative or pan-Canadian Oncology Drug Review (pCODR) for oncology drugs, CADTH will review drugs approved by Health Canada and provide listing and reimbursement recommendations to each provincial drug plan (except Québec). In Québec, the *Institut national d'excellence en santé et en services sociaux* (INESSS) provides a similar review and recommendations for the Québec Régie. If a product is deemed cost effective, CADTH/INESSS issues guidance recommending its use. Public payers will follow the recommendation but are not required to do so.

When developing its recommendation, CADTH will consider clinical evidence, cost-effectiveness, and patient perspectives. It will also consider the cost of therapy relative to other treatments that are available in Canada. The health technology assessment performed by CADTH is a significant determining factor in assessing the price to be paid by public payors for pharmaceuticals.

Before 2010, although the CDR provided a single source for listing and reimbursement recommendations, the actual negotiations still devolved to each drug plan. In 2010, the provinces collectively established the pan-Canadian Pharmaceutical Alliance (PCPA) to conduct the first round of negotiations for drug listing and reimbursement levels on behalf

of the participating provinces. The province of Québec was not part of the PCPA initially, but has now joined as have the federal public plans.

The effect of the PCPA has been to decrease the non-transparent price of drug products, particularly biologics and other specialty drugs. The PCPA, acting as a single representative for the collective public drug plans, negotiates directly with drug manufacturers. The PCPA negotiates to arrive at a confidential Letter of Intent that sets out the effective price which the public payers are willing to pay, and can include other rights and restrictions including rebates, grants, category caps and termination rights. Individual plans then use this Letter of Intent to enter to form the basis for a subsequent (but typically minimal) round of negotiations with each drug plan and execution of a PLA.

The negotiation period with the PCPA and with individual plans thereafter is highly variable. The timing to enter into a PLA and to be listed on the drug plan formulary will vary based on the case load of each plan, and can take days, weeks, or months from the date of the PCPA Letter of Intent.

New dosage forms or line extensions are typically the subject of an amendment to an existing PLA. New indications will typically trigger the PCPA negotiation process, as the terms of the initial Letter of Intent and PLAs typically give the plans the right to renegotiate when there are material market events that may impact the utilisation of the drug or the drug plan's budget.

PLAs will typically contain a termination clause benefitting the provinces, allowing them to terminate each PLA on notice to a manufacturer. Provinces will rely on such termination clauses if they wish to re-negotiate the PLA or the class of drugs subject to the PLA.

Private drug plans do not participate in the PCPA and are not entitled to the rebates that may be negotiated under public PLAs. While historically private plans would provide coverage for any new prescription drug without negotiation with manufacturers, over the last decade, private PLAs have become increasing common. Most specialty, rare-disease and high costs drugs will be subject to private PLAs with multiple insurers. The terms of these PLAs are confidential, and the rebates offered to a private plan by a manufacturer will typically depend on the size of the plan (number of insured persons) and the ability of the manufacturer to negotiate preferential listing criteria with the payor.

Public plans are subject to administrative fairness principles when negotiating with manufacturers but have wide discretion on whether to list a drug on their formulary. A decision of CADTH/INESSS or decisions/policies of the public plans on reimbursement are subject to judicial review and challenged in the court system. These challenges are rare, and would typically result in a court returning the matter to the public plan for re-assessment, as opposed to a court order requiring that a public plan list a drug on the formulary.

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

At a high level, drug prices are controlled by (i) in the case of patented drugs, by a federal body called the Patented Medicine Prices Review Board (PMPRB), and (ii) provincial laws and requirements for listing on public health plan formularies. Note that Health Canada does not regulate the price of drugs sold in Canada, i.e., price at which a drug may be sold is not tied to marketing authorisation in any way.

Federal price control

Under the Patent Act, the PMPRB has jurisdiction to determine whether a patentee of an invention, pertaining to a medicine, is selling the medicine at a price that is excessive in any market in Canada. The PMPRB regulates factory-gate sales (first sale) from a manufacturer to a wholesaler, distributor, hospital or pharmacy. The PMPRB does not regulate retail sales.

If the price of a patented medicine is deemed excessive, the PMPRB can order a manufacturer of a patented medicine to lower the price of the medicine and offset excess revenues. The PMPRB can hold public hearings on the question of whether a price of a patented medicine is excessive if a voluntary agreement on price has not been reached.

Provincial regulation

Subject to ensuring that the pricing of patented medicines is not excessive under the PMPRB framework, pharmaceutical companies are free to set their list price for drug products containing new chemical entities. The public payers rarely pay the list price of the pharmaceutical products – they exert significant downward pressure, discounting the price by 30% or more off the list price. For private-payer plans, employers typically purchase these plans from insurance companies and determine the terms of the plans – for example, which drugs are covered and how much of the cost of the drug the plan will cover. As noted above, it is becoming increasingly common for private drug plans to negotiate rebate arrangements with manufacturers, particularly for high-cost drugs (orphan drugs, biologics).

The Pan-Canadian Tiered Pricing Framework,[3] administered by the PCPA, has created a uniform pricing programme for generics across Canada based upon the number of generic alternatives available in a province. Where one generic is available, its price will be 75% of the brand reference price if the brand manufacturer has negotiated a PLA with the province, and 85% of the reference price if there is no PLA. If two generics are available, the price for the generic drops to 50% of the brand reference price. If three or more generics are available (which is the norm), then the price for each generic is 25% of the brand price for oral solids or modified release drugs, and 35% for non-oral solid drugs. For certain frequently prescribed drugs, the cap for the generic price is set at 10% or 18% of the brand reference price, depending on the product. These percentage caps are subject to amendments every few years, and this framework is not based on therapeutic class, but rather frequency of dispensing.

The provinces have their own legislation on how pharmaceuticals can be priced at the wholesaler and retail levels – i.e., the permitted upcharge, applicable dispensing fee and whether rebates and professional allowances to pharmacies are prohibited or permitted. Wholesale margins are regulated with respect to drugs ultimately dispensed to publicly insured individuals, as the public drug programmes include caps on the wholesale margins that will be reimbursed. For private payers, the wholesale margins are a matter of negotiation between pharmacists and wholesalers.

In many provinces, drug manufacturers, in practice, provide pharmacies with rebates (typically volume discounts) with respect to drug products dispensed by the pharmacies which are not factored into the transparent drug cost (i.e., the established list price). For generic drugs, these rebates can be very significant, typically 60–80% of the generic drug cost. In Ontario and Québec – the two largest provinces of Canada – such rebates are prohibited. There are exceptions to the general prohibition for certain "ordinary commercial terms" such as prompt payment discount, volume discount or distribution service fee. In Ontario, these ordinary commercial terms used to be capped at 10% of the drug price, but recently the cap has been removed – in effect, a generic manufacturer can now offer any quantum of discount that it can justify as an "ordinary" market term.

Biosimilars are not true generic interchangeable drugs, and therefore are subject to different approval and pricing regimes. Because of the higher burden on biosimilar manufacturers to perform independent research, development and clinical studies on biosimilars as compared to small molecule generic drug manufacturers, the cost differential between innovator biologics

and biosimilars is markedly less than that of innovator and generic drugs. Biosimilars are often listed at around 70–75% of the innovator biologic drug list price.

Other issues that affect pricing

Provincial cost containment policies

The public plans curb pharmaceutical spending not only by deciding which pharmaceuticals are listed on the formularies, but also by negotiating the conditions for eligible reimbursement. Pharmaceuticals will be listed with specified criteria and the plan will not reimburse for products that are prescribed outside such criteria. Provinces may also impose restrictions on the formularies – i.e.: which pharmaceuticals are to be offered as first line therapy; second line therapy; and which pharmaceuticals are to be used on naïve patients, etc. Physicians discuss the various pharmaceutical options with their patients and consider a patient's ability to pay in determining which pharmaceutical to prescribe.

The cost-constrained Canadian provinces are becoming more creative in the way that they reimburse high cost specialty drugs through their provincial drug plans. There have been examples where a province has developed off-formulary programmes whereby physicians are incentivised to prescribe a lower cost drug product, for off label use, rather than the higher cost drug. Policies to encourage uptake of biosimilars are becoming common, with multiple provinces adopting or considering the adoption of non-medical switch policies whereby public plan patients are only eligible for reimbursing of a biosimilar product even if they have previously been stabilised on an innovative biologic. Provinces also develop tiering policies where patients are required to try a number of first tier (biosimilar/less expensive) products prior to gaining access to a second-tier product (innovative biologic). In some cases, an innovative biologic may be delisted by the public payor in favour of listing of a biosimilar.[4]

Tendering

While relatively uncommon for public plans, there have been instances where provinces have used a tendering process to select manufacturers to become exclusive suppliers for drugs on the public formulary. This approach is a cost savings tactic for facilitating more favourable supply contracts from drug manufacturers and wholesalers.

Tendering is becoming increasingly common for hospital procured products, including for brand name drugs where there are therapeutic comparators available, with many hospitals participating in group purchasing organisations in order to secure lower prices. Contracts that result from tendering tend to be very purchaser-friendly – purchasers seek broad termination rights so that they are not bound to the contract terms in the event of a new product entry or other market changes, and these contracts may not have any minimum purchase commitments.

Competition law

The competition regime in Canada is governed federally by the Competition Act. While this Act is not specific to the pharmaceutical or medical device industries, the Canadian Competition Bureau conducts inquiries into both criminal and civil matters that relate to pricing of pharmaceuticals or providing rebates to customers. Activities and practices subject to review by the competition tribunal include: bid-rigging; conspiracies to lessen competition; price discrimination; tied selling; abuse of dominance; refusal to deal; exclusive dealing; and market restriction.

Competition considerations can be important in developing pricing strategies, reimbursement plans or purchase agreements involving drugs, particularly for the private market.

Policy issues that affect pricing and reimbursement

Authors' note – Please note that the PMPRB regime is currently in flux at the time of writing this chapter due to multiple court challenges, and the information below may have changed following the submission of this chapter.

The PMPRB, a federal board whose jurisdiction over excessive pricing is founded on patented medicines, does not have a corollary in the United States or Europe. It is a Canadian specific pricing board that has complex regulations and guidelines in assessing whether a price for a patented medicine is excessive.

The government has indicated that drug pricing reform is needed in order to provide the PMPRB with more relevant and effective regulatory tools to better protect Canadians from excessive prices, stating: "…with Canadian patented drug prices outpacing most of our comparators and OECD partners, record low investment in pharmaceutical R&D, and public and private payers struggling to cope with an influx of high-cost drugs, many are questioning the effectiveness of the PMPRB in meeting the government's policy objectives."[5]

After various rounds of stakeholder consultation and publication of draft regulations in late 2017, "final" amendments to the Patented Medicines Regulations (PMR) were formally published on August 21, 2019. The government expects the reform to result in $12.6 billion in drug cost savings over 10 years.[6] Although referred to as final, the amended PMR are subject to legal challenges, and at the time of writing, a portion of the amended PMR has been struck down by the federal court as being beyond the scope of the government's regulation-making authority.

Under the current PMR and PMPRB guidelines (in force at the time of writing), the permissible price ceiling for a patented medicine is based on its therapeutic contribution and the Canadian price of the drug as compared to other jurisdictions including the United States. The amended PMR which are set to come into force on January 1, 2021, would introduce significant changes to the current regime:

- **Price regulatory factors** – The regulations introduce new factors for the PMPRB to use to assess whether the price of a patented medicine is excessive. These include the pharmacoeconomic value of the medicine in Canada, the size of the market for the medicine in Canada and the gross domestic product (GDP) and GDP *per capita* of Canada. These factors will likely have the effect of decreasing the price of patented medicines as they allow for the PMPRB to consider "ability to pay" in its assessment of whether a price is excessive; in particular, complex biologics and rare-disease treatments may be significantly impacted. These new factors would not apply to patented medicines for which DINs were issued before August 21, 2019 (grandfathered medicines) nor to patented medicines for which DINs were issued after August 21, 2019 and launched before January 1, 2021 ("gap" medicines).
- **Basket of comparator countries** – Under the current regime, pricing in Canada is compared to a basket of seven countries (PMPRB7) and the Canadian price of a patented medicine can never be highest of the countries within the basket. The amended PMR will now define a basket of 11 countries (PMPRB11). Neither the United States nor Switzerland, current members of the PMPRB7, are included in the PMPRP11. The US typically has the highest price of the PMPRB7 and was removed on the basis that it does not have pricing policies aligned with the consumer protection mandate of the PMPRB. The PMPRB11 rules would apply to all patented medicines, regardless of their approval date, and the removal of the US and Switzerland is expected to cause a significant decrease on permissible ceiling prices.

- **Reporting requirements and assessment of rebated prices** – Manufacturers would be required to submit cost-utility (pharmacoeconomic) analysis to PMPRB so that pharmacoeconomic considerations may be factored into pricing tests. The amended PMR also include new reporting requirements relating to rebates provided to direct or indirect purchasers, or reimbursing bodies, such as public or private drug plans. This is clearly aimed at requiring the reporting of confidential rebates currently given to public and private payors.
    - Discussed further below, the requirement to report rebates was struck down in a decision of the Federal Court on June 28, 2020. At the time of writing, it is not yet known whether this decision will be appealed to a higher court.
- **Application to certain non-prescription drugs** – The reporting obligations have been reduced for certain patented medicines, including generic drugs, veterinary drugs and most non-prescription drugs, with that information only required on request by PMPRB.

The innovator industry and some patient associations have expressed concerns over the reforms, citing reduction in access to medicines as an unintended consequence of pricing reform. Innovative Medicines Canada (IMC), the innovator drug industry association in Canada, stated in a press release that the regulations "will limit Canadian patients' access to new innovative medicines and discourage investment in Canada's life sciences sector for years to come". Along this vein, the removal of the United States from the PMPRB11 has been controversial given that many innovative medicines are developed in the United States.

As this price control regime hinges on patent protection, and the patent system exists to reward innovation, it is of note that Canada continues to appear on the "Watch List" published by the Office of the United States Trade Representatives in its 2020 Special 301 Report[7] as a country that may not offer adequate and effective intellectual property protections. The pandemic is highlighting the tension between affordable medicines and creating incentives for innovation. The international community is racing to develop vaccine candidates and investigate anti-viral treatments, and questions of priority and access are starting to surface.

The PMPRB issues implementation guidelines setting out procedures and details of price tests to be applied by Board staff under the PMR. A revised set of draft Guidelines was published on June 19, 2020,[8] with a consultation period in place to July 20, 2020 for stakeholders to provide feedback.

Under the current version of the Guidelines, the price tests applied to a patented medicine were based upon international pricing and the level of therapeutic contribution, meaning that breakthrough products or those with substantive improvement over existing therapies would be entitled to a higher price ceiling than a "me too" product. Under the draft Guidelines, generally a new medicine would be classified as either Category I or II based on treatment costs and market size, and for medicines that exceed the thresholds (Category I), the list price and rebated price as offered to payors would be subject to PMPRB oversight. This movement away from therapeutic contribution as a test for "excessive" pricing is consistent with the PMPRB's intent to shift the perspective on pricing to the viewpoint of the public healthcare system.

Emerging trends

Challenges to price control

PMPRB has been adamant that overhaul of the federal pricing regime is necessary for sustainability of the Canadian healthcare system. The Canadian innovative drug industry tends to be less outspoken and litigious than counterparts of other jurisdictions; however, two challenges to the PMR have been brought before the courts:

- **Federal Court** – IMC and 16 industry participants brought an application in Federal

Court to judicially review the amendments to the PMR on the basis that they exceeded the scope of the regulation-making power contained in the Patent Act.

- On June 28, 2020, the Federal Court allowed the application in part, concluding that the requirement to report rebates exceeded the scope of the federal government's regulation-making power. As drafted, the provision would allow the PMPRB to factor third-party rebates that are given to public and private insurers into its calculation of the average transaction prices. The Court held that "price" cannot include rebates to third parties because the Patent Act only contemplates the sale by the patentee to a customer. Insurers do not purchase medicines and are not customers of a patentee.
- However, the Court dismissed the balance of the application, concluding that both the new mandatory factors and the revised comparator basket of countries were consistent with the objective of curbing excessive prices for patented pharmaceutical products, and that the Patent Act clearly authorised the regulations as part of the legislative goal of preventing abuse of patent monopolies.
- Given the mixed success of the application, an appeal to the Federal Court of Appeal may be pursued by either party until the end of September 2020. If an appeal is filed, the matter may be expedited such that it could be decided before the implementation date of the PMR of January 1, 2021.

- **Provincial Court** – The PMR are currently the subject of a second court proceeding, before the Québec Superior Court, launched by six industry participants. This proceeding is a constitutional challenge to the validity of the Patent Act's entire drug-pricing scheme. That case is scheduled to be heard in late September 2020.

With finalised Guidelines still to come and the ongoing court challenges, it remains to be seen how this regime will be crystalised by the coming into force date of January 1, 2021.

The government acknowledged that industry may be more inclined to challenge the PMPRB's jurisdiction and methodologies: "With the proposed new Regulations in place, patentees might be less willing to offer voluntary compliance undertakings and instead press for formal and potentially prolonged hearings… Patentees might also more frequently challenge decisions made under the new regime in the Federal Court."[9]

National Pharmacare

The Canadian publicly-funded healthcare system is a matter of national pride. For years certain proponents have called for the implementation of a national drug insurance programme, to replace the public drug plans currently in place in Canada, arguing that such a plan would improve Canadian's access to drugs and reduce government spending by billions.[10]

An Advisory Council on the Implementation of National Pharmacare was established in 2018. Guided by the Council's consultations and recommendations, in 2019 the current government announced its intention to move forward with a national pharmacare plan and proposed implementation steps.

With the stated goals of lower drug costs and improving drug coverage, the federal government has allocated funds to:

- Establish a single coordinated entity, the National Drug Agency, to assess and negotiate drug prices for listing on a newly established national formulary.
- Develop a national formulary, representing a comprehensive, evidence-based list of prescription drugs covered by national pharmacare for eligible Canadians.
- Develop a national strategy for expanded orphan drug access and coverage.

If implemented, the national pharmacare framework would provide Canadians with access to drugs that are consistent across the country for those eligible for public plan coverage. The proposal does not discuss whether the federal government intends to make any regulations that would impact private drug plan coverage. Nor is it clear whether individual public plans would have discretion to include additional drugs on their formularies that are not part of the national pharmacare formulary.

There has been little movement on this programme to date, and the pandemic is very likely to further slow any progress. Thus, for the time being, Canada will continue to be a "patchwork" from a drug reimbursement and coverage perspective.

Drug shortages

The issue of drug shortages has been on Health Canada's radar for some time. Recently, the FDR was amended to include mandatory reporting obligations on a manufacturer when it is unable to meet demand for a drug product in Canada or when it stops selling a product in Canada. If a drug shortage exists or is likely to occur, the manufacturer must submit details on the shortage for posting in a searchable online database. This mandatory reporting obligation is a tool for Health Canada to monitor shortages. There are no direct regulatory consequences on a manufacturer that experiences a shortage.

Drug shortages are on the minds of Canadians for multiple reasons. Late in 2019, the United States published notice of its intention to make rules to permit the importation of Canadian drugs into the US. Several US states have put in place legislation that would allow the state to import drugs and/or act as a wholesaler for distribution within the state. With Canada's population being about ⅒th of that of the United States, there are serious concerns that if implemented, this proposal would result in empty pharmacy shelves in Canada.

The COVID-19 pandemic has also impacted drug supply in Canada. In a public advisory,[11] Health Canada stated that "the COVID-19 pandemic has resulted in significant shifts in the supply and demand of certain drugs", urging Canadians to not buy more medication than usual in order to ensure access for all.

Continuing shortage and supply gaps could impact the price of prescription drugs in various ways within Canada, and this is an issue that continues to be monitored.

Successful market access

It is important to a deep and complete understanding of the complexities of the Canadian healthcare system to develop a successful market access strategy. This requires consideration of:

- How will your drug product be categorised by Health Canada?
- Is your drug product eligible for expedited review?
- Will new indications be sought, and what is the anticipated time line for submission filing?
- Is your drug subject to patent protection in Canada?
- Is your drug eligible for data protection in Canada?
- Will you have market exclusivity in Canada? For how long?
- Do you have rights to Canadian patents that pertain to your drug? Are those patents in good standing or have they expired or been abandoned?
- How will your drug be priced in the US (geographic proximity to Canada) and how will the Canadian pricing impact the US market?
- Will your drug product be used in the hospital setting or on out-patients?
- What age of patient does your drug treat? What is the expected mix of public *versus* private sales?

- What is the current standard of care in the therapeutic area that the drug treats?
- What treatments are competitive to your product, and how are they priced?

* * *

Endnotes

1. Final Report of the Advisory Council on the Implementation of National Pharmacare, June 2019. See: https://www.canada.ca/en/health-canada/corporate/about-health-canada/public-engagement/external-advisory-bodies/implementation-national-pharmacare/final-report.html#2.
2. Approximately 58% of dispensed prescriptions are either covered by a private insurance plan or paid "out-of-pocket" by a patient. See PMPRB Strategic Plan 2015–2018: http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1197.
3. http://formulary.drugplan.health.gov.sk.ca/PDFs/Updated_Generics_Tiered_Pricing_Framework_FAQs.pdf.
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5. http://www.pmprb-cepmb.gc.ca/CMFiles/Consultations/DiscussionPaper/PMPRB_DiscussionPaper_June2016_E.pdf.
6. *Canada Gazette* Part I, Vol. 151, No. 48; December 2, 2017; see http://205.193.152.60/rp-pr/p1/2017/2017-12-02/html/reg2-eng.html?wbdisable=true.
7. https://ustr.gov/sites/default/files/2020_Special_301_Report.pdf.
8. https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/draft-guidelines.html#sec5.
9. *Canada Gazette* Part I, Vol. 151, No. 48; December 2, 2017. In describing the costs of reform, the RIAS states: "The base (2018–19), second (2019–20), third (2020–21), and fourth years (2021–22) would be anticipated to cost $1.0 million, $1.8 million, $2.8 million, and $3.8 million, respectively." From the fifth year onwards, it is anticipated that costs to Government would be $2.0 million/year to maintain the PMPRB's increased SPA funding.
10. http://www.parl.gc.ca/Content/HOC/Committee/421/HESA/Brief/BR8290924/br-external/CanadianHealthCoalition-2016-05-16-e.pdf.
11. https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/73223a-eng.php.

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China

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Abstract

PRC Law in terms of pharmaceutical law has developed very quickly over the past few years especially in an effort to encourage new drugs, technology transfer, as well as to adapt to the increasing development of the Chinese health situation. Through different kinds of regimes, such as modification of foreign investment catalogue in terms of pharmaceuticals, reform on the simplification of pharmaceutical registration, market authorisation holder regimes, two-invoice regimes, pricing regimes, reform of public hospitals in connection with pricing of medical services, telemedicine, reform of the online sale of pharmaceuticals, reform of the public health with elder caring systems, 4+7 target-quantity procurement, and reform on the medical system on encouraging private medical institutions, the PRC government would like to update its medical healthcare system in an effort to facilitate the medical service system and encourage the development of new drugs in this sector for the boom of this market in China. Amongst all these factors, the pricing and reimbursement policies are two important and sensitive factors for the fast development of this industry in China.

Market introduction/overview

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

According to the statistics published on 5 June May 2020 by the National Health Commission of the PRC (which replaced the Health and Family Planning Commission of the PRC), the PRC had 34,354 hospitals at the end of 2019 including 11,930 public hospitals and 22,424 private hospitals. All the medical institutions throughout the country received 8.72 billion visits in 2019. The average outpatient expenses per time are RMB 290.8 in 2019.

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

According to the *negative list for foreign investment* ("*Negative List*"), a medical institution

can only be established by foreign investors and its Chinese partners in forms of Sino-foreign equity joint venture or Sino-foreign cooperative joint venture. Furthermore, according to the recent *Negative List* to be effective as of 23 July 2020, a foreign invested medical institution can only be established in the form of a Sino-foreign equity joint venture.

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

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

In 2016, the PRC implemented the market authorisation holder regime for the majority of drugs except narcotic drugs, psychotropic drugs, medical toxic drugs, radioactive drugs, vaccines and blood products, in order to encourage medical research institutions and research persons in China to register and hold the drug market authorisation. Such pilot regime will last for two years until 4 November 2018. The pilot period has been extended for another one year until 4 November 2019. The *Drug Administration Law of PRC* was revised accordingly and the market authorisation holder regime has become the official regime after the revised *Drug Administration Law of PRC* has come into force as of 1 December 2019. To implement this measure, the *Drug Registration Administrative Measures* was revised and entered into force on 1 July 2020. This new regime gives more flexibility with regard to the application and transfer of drug market authorisation in China in an effort to encourage the development of innovative drugs. This new regime will also trigger high initiatives for pharmaceutical manufacturing companies in the structuring of their business in China in an effort to seek for funding investment for the purpose of the development of innovative drugs.

Pharmaceutical pricing and reimbursement

Regulatory classification

- How are pharmaceutical products regulated?

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

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

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

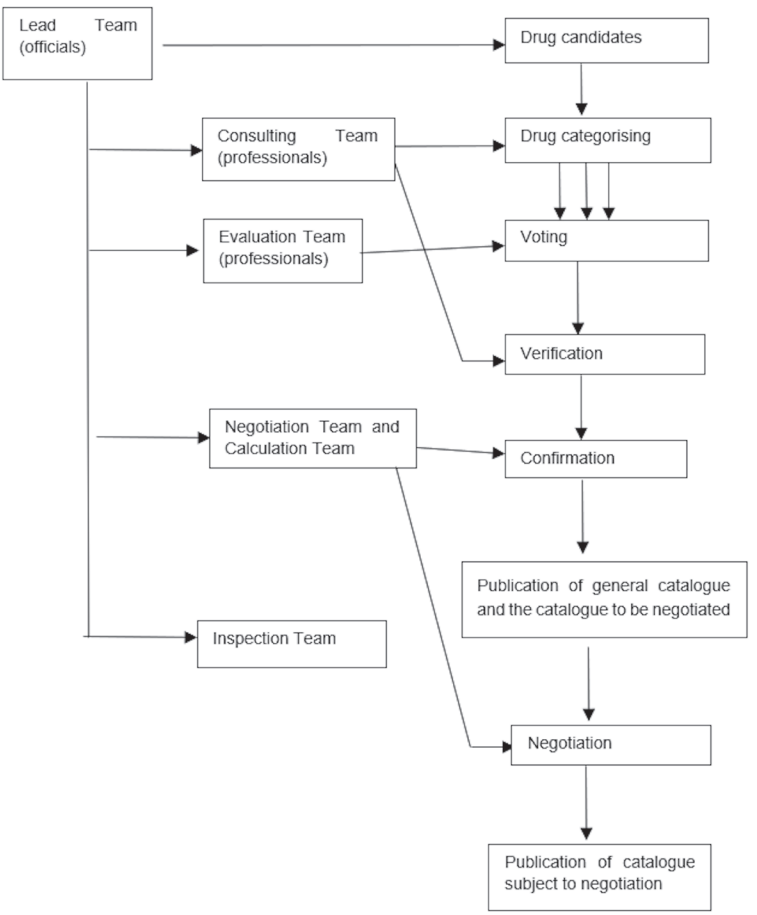
- What pharmaceutical products are eligible/ineligible for reimbursement?

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

(1) the National Catalogue of Drugs issued by the NHSA; and
(2) the Provincial Catalogue of Drugs issued by the provincial bureau of healthcare security administration.

The NHSA selects the drugs to be added to the National Catalogue with the assistance of its provincial counterparts. The NHSA must also consult with the NDRC, Ministry of Finance, National Health Commission, NMPA and the State Traditional Chinese Medicines

Administration and their respective provincial counterparts. The procedure for the selection of drugs to be included in the National Catalogue is as follows:



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

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

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

Who is/who are the payer(s)?

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

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

A new pharmaceutical product can only be reimbursed if it is selected by NHSA to be included

in the National Catalogue or by the provincial level healthcare security administration to be included in the Provincial Catalogue. The drug manufacturer is not entitled to apply for the selection of the drug to be included in the Catalogues.

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

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

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

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

According to the *Circular of the National Healthcare Security Administration on Issuing the Opinions on Effectively Carrying out Drug Price Administration at Present*, effective as of 26 November 2019, narcotic drugs and first class psychotropic drugs shall be subject to government guided price, instead of a government fixed price regime, whereas other drugs shall be subject to market price. This implies that the *Measures related to the Government Fixed Pricing for Pharmaceuticals*, effective as of 25 December 2000, are no longer applicable although they have not yet been officially abolished.

Therefore, according to the above Circular, except narcotic drugs and first class psychotropic drugs, the pricing of other drugs should be determined according to the market, by taking account of the reasonable difference of the prices in terms of dosage, specifications, packaging, clinical effects, costs, technology level, etc. The detailed rules regarding price difference will be implied by the NHSA. The medical insurance, especially the catalogues of reimbursable drugs, should play an important role in the guidance of drug prices with the aim to reducing the price by increasing the quantity of the drugs to be purchased.

Relationship between pricing and reimbursement

NHSA promulgated the *Catalogues of reimbursement for basic medical insurance, work injury insurance and maternity insurance* effective as of 1 January 2020 in order to unify as much as possible the medical reimbursement regime nationwide. According to this Catalogue, local authorities can no longer formulate or adjust the drugs in this Catalogue or the way of reimbursement set forth in the Catalogue, and the Catalogue provides for a transition period of three years for local authorities to reduce those Category II products which were added in the past by local authorities on their own. Those products which are not included in the said Catalogue can be further added through negotiations between NHSA and the manufacturers. Also, NHSA has the right to remove some drugs from this Catalogue if they are no longer qualified. NHSA is formulating the detailed rules related to the use of drugs subject to basic medical insurance to provide detailed rules on how to add and remove the related drugs from the Catalogue.

Issues that affect pricing

Except for narcotic drugs and Class I psychotropic drugs, the drug prices are set mainly

through market competition. The pricing of different categories of drugs are affected by different issues:

(1) for the drugs covered by the medical insurance funds, the reimbursement standards formulated by the government authorities will act as a mechanism for guiding the setting of drug prices in a reasonable manner;
(2) with regard to patent drugs and exclusively produced drugs, the prices thereof are set through establishing a public and transparent negotiation mechanism for setting prices which is participated by multiple parties;
(3) with regard to blood products not listed in the catalogues of reimbursable drugs, immunity and prevention drugs that are purchased by the State in a centralised manner, and AIDS antiviral drugs and contraceptives provided by the State for free, the prices thereof are set through bidding purchase or negotiation;
(4) narcotic drugs and Class I psychotropic drugs are still subject to the maximum factory prices and the maximum retail prices for the time being; and
(5) with regard to other drugs, the prices thereof are set by the producers and retailers thereof of their own accord to their production and operation costs and the market supply and demand.

In addition to the above factors, other factors may also affect the pricing, especially the two-invoice system which may change the commercialisation model of pharmaceutical manufacturers with their distributors, 4+7 target-quantity procurement, price difference in terms of dosage, specifications, packaging, clinical effect, technology standards of which the rules will be further promulgated by NHSA, tax regulations in connection with deductibility of related sales commission and sales expenses, and cooperation models with their Chinese distributors.

Policy issues that affect pricing and reimbursement

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

- *Two-Invoice System for Drug Procurement among Public Medical Institutions* taking effect as of 26 December 2016 on a trial basis. The two-invoice system is a system under which invoices are issued by drug manufacturers to drug distributors on a once-off basis while invoices are issued by drug distributors to medical institutions on a once-off basis. This policy is aiming to improve transparency in drug prices and eliminate excessive profit margins associated with multi-tier distribution models.
- *Healthy China 2030* and *13th Five Year Plan for Deepening the Reform of the Pharmaceutical and Healthcare System.* According to the aforesaid policies, the *Circular on Fully Carrying out the Work of Promoting the Comprehensive Reform of Public Hospitals* which took effect as of 19 April 2017 was promulgated. According to this new law, the decades-long policy of drug mark-ups amounting to 15% in public hospitals must be completely cancelled in order to fully promote the comprehensive reform of the public hospitals.
- *Circular of the General Office of the State Council on Issuing the Pilot Program for Conducting Centralized Drug Procurement and Use by the State* taking effect as of 1 January 2019. Eleven cities including four municipalities (Beijing, Tianjin, Shanghai and Chongqing), and seven cities (Shenyang, Dalian, Xiamen, Guangzhou, Shenzhen, Chengdu and Xi'an) have been selected to choose pilot varieties from generic drugs which have passed the evaluation of consistency in quality and efficacy (including approval for marketing based on the new classification of registration of chemical drugs, hereinafter referred to as "consistency evaluation"), and carry out pilot work

for centralised drug procurement and use conducted by the state ("4+7 target-quantity procurement"), in order to: (i) achieve a significant reduction of drug prices, to lower drug cost burden on patients; (ii) lower corporate transaction costs, purify the drug trading environment and improve the industry's ecology; (iii) guide medical institutions to regulate the use of drugs, and support the reform of public hospitals; and (iv) explore and improve the centralised drug procurement mechanism and market-oriented drug pricing mechanism. Such regime has been enlarged nationwide according to the Circular of NHSA on *Enlarging the Pilot Regions for Conducting Centralized Drug Procurement and Use by the State* effective as of 30 September 2020.

- *Opinions of the General Office of the State Council on Reforming and Improving Policies on the Guaranteed Supply and Use of Generic Drug* effective as of 21 March 2018. According to the aforesaid opinions, research and development of generic drugs, including those generic drugs whose registration applications have not been filed within one year prior to the expiration of patents rights of the corresponding innovator drugs, shall be encouraged for manufacturing, and the quality and efficacy of generic drug shall be improved and the capability of securing the drug supply shall be enhanced to satisfy demands for drugs in clinical treatment and public health security. To implement the aforesaid opinion, the National Health Commission and the other 11 commissions and ministries jointly promulgated the *Notice of Working Plan to Accelerate the Implementation of the Policies on the Guaranteed Supply and Use of Generic Drugs* effective as of 18 December 2018, according to which the first list of recommended and encouraged generic drug catalogue should be promulgated before the end of June 2019. On 9 October 2019, the *First List of Recommended and Encouraged Generic Drug Catalogue* has been jointly published by National Health Commission, Ministry of Science and Technology, Ministry of Industry and Information Technology, NMPA and the China National Intellectual Property Administration.
- *Catalogues of reimbursement for basic medical insurance, work injury insurance and maternity insurance* effective as of 1 January 2020. This Catalogue is the first catalogue after the establishment of NHSA to comprehensively adjust the reimbursable drugs in the said list and update the structure of drugs to be reimbursed.
- *Circular of the National Healthcare Security Administration on Issuing the Opinions on Effectively Carrying out Drug Price Administration at Present* effective as of 26 November 2019. According to the aforesaid Circular, in order to implement the major policies and plans of the Central Committee of the Communist Party of China and the State Council for safeguarding drug supply and stabilising drug price and further improve the drug price formation mechanism, the following opinions on effectively carrying out drug price administration at present are put forward: connecting and perfecting existing drug price policies; establishing and improving a normalised mechanism of drug price monitoring regulation; effectively carrying out price tendering and procurement related to safeguarding the supply; and stabilising the prices of drug in short supply and strengthening organisation and implementation.

Emerging trends

In October 2016, the Chinese government approved a blueprint called "Healthy China 2030", pledging to build a healthy China in the next 15 years with the public health services covering all people. According to "Healthy China 2030", China will comprehensively advance the reform of the medical insurance reimbursement methods, actively promote payment methods according to disease types and capitation, and take the initiative to explore payment by

Diagnosis Related Group System (DRGs) and service performance to form a composite payment method under the total budget management, and improve the negotiation and risk sharing mechanisms for health insurance agencies and medical institutions. Under "Healthy China 2030", the government will accelerate the settlement of cross-provincial medical expenses under the basic medical insurance and improve the mechanism of cooperation between medical and health institutions and elderly care institutions, to support the latter to engage in medical services.

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

On 25 February 2020, the *Opinions on Deepening the Reform of the Healthcare Security System* were promulgated by the Central Committee of the Communist Party of China and the State Council. According to the aforesaid opinions, by 2030, a comprehensive medical security system shall be fully established based on basic medical insurance, and supported by medical aid, supplemental medical insurance, commercial health insurance, charity donation and mutual medical insurance.

On 1 June 2020, the *Law of the People's Republic of China on the Promotion of Basic Medical Care, Hygiene and Health* promulgated by the Standing Committee of the National People's Congress came into effect as of 1 June 2020. This law is enacted in accordance with the *PRC Constitution Law* in order to develop the medical, hygiene and health services, ensure the basic medical and health services for citizens, improve citizens' health level, and push forward the construction of Healthy China and establish the above-mentioned comprehensive medical security system. The Law also expressly stipulates that the State shall establish a drug pricing monitoring system, carry out cost and price investigation and enforce the monopoly of price and price cheating and unfair competition in order to maintain the current drug price on the market.

Successful market access

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

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

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France

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Abstract

The French healthcare system is widely considered to be one of the most comprehensive and technically advanced in the world. Its financing is supported mainly by activity-based pricing that favours the amount of care produced, which can vary greatly according to the type of treatments and a patient's needs.

Deloitte's health barometer shows that the French are very strongly attached to their system, with 81% of respondents declaring themselves satisfied with the quality of care, 80% with the safety of care, and 75% with the competence of healthcare staff. Many rural residents, however, remain dissatisfied with the issue of geographical proximity of doctors, clinics or hospitals, with many complaining they live in a "medical desert" that requires extensive and onerous travel requirements (54% dissatisfied compared to only 28% in the Paris area).

France's solidarity-based system creates relatively high expenditures that are becoming harder for the government to sustain, especially now that officials are considering a transfer of the debt stemming from COVID-19 recovery efforts to the health system. The resulting financial strain could require a need for increased pricing or reduced treatment reimbursements that would impact low-income users in particular.

French policy is to ensure the highest reimbursements possible for drugs and treatments that are determined to be the most necessary, though developments in medical research, as well as policy changes, can influence prices as well. Only products and techniques that have received stringent regulatory approval are reimbursed by the state, while some of those that have not been covered by optional supplementary insurance policies are usually offered as part of employment contracts.

Market introduction/overview

The French population has a high life expectancy of 82.8 years, slightly exceeding the average for all OECD countries (82.4 years). Among these developed economies, France has the eighth highest life expectancy, with Japan remaining in the lead at 84.2 years.

France's Social Security system is ranked the best by the World Health Organization among its 191 members according to a study published by the British medical journal *The Lancet* in April 2017. It was ranked 16th among 167 countries and territories in terms of quality and accessibility by the 2019 Legatum Prosperity Index.

National Health System

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

France's healthcare system is broken down into various sectors.

- Professional service providers, which include:
  - Health establishments: public hospitals; and private clinics.
  - Mobile professionals and auxiliaries: doctors; pharmacists; midwives; nurses; and physiotherapists.
  - Emergency medicine.
  - Social welfare services and associations.
  - Ambulatory surgery.
  - Online consultations (telemedicine).
  - Home hospitalisation and treatments.
  - Nursing home services.
  - Specialised establishments for accommodating patients with specific needs, such as neurovascular units or centres for obese patients.
- Producers of goods and services (pharmaceutical industry).
- Public health institutions: the French system is managed by the Minister of Health and the Minister of Social Affairs.
  - At the *national* level, the central government implements public health and safety policies. It oversees all health institutions, setting prices for products and treatments while maintaining funding for health institutions.
  - At the *regional* level, departmental health agencies adapt national policies to a community's needs and constraints. They ensure the coordination between prevention, care and support as well as consistent resource management to ensure equal access to healthcare.
  - At the *local level* are the institutions and professionals in closest contact with patients and other participants. They are supervised by the regional health agencies.
- Providers of compulsory or supplementary health insurance plans.
- Recipients of healthcare (patients).

There are different types of health insurance depending on a person's professional situation:

- The general system covers more than four people out of five in France. It funds 78% of health expenses and includes employees in the private sector and, since January 1, 2018, self-employed workers (Article L. 311-2 of the Social Security Code). It is managed by the sickness insurance primary fund ("*Caisse nationale de l'Assurance maladie*", "CNAM").
- The agricultural system concerns farm and ranch workers.
- A series of smaller public systems address the needs of specific professions, such as railway workers, notary clerks and employees, and public servants.

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

Family members of insured people usually benefit from the same rights, including a spouse or children under 16 years old (or until 20 years old if they are students). They must register separately for Social Security and obtain their national health service card (*Carte Vitale*) which proves their affiliation and is used to process payments and reimbursements.

The CNAM general fund partially reimburses most healthcare costs, but in order to receive full compensation for outlays, users often must adhere to supplementary healthcare policies, known in France as "*Mutuelles*".

Since January 2016, the French universal disease protection programme (formerly known as "CMU", today "*Protection Maladie Universelle*", "PUMa") simplified procedures so that any person residing in France on a continuous and legal basis is able to benefit from medical fees reimbursement.

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

Important issues discussed in the national media

"Medical desert"

Healthcare coverage has increasingly focused on a shrinking number of doctors and other practitioners in rural areas, reflecting population declines as more households move to larger cities. For those remaining in such "medical deserts", often the elderly or families with limited financial resources getting timely treatment can require long car or train trips.

A report issued in October 2018 by the national delegates on access to care issued a series of recommendations, including:

- efforts to encourage outpatient internships and support installation projects, in particular by young doctors and other practioners;
- developing the coordinated exercise;
- an increase in online consultations;
- supporting new modes of practice;
- promoting inter-professional delegations and cooperation; and
- simplifying liberal practice and freeing up medical time.

Euthanasia

France has maintained a strict ban on euthanasia, despite a handful of high-profile cases in recent years that have sparked intense public debate, including within the medical profession. Only in extreme circumstances where a person suffers from irreversible brain damage or other severe injuries will health experts consider requests by family members to remove life support, or advise a family that such a move is advisable.

However, governments on both the left and right have shown no willingness to consider right-to-die legislation for other cases.

Social Security gap in light of the COVID-19 sanitary crisis

The unprecedented sanitary and economic crisis stemming from the COVID-19 virus pandemic has intensified the problem of financing French healthcare (the "Social Security gap"), a subject omnipresent in the media. The French Senate recently voted a law project to transfer the massive debt generated from spending on emergency supplies as well as unemployment benefits to the Social Security system's fund. The move would widen the financing gap by €136 billion, compared with an estimated gap of not more than €4 billion for 2019.

The return of balance to Social Security had been expected for 2024, but the crisis has pushed back the elimination of debt to 2033, and the financial strategy for doing so is yet to be established.

Media reports have warned the crisis could significantly impact the quality of care over the long term, jeopardising the system's goal of ensuring extensive and affordable coverage to all.

Pharmaceutical pricing and reimbursement

Regulatory classification

Medicines are a fundamental component of both modern and traditional medicine. According to Article L.5111-1 of the Public Health Code:

> "*A drug is any substance or composition presented as having curative or preventive properties against human or animal diseases, as well as any substance or composition*

that may be used or administered to humans or animals, with a view to establishing a medical diagnosis or restoring, correcting or modifying their physiological functions by exercising a pharmacological, immunological or metabolic action.

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

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

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

Different types of pharmaceutical products

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

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

Also, Article L. 5121-1 of the Public Health Code distinguishes drugs according to their preparation, for instance:
- *Bulk compounding*: drugs prepared for a specific group of patients because of a lack of adapted pharmaceutical products on the market.
- *Hospital preparation*: drugs prepared according to pharmacopoeia instructions and in compliance with proper practices mentioned in Article L. 5121-5 of the Public Health Code due to the lack of available or adapted pharmaceutical products.
- *Compounded medication*: drugs prepared in a pharmacy that are registered to the pharmacopoeia or on a national form allowing them to be directly dispensed to patients by the pharmacy.
- *Generic drug*: prepared with the same molecule of the reference medicinal products and with the same composition of active substances, the same pharmaceutical form and efficacy as the model of reference.
- *Biologic drugs*: the active substance of which is produced from a biological source and the quality of which requires a combination of physical, biological and chemical tests.
- *Biosimilar drugs*: biological drugs that have the same composition of active substances and pharmaceutical form as a reference biological medicine, which cannot be considered as generic drugs due to differences linked to the raw material or production process.

Refundable pharmaceutical products

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

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

As of January 2020, homeopathic drugs are no longer reimbursed by the state system.

Process for getting a new drug approved

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

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

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

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

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

In Europe, in the centralised procedure, the timeframe for obtaining a marketing authorisation is 210 days, and may be shorter in the case of accelerated approval, usually for urgently needed treatments whose safety and effectiveness have been sufficiently demonstrated. In France, in the case of national procedures or national phases of decentralised or mutual recognition procedures, the timeframes are also defined by the regulations. However, there are regular delays in these procedures. At the end of the mutual recognition procedure, the marketing authorisation shall be issued at national level within 30 days.

Who pays?

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

The national health insurance programmes are characterised by compulsory participation that reflects French goals of solidarity between generations and professions. Contributions are therefore based on income, and access to care defined according to need. In most cases, Social Security reimburses the bulk of a patient's outlays.

Supplementary schemes – "*Mutuelles*" offered by private insurance companies, insurance cooperatives or other groups – are often focused on particular professions and provided via a person's employer, though individuals can also search out separate providers. Coverage varies according to the type of contract, since both employers and employees often contribute, but they generally pay for the percentage of treatment not covered by the national system.

The French state covers a wide range of Social Security expenditures, including investments in prevention, medical and pharmaceutical research, the training of health professionals, universal complementary health insurance (available to low income households, "*Complémentaire santé solidaire*" (CSS), formerly "*Couverture Médicale Universelle*" (CMU-C)), grants for military hospitals, emergency care, as well as benefits paid to beneficiaries of State Medical Assistance "*Aide médicale de l'état*" (AME).

Despite the extensive coverage, care recipients may in some cases remain responsible for paying a portion of treatment expenses.

Prescribed drugs are covered entirely or partially by the health insurance system. In general, a patient purchases the drugs and is later refunded. The rollout of national healthcare cards equipped with electronic chips, and increased use of internet-connected card readers, is gradually eliminating the need to fill out paper forms to be sent by post for reimbursement, and often refunds are applied automatically at the time of purchase.

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

Basic health insurance

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

How is Social Security funded?

Resources which fund the social protection are:

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

Complementary health coverage

Any person can subscribe to complementary coverage plans in addition to Social Security, which may also benefit family members. Many people do so because in general, the system does not fully refund doctor visits, drug prices or other treatments.

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

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

Pharmaceutical products eligible/ineligible for reimbursement

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

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

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

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

Marketing authorisation

The marketing authorisation is issued by either:

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

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

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

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

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

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

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

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

The Commission on Transparency's opinion is transmitted to the Economic Committee of Health Care Products "*Comité Economique des Produits de Santé*" (CEPS) of a health product and the national union of medical insurance funds.

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

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

Both the Health Minister and the Social Security minister must sign off on a final decision on a drug's reimbursement.

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

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

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

Drugs that are no longer reimbursable

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

Who influences decisions?

According to Article R. 163-16 of the Social Security Code, the opinions of the Transparency Commission are subject to a dual requirement of motivation and publicity. Where the notice relates to the listing, amendment of listing conditions or renewal of the listing of a drug on the list of reimbursable specialties or on the list of drugs approved for community use, the notice is communicated immediately to the drug's producer.

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

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

Process to appeal a decision

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

In the event of refusal to include a product on the list of reimbursable drugs, it is possible

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

How is the reimbursement amount determined?

Article L. 162-16-4 of the Social Security Code provides that the CEPS sets the price based on: the results of economic and medical evaluations; the prices of other drugs with same therapeutic effect; expected volume sales; and foreseeable and actual conditions of use of the drugs.

France's national federation of medical insurance funds (*Union Nationale des Caisses d'Assurance Maladie*) is composed of representatives of the general system and the agricultural system. It sets the support rate of healthcare as well as the reimbursement rate of drugs. The medical service provided "*Service Medical Rendu*" (SMR) takes into account the severity of the concerned disease, the degree of undesirable side-effects, the therapeutic strategy and the preventive, curative or symptomatic character of the treatment.

Drugs in which a sufficient SMR has not been established will not be eligible for the list.

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

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

The reimbursement rate applies to the current sale price (or "flat rate of responsibility") that is a reference rate for the reimbursement of drugs in a particular category. The "flat rate of responsibility" aims to cover equivalent products in terms of efficiency (generic drugs) on the basis of a single tariff, based on the of the least expensive generic drugs.

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

Social Security reimburses part or all of the medicines purchased in pharmacies, depending on the drug concerned and the conditions of prescription and delivery. The reimbursement rate depends on the medical service provided for the drug.

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

Fixing the price

Two types of drugs may be distinguished:

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

Criteria for fixing the price

As mentioned above, in setting the price the CEPS takes into account: the improvement provided

by the drug; the results of economic and medical evaluations; the price of drugs with the same therapeutic effect; sales volumes; and the foreseeable and actual conditions of a drug's use.

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

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

Retail drug prices

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

It comprises the payment to wholesalers, including margins and discounts. A ministerial order from December 26, 2011, created a unique payment by wholesalers equal to 6.68% of the pre-tax manufacturer's price. However this coefficient concerns the portion of a price ranging from €0 to €450. Beyond this amount, the coefficient is equal to 0.

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

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

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

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

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

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

The average price of drugs, in pharmacies:

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

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

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

Discounts

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

- *Conventional discounts*
  Article L. 162-18 of the Social Security Code provides that companies (laboratories) may offer a discount through an agreement with the National Health Insurance Fund. These discounts correspond to sums due in application to the clauses provided in the contract between the CEPS and the laboratories. In 2016, the gross amount of such discounts amounted to €1,005 million. Most of these discounts concern only a small number of laboratories and certain drugs (50% of the rebates involve the five main laboratories operating in France, and 44% are made up of just 10 drugs). Price or volume clauses represent a combined 41% of the total discounts, an amount of €409 million.
- *Unconventional discounts*
  Article L. 162-16-5-1 of the Social Security Code contains provisions regarding discounts for drugs which benefit from a temporary authorisation of use.

According to a report by the CEPS, in 2016, the amount of such rebates amounted to €136 million.

Since December 21, 1988, the European Directive 89/105/EEC, known as the Transparency Directive, has imposed a regulatory framework for European countries to set prices. These provisions essentially concern regulators, which must publish the criteria used to determine a pre-tax drug price, respect response times, and justify their decisions. Marketing authorisation holders must provide information for regulators to determine their decision.

In France, the vast majority of drug prices are regulated, though laboratories are free to set prices for some specialties. Prices for non-refundable specialities are completely unregulated, as are distribution margins. These are either drugs for which the manufacturer has not claimed reimbursement from health insurance (the most common case), or drugs that have not been included on the list of products that can be reimbursed in a particular town or hospital.

Ambulatory drugs are reimbursed at an administered price, and were regulated until 2003. The prices are the result of negotiations between the laboratory and the CEPS.

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

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

Issues that affect pricing

Several factors can affect the price of drugs in France.

The presence of generic and biosimilar drugs on the market

The availability of generic drugs most often reduces the price of a drug for two reasons:

- The partial substitution of the original drug for the generic, which sees the price of the original decrease automatically under French regulations. Minimum price decreases are implemented at the time of the generic product's launching on the market (20%) and 18 months later (12.5%).
- The price of the original is often also cut by laboratories themselves, in order to keep their product competitive.

The price of the generic drug is also automatically decreased 18 months after its marketing launch, by 7%.

Prices decrease in tandem for both the generic and the original, since the prices of generics are calculated according to the price of the original, and apply to the pre-tax manufacturer's price.

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

- The "flat rate of responsibility", "*Tarif forfaitaire de responsabilité*" (TFR), which concerns drugs where the market penetration of generic drugs is considered to have been too low. In this instance, authorities calculate the reimbursement rate based on the lowest price of available generic drugs. While labs are free to maintain the prices of brand-name drugs, in practice they tend to align with the price of generic options.
- The so-called "third-party payment against generics": Automatic reimbursement at the time of purchase (for example, in pharmacies) is possible only if patients accept generic versions of drugs. If patients insist on the brand-name product, they must pay the full price immediately, and claim reimbursement later.
- Various policies aimed at encouraging both doctors and pharmacies to favour the use of generics.

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

The public authorities also assign annual price decreases to the CEPS. In 2016, for example, these directives led to savings of €794 million.

Supply chain

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

To decrease the cost of distribution, the French court of audit "*La Cour des comptes*" recommends regular reviews of remunerations for pharmacies and wholesalers. The goal is for overall remuneration to be based on the volumes delivered and not on a drug's price.

Drug counterfeiting

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

On May 29, 2017, the seventh World Health Assembly of the World Health Organization (WTO) agreed to adopt the new designation of "substandard and falsified" (SF) for medical products considered "substandard/spurious/falsely-labelled/falsified/counterfeit" (SSFFC). The new reference focuses only on the public health implications and not on intellectual property rights.

The WHO uses the following definitions:

- *Substandard*: also called "out of specification", which covers authorised medical products that fail to meet either their quality standards or specifications, or both.
- *Unregistered/unlicensed* medical products that have not undergone evaluation and/or approval by the national or regional regulatory authorities for the market in which they are marketed, distributed or used.
- *Falsified* medical products that deliberately and fraudulently misrepresent their identity, composition or source.

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

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

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

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

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

The link between the price of a drug and research and development spending

According to the pharmaceutical industry,[3] the price of drugs is linked to the necessary investments in researching, developing and manufacturing processes that can require the spending of millions of euros over several years. The higher the costs of bringing a new and innovative treatment to market, the higher the cost is likely to be for consumers, especially if the number of patients benefiting is relatively small.

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

Competition

Competition authorities look very carefully at the medicines market and pricing. For instance, on December 19, 2013, the French Competition Authority (*Autorité de la Concurrence*) issued opinion n°13-A-24 about competition in the sector of drugs distribution downstream. The Authority held that dysfunctions in full competition can influence the development of the market, and thereby keep some drug prices higher than they might be. Thus, the Authority determined a lack of information about drug pricing overall, and suggested more transparency so that consumers would be able to compare prices between different pharmacies promoting competition.

On April 26, 2016, the Competition Authority issued an opinion on the online sales of medicine. Furthermore, since November 21, 2017, the Competition Authority has been investigating competition in the medicine and biological markets. Also, the European Commission has initiated formal investigation regarding Aspen Pharma's pricing practices, and the European Court of Justice ruled on drug pricing in Germany.[6]

More recently, on January 30, 2020 (case C-307/18), the European Court of Justice held that a settlement agreement regarding a dispute between a holder of a pharmaceutical patent and a manufacturer of generic medicines related to patented medicine that had fallen in the public domain and that contained pay-for-delay provisions as well as commitments not to pursue patent invalidity claims, and value transfers, was contrary to EU competition law.

Transparency

In response to an overall increase in drug prices, a group of associations called on the French government to commit itself to the "transparency" resolution presented to the WHO General Assembly on Health on May 20–28, 2019, in Geneva, Switzerland.

They noted that in France, unprecedented rationing was introduced for Hepatitis C treatments between 2014 and 2017 because it was impossible to provide it to all those who needed it. Similarly, treatments for various cancers are subject to administrative barriers that limit their prescription, because of their high prices.

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

Foreign direct import

According to the Leem organisation that represents drug companies, France imported €18.3 billion worth of medicines in 2017. These imports came mainly from Germany (17.1%), the United States (16.1%), Switzerland (12%) and Ireland (9.6%). While foreign trade in medicines overall represented a trade surplus of €6.8 billion for France that year, that surplus was down 12% from the previous year.

Parallel intra-community import of medicinal products is originated by the coexistence of free movement and price discrepancies due to the right of States to set an administrative price for reimbursable medicinal products, particularly in some southern European countries (Greece, the Iberian Peninsula, but also France).

In the States concerned, while parallel trade may benefit intermediaries and social protection bodies, patients can be exposed to supply disruptions in the French market.

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

Policy issues that affect pricing and reimbursement

Population growth

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

In France, the ageing of its population has coincided with an increase of diagnoses of certain diseases. The main expenditure item remains as one-off hospitalisation, at more than €31 billion per year. Growth has been very rapid in six years, with 566,000 more patients requiring hospitalisation, for a total of €4 million. To give one example, diabetes, with 3.2 million patients treated in France each year for a total cost of €7 billion, is closely associated with age.

According to the *Quotidien du Pharmacien* trade magazine, France has 20 million patients with chronic conditions. A medicalised mapping of health expenditures for 2017, presented by the CNAM, reveals that 20 million French people have used care related to the management of a chronic pathology, representing 35% of the 57.6 million beneficiaries of the general scheme.

Cost of healthcare as a percentage of GDP

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

Cost of research and development

The costs associated with the development of new medicines are increasing (almost €1 billion), according to the Leem organisation, which it says justifies a strong protection of profit margins for innovation. With the global COVID-19 pandemic, the supported efforts to produce an efficient vaccine have also contributed to an increase of research and development costs in the medical field. This is why intellectual property is one of the fundamental elements in the development of innovation. Because research companies invest in long and costly scientific programmes, they must be able to rely on such rights to secure an acceptable return on investments.

Cost of innovation

Therapeutic innovation is contributing to increased spending. In total, 2.6 million people are now treated for cancer worldwide, including 1.2 million in the active phase, for an annual cost of €15 billion. Lung cancer costs alone cost on average €20,000 per patient per year, for a total expenditure of €1.6 billion.

Affordable access to care

Access to care is a fundamental right for citizens across the developed world. It can be defined as the right of everyone to receive preventive or curative care without reference to a pre-existing social or health situation. This is why, on January 1, 2000, France introduced universal health coverage (CMU), today known as PUMa, for low income households to ensure access to health insurance and that everyone has effective access to care.

Global health impact on national health

The global COVID-19 pandemic prompted the implementation of exceptional measures to curtail the virus's spread and pay for the surge in treatment costs. More generally, the re-emergence of infectious diseases raises the question of both the long-term and short-term effects on pricing and reimbursement. With the development of new vaccines as well as preventive measures such as distribution of face masks and other personal protection equipment (PPD), the French government like others around the world has had to reconsider its financial strategy for the health system, often in response to fast-breaking developments.

For example, during the first months of the new coronavirus outbreak, COVID-19 tests were fully reimbursed only for people presenting symptoms of the virus, or the "contact cases" that doctors certified were exposed to someone carrying the virus. This was because testing kits were in short supply in many countries after the outbreak struck. Only recently has France allowed free testing for all, without a medical prescription, though many health experts admit the number of available test kits remains insufficient.

Similarily the free distribution of face masks has been limited to people in possession of a medical prescription certifying they are in "fragile" health or "vulnerable" to the virus. Otherwise, the maximum price for a disposable surgical mask is fixed €0.95, a price that critics say is out of reach for low-income households. The price of other mask types is not regulated.

How do politics affect pricing and reimbursement policies?

Unlike in other European countries, in France it is not Social Security that negotiates drug prices and reimbursement rates, but an inter-ministerial committee, the CEPS, which operates under the joint authority of the Ministry of Health and the Ministry of the Economy.

Even if the pharmaceutical industry is not a member, the CEPS sometimes forces the authorities to accept relatively high prices, as noted by a Court of Auditors' report from 2017 on Social Security financing. For example, Crestor, a very expensive statin for lowering cholesterol levels, achieved a price four times higher than other similar generic drugs, without improving the medical service provided.

The Court of Auditors report noted several cases where a drug manufacturer, in defending a relatively high price, successfully presented its needs to cover high employment and investment costs for developing a drug.

Emerging trends

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

Possibility for pharmacists to dispense certain medicines

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

Social regime for students

On February 15, 2018, the government ended a separate social security regime for students by adopting a law on guidance for "student success". With the regime's definitive disappearance on August 31, 2019, students are now linked to the general social security system, and no longer pay contributions.

Therapeutic cannabis

The ANSM has recently announced the conditions for the delivery of cannabis treatments for therapeutic purposes, which will initially be carried out on an experimental basis, subject to validation by the Ministry of Health.

The experimental treatments will be reserved for a limited number of patients whose symptoms can not be relieved by other medications.

Five indications have been selected by a Temporary scientific specialty committee "*Comité Scientifique Spécialisé Temporaire*" (CSST): neuropathic pain; certain forms of severe epilepsy; supportive cancer care; palliative care; and painful spasticity (contraction) due to multiple sclerosis or other diseases of the central nervous system.

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

Cannabis will be prescribed by doctors specialising in the diseases concerned and working in multidisciplinary referral centers. It will then be available, from next year, in pharmacies, in the form of capsules, oil or dried marijuana flowers.

Online drug sales

A draft law was examined in February 2020 to ease regulations on the sale of medicine on the internet. Currently, medicines sold without prescription can be commercialised online only after the authorisation of the national health agency. This draft law, whose debate was suspended during the COVID-19 crisis, would have removed this requirement.

Free masks for the most precarious

After the government implemented the obligation to wear a mask in closed public spaces in July 2020, the Ministry of Health had to guarantee the distribution of free masks to the most vulnerable, to ensure a continuity in the providential nature of the French health system. Considering the issue of the cost of virus prevention, the government is coordinating a plan of free access to masks for the beneficiaries of the CSS.

Successful market access

Successful market access will necessarily involve a balance between compensating research costs and the limitation of competition in the drugs market. Given the challenges of population ageing in France, constant innovation with sufficient protection of patents is key to ensuring reliable revenue streams that encourage further investments, even while sustaining the steady introduction of generic alternatives.

* * *

Endnotes

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

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Germany

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Abstract

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

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

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

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

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

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

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

Market introduction

Market overview

Statutory and private health insurance

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

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

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

Health expenditure

Total health expenditure in Germany reached €391 billion (approx. 11% of GDP) in 2018, 29% of which was spent on care-related and therapeutic treatment, 26% on treatment by physicians, 15% on pharmaceuticals, and the remaining 30% on additional services and/or administration. The annual average spent of SHIs between 2009 and 2019 was €252 billion.

As to pharmaceuticals, approx. 6% of the total health expenditure is spent on patent-protected products, and 10% relates to other pharmaceuticals such as generic products.

In 2019, 25 pharmaceuticals (excluding biosimilar) with new active substances were launched in Germany. Ten of them are licensed for the treatment of cancer and five for orphan diseases. The launch of 25 pharmaceuticals with new active substances is comparatively low and falls behind 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 2017, 81% of all prescriptions issued for treatments with pharmaceuticals referred to products regulated by the reference price system, thereby covering 37% of the overall expenditures by the SHIs for pharmaceuticals.

Under the reference price regulation, pharmaceuticals are allocated to specific 'reference price groups'. These groups can be established on the basis of: (i) products having the same API; (ii) products having pharmacological or therapeutically comparable APIs; or (iii) products having comparable therapeutic effects, including combination products consisting of more than one API. These reference groups are established by the G-BA and can also combine generic and patent-protected products. Patent-protected products can only be exempted from the reference price system if a pharmaceutical company can prove that such product has an additional therapeutic benefit compared to other pharmaceuticals of the same group. This additional therapeutic benefit must generally be established on the basis of 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 July 2019 (see emerging trends below), 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; which is followed, secondly, by price negotiations between GKV-SV and the respective pharmaceutical company.

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

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

HTA process

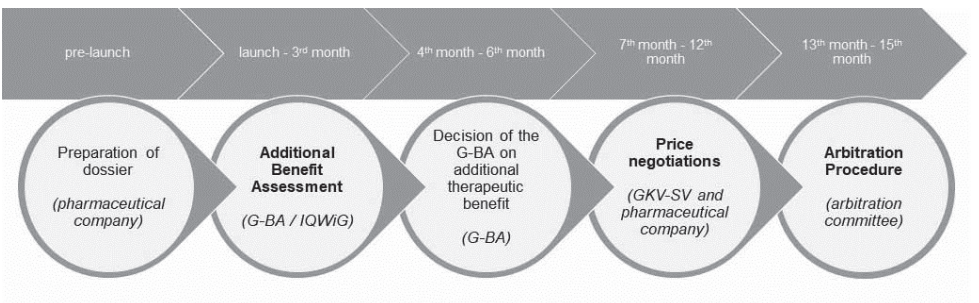
The AMNOG process does not change the general principle that pharmaceutical companies remain free to determine the launch price for innovative pharmaceuticals. Upon launch, however, they are obliged to submit a dossier to the G-BA in order to establish the cost-effectiveness of the new pharmaceutical.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

Once the IQWiG has completed its scientific assessment, the G-BA takes a final decision within six months. This decision contains the final rating of the additional therapeutic benefit of the relevant pharmaceutical with respect to the selected comparator. The additional

therapeutic benefit must be specified across a range of different levels. While level 1 reflects an extensive additional benefit over the defined comparator, level 6 is equal to a 'negative additional benefit'. Moreover, the G-BA also states the level of evidence by which such benefit is established. Again, these levels of evidence cover a broad range, including a proof of an additional therapeutic benefit as well as a mere indicator.

If no additional therapeutic benefit can be established, the respective pharmaceutical shall be allocated to an existing reference price group, if possible. If a suitable reference group neither exists nor can be established, the reimbursement price will be negotiated between the GKV-SV and the pharmaceutical company. However, the negotiated reimbursement price must generally not exceed the annual costs of treatment of the comparator, unless specific circumstances justify a higher reimbursement price.

Reimbursement price negotiations



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

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

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

Reimbursement price agreements can be terminated, at the earliest, one year after signing.

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

Arbitration procedure

If no reimbursement price agreement can be reached within the statutory period of six months, an arbitration committee shall determine over a period of three months those elements of the reimbursement price agreement on which the original parties had been unable to reach a consensus. The arbitration committee is composed of representatives of the GKV-SV and the respective associations of the pharmaceutical companies. It is further composed of three impartial permanent members, as well as two further members of each party. This arbitration procedure is technically an administrative procedure. The arbitration committee is bound by the legal criteria set out under the German social law system but enjoys broad discretion when it comes to the actual determination of the reimbursement price.

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

Special problems: Blended pricing in case of a mixed HTA

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

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.

Judicial review

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

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

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

Policy issues

Background of AMNOG process

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

Main challenges of AMNOG process

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

High number of negative assessments

The percentage of assessments in which no additional therapeutic benefit could be proven is considerably high (43% of overall 349 assessments by G-BA made between 2011 and 2018). 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 for respective sub-groups. This lack of evidence has triggered criticism from the pharmaceutical industry with regard to the G-BA's practice of possibly 'slicing' patient populations into sub-groups and demanding data which cannot be available at the early stages of market entry of an innovative product.

Determination of low-cost comparators

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

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

Unbalanced governance

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

Transparency of reimbursement prices

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

Opt-out

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

In this context, data published in 2017 show that the availability rate of innovative products has dropped from 98.5% to 80.24% due to pharmaceutical companies not entering the German market. As of 2018, a total of 37 products were withdrawn from the market, although nine of these pharmaceuticals are now again available in Germany.

Free pricing in first year after product launch

Then again, the pharmaceutical industry has been criticised by the SHI for setting 'astronomically high' prices for certain products and thereby allegedly abusing the possibility of free pricing during the first 12 months of a product's launch (a prominent example is the launch price for the Hepatitis C drug *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

New Framework agreement on the supply of medicinal products

Since 1 July 2019, a new framework agreement on the supply of medicinal products is in force, which is the first major revision since 2016. In particular, the rules governing the dispensing of medicines in pharmacies were substantively changed. Among other things, the requirements for the priority dispensing of pharmaceuticals for which a rebate agreement between the concerned SHI of the patient and the pharmaceutical company exists have been simplified. In addition, certain terms and procedural requirements were specified, particularly aiming at a clarification of the recourse procedure (retaxation) between SHIs and pharmacies in case of incorrect dispensing of pharmaceuticals.

EU harmonisation on HTA

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

Eventually, since, *inter alia*, the German Parliament considered the approach as non-compliant with subsidiarity, it sent a reasoned opinion to the European Commission, which was found to be justified. The EU lacks competence for harmonising clinical assessment; it is especially not permitted to bypass Member States' responsibility for health services by way of the internal market competence. The obligations connected to a joint assessment entail intervention in the health policies of the Member States, because the HTAs that are the subject of the legislation constitute an essential element of the 'management of medical care'. Hence, the EU Parliament mitigated the draft in several points; it shall, for example, be possible for Member States to conduct additional HTAs, and the HTA shall not be exclusive. The legislative process is still ongoing. It is expected to be concluded in the course of the year 2020.

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 is subject to consultation with the European Commission, which is currently still pending. The legislative procedure of the German draft bill is suspended until alignment with the European Commission is reached.

Finally, against the background of the ECJ judgment, a verdict of the Federal Administrative Court is regarding 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.

Security in supply with medicinal products

The Act for More Security in Supply with Medicinal Products ('**GSAV**'), came into force in August 2019 as a reaction to the recall of contaminated *Valsartan* products. While it focuses on supply security aspects, it also entails relevant changes regarding the additional benefit assessment and the competences of the G-BA.

First, the GSAV promotes the use of biosimilars. For this purpose, the rules on substitution of originators by biosimilars were loosened. Previously, a substitution was only possible with so-called bioidenticals. The G-BA now has three years to publish guidelines governing which originators can be substituted by biosimilars. Additionally, target agreements concerning minimum quotas for prescribing biosimilars, and for efficient prescription on regional levels, shall be concluded.

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

The GSAV also targets special pricing and reimbursement rules for medicinal products for the therapy of coagulation disorder in case of haemophilia. These pharmaceuticals are now regulated uniformly and made subject to fixed prices. The manufacturer's price for such medicinal products is supposed to be oriented towards the volume-weighted arithmetic average purchase prices which hospitals and physicians have paid for these products in 2017 and 2018. Pharmaceutical companies had to report this price to the GKV-SV until the end of November 2019 where it was checked for plausibility. If either pharmaceutical companies did not announce the respective average price, or the GKV-SV did not consider the reported price plausible, it may determine the future manufacturer's price itself. This price would then apply starting from the end of August 2020.

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

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.

Revised regime for the pricing of vaccines

Especially due to shortages of vaccines in 2018, the German government wanted to reopen the market to all vaccine manufacturers and move away from selective contracting schemes. To this end, the legislator included related provisions in the Act for Earlier Doctor's Appointments and Better Medical Care ('**TSVG**'), entered into force in May 2019. Although not a new regulation in substance, since then, the statues include an additional clarifying sentence that rebate agreements for vaccines under the SHI regime to be agreed between SHIs and pharmaceutical companies are no longer permissible. Furthermore, the TSVG limits the SHI reimbursements for pharmacists to the pharmacists' actual purchase price paid to the respective manufacturer when dispensing vaccines. By this means, incentives to pharmacists regarding lower individual price negotiations with vaccine manufacturers were eliminated.

Earlier drafts of the TSVG also provided for mandatory rebates on vaccines in general (5%) and increasingly on influenza vaccines (10%). However, in the course of the legislative procedure, this provision was not included in the final legislative text.

Successful market access

Even in the absence of a fourth hurdle, successful market access by pharmaceutical companies

in Germany requires careful preparation and a well-structured approach. It is crucial that this process is only initiated after marketing authorisation has been granted. Market access and regulatory experts should therefore work closely together in integrated teams throughout the whole marketing authorisation application process.

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

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

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

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India

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Abstract

Healthcare is the largest industry in India in terms of revenue and employment. Being the fastest growing sector, the Indian healthcare market is expected to reach US$ 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, over the past year, the country, as well as all over the world, 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 per cent of the generic demand in the US, 25 per cent of all medicines in the UK and 50 per cent of the world's vaccine requirements.[1]

India is additionally the fourth largest medical devices market in the world.

The hospital industry in India is estimated to reach US$ 372 billion by 2022 from US$ 160 billion in 2017. Indian medical tourism market is growing at the rate of 18 per cent year on year and is expected to reach US$ 9 billion by 2020.[2]

For the financial year 2020–21, the Ministry of Health has received an allocation of INR 67,112 Crore. This is an increase of 3.9 per cent over the revised estimates of 2019–20 (INR 64,609 Crore).[3]

Pharmaceutical pricing & reimbursement

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 availability of quality healthcare on an equitable, accessible and affordable basis by establishing a comprehensive primary healthcare delivery system and well-functioning linkages with a secondary and tertiary healthcare delivery system. As per the Union Budget 2019–20, the allocation to the Ministry of Health and Family Welfare has increased by 13.1 per cent to INR 61,398 Crore (US$ 8.98 billion).
   The MoHFW has two departments *viz*., The Department of Health & Family Welfare and the Department of Health Research ('DHR'). The Directorate General of Health Services ('DGHS') is the attached office of the Department of Health & Family Welfare and has subordinate offices spread all over the country. The DGHS renders technical advice on all Medical and Public Health matters and is involved in the implementation of various Health Services.
   The Central Drugs Standard Control Organisation ('CDSCO') under the DGHS, is the National Regulatory Authority ('NRA') of India. The CDSCO is responsible for 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 to bring about the uniformity in the enforcement of the Drugs and Cosmetics Act, 1940 ('D&C Act') and the Drugs & Cosmetics Rules, 1945 ('D&C Rules').
   On the other hand, the aim of the DHR is to bring modern health technologies to the people through research and innovations related to diagnosis, treatment methods and vaccines for prevention, to translate them into products and processes and, in synergy with concerned organisations, introduce innovations into the public health system.
2. **Ministry of Chemicals & Fertilizers**: The Ministry of Chemicals and Fertilizers in India is the administrative unit of the following three departments:
   a) Department of Chemicals and Petrochemicals.
   b) Department of Fertilisers.
   c) Department of Pharmaceuticals ('DoP').
   The DoP was created with the objective 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, as an independent Regulator for pricing of drugs and to ensure 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')**[4] – 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**[5] – 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 as 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[6] 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**[7] – The Rules were notified by the MoHFW, in exercise of its powers under Sections 12 & 33 of the D&C Act, on March 19, 2019, primarily with an intention to regulate clinical trials in the county. One significant change is the automatic approval granted to New Drugs in the country if the said drugs have been previously approved in select developed markets, and if global trials included Indian patients.
4. **Essential Commodities Order, 2020**[8] – By invoking the relevant provisions of the Essential Commodities Act, the government notified the Essential Commodities Order on March 13, 2020, declaring masks (2ply & 3ply surgical masks, N95 masks) and hand sanitisers as essential commodities in the country. This has been done in the wake of the COVID-19 crisis and was to remain in force until June 30, 2020.
5. **Fixation of prices of Masks (2ply & 3ply), Melt Blown Non-Woven Fabric & Hand Sanitizers Order, 2020**[9] – Having declared masks and hand sanitisers as essential commodities in the wake of COVID-19 crisis, the Government of India, by this Order dated March 21, 2020, capped the retail prices of hand sanitisers, masks and the raw materials used in the production of masks. This Order too was valid until June 30, 2020.

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 per cent 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 March 25, 2020,[10] the prices of a total of 869 drugs are controlled by the NPPA.

As detailed above, price control now extends to medical devices as well. Of these, only four – cardiac stents, drug-eluting stents, condoms and intra-uterine devices – are included in the NLEM and are, therefore, subject to notified price caps. 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 per cent of prices prevalent in the preceding 12 months.

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 June 1, 2020, the price regulator has proposed guidelines for dealing with cases of discontinuation[11] of price-controlled drugs. Comments were invited from the stakeholders in this regard within a period of 15 days from June 1, 2020. One of the amendments, which could be of interest to drug manufacturers, is a proposal to permit an upward price revision by the companies, provided they make out a case of having to discontinue the product on account of non-remunerative pricing.

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 per cent. 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 effect 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[12] in respect of 42 anti-cancer drugs and it proposed that capping of trade margins of other drugs/medical devices would follow suit. It remains to be seen if the mechanism adopted by the regulators to cap the trade margins, as opposed to the capping the prices of formulations, is legally tenable or not.

Patented drugs

In January 2019,[13] 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 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 tends to introduce artificial product differentiation in the market, with no corresponding difference in the therapeutic efficacy of branded and non-branded generics.

Online pharmacies[14]

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 chaper, 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,[15] 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.

As of June 26, 2020[16] a total of 21,232 hospitals have been empanelled and 12,50,35,644 cards have been issued. In fact, in the 2020 Budget, INR 69,000 Crore has been allocated to the healthcare sector, out of which INR 6,400 Crore has been provided to Ayushman Bharat-Pradhan Mantri Jan Arogya Yojana ('AB-PM-JAY').

Other policies and 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**[17] – 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 & 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**[18] – 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**[19] – 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.
- P**roduction Linked Incentive ('PLI') Scheme** for promotion of domestic manufacturing of critical KSMs/Drug Intermediates and APIs in India.
- **Production linked incentive scheme for promotion of domestic manufacturing of critical KSMs/Drug Intermediates and APIs in India**[20] – With an intent to make India self-sufficient and to promote pharmaceutical industry and to ensure availability at affordable prices, the Government launched this Scheme on June 2, 2020. 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 Crores 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. Detailed guidelines are awaited.

- **Scheme for promotion of Bulk Drug Parks**[21] – 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 Crores for providing financial assistance for construction of Common Infrastructure Facilities in three Bulk Drug Parks. The tenure of the Scheme is for the years 2020–21 to 2024–25. Detailed guidelines are awaited.
- **Production Linked Incentive Scheme for Promoting Domestic Manufacturing of Medical Devices**[22] – 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. Detailed guidelines in this regard are awaited.
- **Scheme for Promotion of Medical Device Parks**[23] – 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. Detailed guidelines in this regard are awaited.
- **National Health Policy, 2017**[24] – 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 Uniform Code of Pharmaceutical Marketing Practices ('UCPMP')**[25] – 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**[26] – 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.
- **Pradhan Mantri Bhartiya Janaushadhi Pariyojana 2015**[27] – 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. By March 31, 2016 the repertoire contained 900+ drugs and 154 surgical items.
- **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 & 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 per cent 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 per cent, while that of patented drugs is 21 per cent.

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 per cent FDI through an automatic route; 100 per cent is permitted for greenfield pharmaceuticals; 100 per cent is permitted for brownfield pharmaceuticals; 74 per cent through automatic route; and the remaining (up to 100 per cent) 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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Ireland

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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. Other than for cancer drugs, there is a uniform application procedure to have a product added to the reimbursement list. There currently is no distinct approval pathway for rare disease medicines or hi-tech products.

Ireland has an ageing population and therefore demand for medicines, especially for chronic diseases, is increasing. In recent years, the State has reformed the Irish pricing and reimbursement system and introduced a number of measures to reduce healthcare expenditure. Suppliers are also entering into novel contractual arrangements to add value and demonstrate the cost-effectiveness of their products. Despite this, suppliers face significant challenges in securing reimbursement of new medicinal products in Ireland, especially hi-tech medicines and those for rare 'orphan' diseases.

Market introduction/overview

The Irish healthcare system is a two-tier one, comprising the public healthcare system and the private healthcare system. The public healthcare system is funded by the State through taxation and social security contributions. Any person ordinarily resident in Ireland is entitled to receive healthcare through the public healthcare system. The private healthcare system is funded by private insurance and private funds. Private healthcare remains a popular option in Ireland, with around 40% of residents taking out private insurance.

In Ireland, healthcare policy and expenditure are determined by the Department of Health and Children, and administered through the Health Services Executive (HSE). The HSE operates a positive reimbursement list and HSE expenditure on medicines is approximately €2.7 billion *per annum*.

Over the past decade, the population of Ireland has increased by nearly 7% to approximately 4.8 million. The demographic ageing of the population means demand for medicines, especially for chronic diseases, is increasing. As a result, pharmaceutical expenditure is expected to grow, with key drivers for increased spending being hi-tech drugs and new hospital drugs.

The pricing and reimbursement landscape in Ireland has undergone significant change in recent years. New legislation introduced a number of measures to reduce healthcare expenditure, primarily a system of generic substitution and reference pricing. The State also entered into a four-year framework agreement with industry in 2016 for the supply and pricing of medicines to help contain pharmaceutical costs. The current framework agreement is due to end in July 2020.

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 inevitably are deemed cost-ineffective when assessed on standard pharmacoeconomic criteria. However, even those products that are deemed to be cost-effective are facing reimbursement delays due to the lack of overall affordability for the Irish healthcare system. 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 non-prescription items are reimbursable where a doctor prescribes them.

The Medicinal Products (Control of Placing on the Market) Regulations 2007 (SI 540/2007), as amended, set out the criteria for determining the legal supply status of medicinal products. Generally, new medicines may only be supplied on prescription. After several years of use of the medicine, sufficient information may be available to justify a change in its legal supply status to non-prescription supply by a pharmacist. It may also be possible for medicines previously supplied only by a pharmacist to be supplied on general sale, if appropriate.

Who is/are the payors?

In Ireland, the State pays for nearly 80% of all medicines through reimbursement of community pharmacists. The cost to the State of medicines dispensed in the community depends on the different reimbursement schemes an eligible patient may use. The HSE Primary Care Reimbursement Service (PCRS) operates four principal reimbursement schemes:

- *General Medical Services Scheme (GMS)*: a patient receives their medicines after paying a €2.00 per item prescription charge (up to a maximum charge of €20.00 per person or family per month) or for a patient aged over 70, the prescription charge is €1.50 per item (up to a maximum charge of €15.00 per person or family per month). The prescription charge per item for all patients is due to be reduced by €0.50 in September 2020. The pharmacist receives a dispensing fee. The GMS scheme applies to those who do not have sufficient means to pay for their medicine, while prescription charges for people in emergency accommodation are to be phased out.
- *Drug Payment Scheme (DPS)*: a patient pays a maximum of €124 per month for medicines supplied to them and their family, which is set to reduce by €10 to €114 per

month from September 2020. If an interchangeable medicine is supplied, the reference price is used to calculate the monthly cost. The pharmacist receives a dispensing fee.

- *Long Term Illness Scheme (LTI)*: provides medicines to patients with specific long-term medical conditions, such as diabetes, epilepsy, multiple sclerosis and cystic fibrosis, free of charge. The LTI scheme is not means-tested and therefore does not depend on a patient's income or other circumstances. Similar to the DPS, the pharmacist receives a dispensing fee.
- *Hi-Tech Scheme*: a patient receives expensive medicines required for long-term care and either pays the first €124 a month of the cost in accordance with the rules of the DPS, or receives the medicines free of charge, if they hold a medical card or the medicine is for a specific condition covered by the LTI. Under the hi-tech scheme, pharmacists receive a patient care fee of €62.03 per patient in the month when an item is dispensed, and €31.02 in the months where no item is dispensed. The non-dispensed patient care fee may only be paid for a maximum of three consecutive months in respect of a particular patient between each dispensing.

Payments to pharmacists are regulated by 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 medicines (Reimbursement List).

For most medicines, other than medicines restricted to hospital or medical specialist use, the only route to state reimbursement is to appear on the Reimbursement List. Other than for cancer drugs, there is a uniform application procedure to have a product listed on the Reimbursement List. Unlike other EU Member States, there is no distinct approval pathway for rare disease medicines or hi-tech products.

For a medicinal product to appear on the Reimbursement List, the supplier must make a reimbursement application to the HSE. The HSE is required to make a decision on whether to add the item to the Reimbursement List within 180 days from the date on which it receives the application. In the event that additional information is required from the applicant, the HSE may extend this timeframe for as long as required to determine the application.

The 2013 Act provides that in reaching its decision, the HSE must take into account: (i) Health Technology Assessment guidelines published by the Health Information Quality Authority (HIQA), where the HSE considers these to be relevant; and (ii) the criteria under Schedule 3 of the 2013 Act.

In particular, Part 3 of Schedule 3 requires the HSE to have regard to:

- the health needs of the public;
- the cost-effectiveness of meeting health needs by supplying the item concerned rather than providing other health services;
- the availability and suitability of items for supply or reimbursement;
- the proposed costs, benefits and risks of the item or listed item relative to therapeutically similar items or listed items provided in other health service settings, and the level of certainty in relation to the evidence of those costs, benefits and risks;
- the potential or actual budget impact of the item or listed item;
- the clinical need for the item or listed item;
- the appropriate level of clinical supervision required in relation to the item to ensure patient safety;

- the efficacy (performance in trial), effectiveness (performance in real situations) and added therapeutic benefit against existing standards of treatment (how much better it treats a condition than existing therapies); and
- the resources available to the HSE.

The 2013 Act also provides that the HSE may take into account any pricing and supply framework agreement with the Irish Pharmaceutical Healthcare Association (IPHA). The current framework agreement came into effect on 1 August 2016 and is operative for four years until July 2020 (2016 Agreement).

The 2013 Act, together with the 2016 Framework Agreement, set out the following procedure for assessing reimbursement applications for new medicinal products:

Upon receipt of a reimbursement application, the HSE commissions the National Centre for Pharmacoeconomics (NCPE) to conduct a cost-effectiveness or pharmacoeconomic analysis of the medicine. Initially, the NCPE (which is a team of clinicians, pharmacists, pharmacologists and statisticians) assesses all medicines in accordance with its "Rapid Review" procedure. The Rapid Review process takes approximately four weeks and is based on an abbreviated company submission intended to provide a summary of relevant information in relation to the cost-effectiveness of the product.

For high-cost products and those with significant budget impact, the HSE requests the NCPE to conduct a more in-depth pharmacoeconomic assessment, or Health Technology Assessment (HTA). Similarly, the HSE may request a pharmacoeconomic assessment for a product where concerns arise in relation to value for money. The aim of an HTA is to understand the cost-effectiveness of a product in more detail, particularly by comparison to alternative therapies available.

Generally, the NCPE has preliminary scoping discussions with the applicant before the company prepares a pharmacoeconomic dossier for submission. When assessing an applicant's submission, the NCPE considers the clinical effectiveness and health-related quality of life benefits and all relevant costs including potential savings from reduced healthcare resource use (e.g. hospitalisation), which the new product may provide. The main assessment criterion is the Incremental Cost Effectiveness Ratio (ICER) of the drug per Quality Adjusted Life Year (QALY).

Following assessment, the NCPE sends an appraisal report outlining its conclusions and recommendations to the HSE. In the case of cancer drugs, the report is also sent to the National Cancer Control Programme for consideration under the NCCP Therapeutic Review Process.

The HSE may, without further assessment, approve the product for reimbursement. Usually, this is the case for drugs that the NCPE considers to be cost-effective, i.e., those that in the NCPE's assessment have an ICER of €45,000 or lower per QALY.

For products falling outside this criterion, the HSE requests a recommendation from the HSE Drugs Group, which performs an in-depth assessment of the product. As part of the Drugs Group review, the HSE's Corporate Pharmacy Unit (CPU) may interact and lead any commercial negotiations with the applicant. In the case of orphan products, the Drugs Group may refer the assessment to the Rare Diseases Medicinal Products/Technology Review Committee for recommendations.

The Drugs Group then provides its recommendation to the HSE senior leadership, which is the delegated decision-making body within the HSE that makes the final decision as to whether to add an item to the Reimbursement List. The HSE senior leadership may take one of three decisions:

- to add the product to the Reimbursement List;

- not to add the product to the Reimbursement List; or
- to meet with the applicant to address any issues arising or seek clarifications.

The 2013 Act requires the HSE to provide the applicant with a formal notice of its proposed decision on whether or not to reimburse. The notice must include a statement setting out the reasons on which the HSE's proposed decision is based and also inform the applicant of its right to make representations in writing to the HSE with respect to the proposal. The HSE must consider any representations made by the applicant, if applicable, prior to adopting a final decision on pricing and reimbursement, which it must notify to the applicant.

According to the 2016 Framework Agreement, where the HSE recommends a drug for reimbursement, but is unable to fund the product from within existing resources, it may inform the Department of Health. The Department of Health has discretion to submit a memorandum to the Government to request funding for such product.

Under the 2013 Act, an applicant may appeal the final decision of the HSE to the High Court within 30 days from the date of receiving notice of the relevant decision. The High Court will examine the decision and how it was reached by the HSE to determine if the decision was unconstitutional or illegal. If there are sufficient grounds, the Court may: (i) annul the decision and replace it with a decision that the HSE could have made and that the Court thinks appropriate; (ii) refer the matter back to the HSE for further consideration; or (iii) give the HSE such directions as the Court considers appropriate.

In practice, where a drug is not approved following assessment, an applicant will often first engage with the HSE in pricing negotiations to reach an acceptable price or enter into patient access schemes. As there is no explicit process for post-assessment negotiation, this stage lacks structure and set timelines, and often leads to delays in reimbursement.

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

In Ireland, the reimbursement price of drugs included on the Reimbursement List consists of two components: (i) the ex-factory price; and (ii) the wholesale mark-up.

The ex-factory price of a medicine is set under national pricing frameworks, currently the 2016 Agreement, and is underpinned by the 2013 Act. The 2016 Agreement should only strictly apply to IPHA members that are listed in Schedule 2 of the agreement. In practice, most suppliers follow the terms of the 2016 Agreement when seeking reimbursement.

The 2016 Agreement sets the ex-factory price at the currency-adjusted average ex-factory price (price to wholesaler) in 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 the 14 reference countries and only downwards price realignments are permitted. Suppliers must pay the HSE a rebate of 5.25% (1 June 2016–31 July 2018) and 5.5% (1 August 2018–31 July 2020) of the ex-factory price.

The 2016 Agreement also provides for a 50% price reduction in the original ex-factory price of a medicinal product (excluding biologics) that has lost patent protection once a competing generic is available on the Irish market. For patent-expired biologics, the 2016 Agreement requires a 30% reduction in its ex-factory price once a competing biosimilar enters the market. In addition, suppliers of the biologic must pay the HSE a rebate of 12.5% of the value of the reduced price.

The wholesale mark-up for community reimbursement schemes is set out in statutory instruments. The current statutory wholesale mark-up is 8% for room-temperature medicines and 12% for medicines which require refrigeration.

The 2013 Act also introduced a system of reference pricing for generic and brand-named medicines that are deemed interchangeable. The Act permits pharmacists to substitute lower-cost or generic medicines when a more expensive product is prescribed, provided all the medicinal products fall within the same group of interchangeable products. The Irish Health Products Regulatory Agency (HPRA) decides (on a case-by-case basis) which products are interchangeable and publishes the national list of interchangeable product groups. The 2013 Act specifically excludes biological medicines from being considered interchangeable.

The HSE then establishes a single reimbursement price for each interchangeable group, known as the reference price. A supplier can set the price of a product above the reference price, but the HSE will only reimburse at the reference price.

Under the 2013 Act, the HSE is required to take into account the following criteria when setting the reference price:

- ability of suppliers of the relevant items to meet patient demand;
- value for money provided by the relevant items;
- equivalent relevant prices (if practicably available) of the relevant items in all other EU Member States where one or more than one of the relevant items is marketed;
- relevant prices of therapeutically similar items;
- resources available to the HSE; and
- the terms of any agreement in place (whether entered into before, on or after the commencement of the 2013 Act) between the HSE and any representative body of the suppliers of drugs, medicines or medical or surgical appliances where the agreement relates, whether directly or indirectly, to the price of one or more of those items.

The final criterion above requires the HSE to take into account the terms of the 2016 Agreement and agreements between the HSE and the Irish Generic Medicines Association (IGMA). It is important to also note the penultimate criterion which specifically states that the "resources available to the HSE" must be taken into account. Lack of resources has been a factor which has been cited in decisions to not reimburse a number of drugs in recent times.

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

A supplier does not need to agree a price for a medicinal product before it is placed on the Irish market if reimbursement will not be sought. Where the product is to be included in the Reimbursement List, the price of the new medicine is subject to the criteria in the 2013 Act and the 2016 Agreement. That is, the product must be priced at the currency-adjusted average ex-factory price in the 14 reference 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 not to be cost-effective, the HSE can meet with the supplier to negotiate and try to agree a price. Often pharmaceutical companies agree a straight rebate or discount, or offer a rebate or discount as part of a patient access scheme or another pricing mechanism, such as a risk-based sharing agreement, to add value and reduce the cost of the product. However, the details of these negotiations are highly confidential and where an agreement is reached between the HSE and the supplier, the outcome is rarely made public.

For medicinal products deemed interchangeable, suppliers are free to set the price of the product below or above the reference price. In the case of the latter, the HSE will only reimburse at the reference price. The patient must pay the additional cost above the reference price, unless a clinical exemption applies.

Issues that affect pricing

The price of medicinal products in Ireland is driven by a range of factors associated with demographic trends, competition, mandatory substitution, the resources available to the HSE and pharmaceutical policies. These factors are not mutually exclusive.

With an ageing population, the demand for medicines, especially for chronic diseases, is increasing. The 2013 Act introduced a number of measures to reduce the concomitant rise in healthcare expenditure, primarily generic substitution and reference pricing. In practice, this system results in suppliers of interchangeable medicines setting the price of their products at or below the relevant reference price.

Generic and biosimilar competition also affects the price of innovator products on the Irish market. Under the 2016 Agreement, the entry onto the market of a generic or biosimilar following the expiry of the innovator's patent, results in a significant mandatory cut in the price of the innovative product.

Policy issues that affect pricing and reimbursement

In Ireland, State expenditure on medicines is currently approximately €2.7 billion *per annum*. This is approximately 17% of the total health budget and represents over 7% of GDP. The long-term expenditure on medicinal products is expected to increase due to factors such as demographic trends and the development of hi-tech drug treatments.

Similar to other developed countries, Ireland is experiencing demographic change. By 2021 the Irish population aged 65 or over will increase by 40% from 2011 levels, representing an additional 200,000 people. Over the past decade, Ireland also has achieved significant improvement in life expectancy. As Irish patients live longer, they are likely to do so with an increasing burden of chronic disease.

In the context of such an ageing population, demand for medicines, especially for chronic diseases, will increase. As a result, there is likely to be additional pressure on future State funding and supply of medicinal products. This funding challenge is exacerbated by the fact that new innovative medicines are in the main hi-tech products that have a high cost attached to them. This is due to the significant research and development costs involved with bringing these innovative medicines to market.

Despite an ageing population, there has been little growth in the public expenditure budget for medicinal products in recent years due to the difficult economic climate. In 2019, the additional budget for innovative medicines was €10 million (0.4% of the annual medicines budget), which the HSE had nearly exhausted after eight weeks. In 2020, no specific funding was allocated for new medicinal products and new indications of existing products. Instead, the HSE must 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. 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.

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. The introduction of additional severe price control measures in the reimbursement of innovative medicines to constrain public expenditure risks significantly impacting the future development and manufacture of innovative medicines, a key industry for the Irish economy.

Emerging trends

The pricing and reimbursement of medicinal products in Ireland has undergone significant changes in recent years. The 2013 Act and the 2016 Agreement introduced a number of measures to reduce healthcare expenditure; however, the pricing of drugs and market access remains controversial. The 2016 Agreement is due to end in July 2020 and any new framework agreement negotiated 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.

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.

The 2016 Agreement was intended to have a dual purpose: to provide significant cost savings to the State; whilst on the other hand, facilitating the reimbursement and market access of new medicines. Over recent years, there has been a growing trend in reimbursement delays. For example, for 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 increasingly delays are also occurring after a new medicinal product has received a positive HSE decision that it will be added to the Reimbursement List. This is due to a lack of affordability of the HSE to fund these medicines within its current budget. Consequently, there are considerable delays in market access for innovative medicinal products in Ireland compared to the 14 reference countries. This is leading to increasing frustration and lobbying from the Irish innovative industry and from patient groups.

Recently, the reimbursement process has come under scrutiny in relation to orphan products. In 2017, the marketing authorisation holder for the orphan product Translarna® (INN: Atularen) launched the first legal proceedings in the Irish Courts appealing a HSE reimbursement decision. Ultimately, the proceedings were discontinued and the product subsequently

received reimbursement. Also, in 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 co-ordination on access to medicines and has joined two cross-border initiatives, the BeNeLuxa Initiative and the Valleta Declaration, that seek to collaborate on HTAs and price negotiations of new medicines across various EU Member States.

Successful market access

Cost and efficacy are the main issues of concern for the HSE. In order to successfully gain market access in Ireland, adherence to the criteria set out in the 2013 Act and the 2016 Agreement is key. The 2016 Agreement provides a good foundation for pharmaceutical companies to follow to ensure that they meet the requirements, but evidence of good clinical efficacy remains one of the critical success factors. 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.

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Italy

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Introduction

In Italy, the structure of the public healthcare system revolves around the "*Servizio Sanitario Nazionale*" (SSN, national health service), a complex articulated group of entities, bodies and functions established with Law no. 833 of 1978, which draws its inspiration from the principles of universality, equality and equal access to medical care laid out in art. 32 of the Italian Constitution. As with all universalised models, one of the most critical aspects of the SSN is its economic and financial sustainability.

Pharmaceutical assistance is one of the spheres of competence of the SSN, so in the constant search for an equilibrium between universalised provision and limited financial resources, market access for pharmaceuticals is fully involved. Regulation of the reimbursement prices of medicines plays a fundamental, although not exclusive role, in this: the sector regulations envisage additional and competing tools of governance, such as the imposition of expenditure limits (caps); patient co-payment; activation of alternative forms of distribution; centralised procurement; and recommendations for prescribing physicians (e.g. to address the prescription of lower-cost products), etc., which make up the body of rules governing the pharmaceuticals market.

A singular element of Italian law is the plurality of pharmaceutical policy-making centres. The organisation of the SSN implements two levels of governance: the State; and the Regions. The State is responsible for identifying the fundamental principles of the sector and for determining the Essential Levels of Assistance (LEA) that must be uniformly guaranteed throughout the country, and this cannot be otherwise limited or conditioned by the Regions. The Regions are responsible for defining healthcare policy, organisation and expenditure.

Recent studies show that action taken by the Regions with regard to pharmaceuticals, in order to reduce deficits or to prevent spending over the established limits, have created territorial differences with regard to access to pharmacological treatment and the penetration rate of drugs recently introduced on the market.

The correct form of interaction between the two levels of governance is still a topic for debate and also a matter of disputed jurisdiction, which has not yet reached a sufficiently acceptable conclusion, and this is one of the critical elements conditioning access to the market: when an agreement is reached at central level with the competent regulatory body, the subsequent regional processes may turn out to be complex and lengthy, with obvious consequences for access to the market for new drugs.

In this situation, successful market access in Italy depends on careful prior process planning, starting from the approach taken in the design of the clinical trials, to ensure that the endpoints are meaningful and measurable with respect to the assessment parameters adopted by the

regulatory authorities to establish reimbursement and pricing. In Italy, a detailed understanding of the legal and regulatory process on which the procedure is based is crucial to deliver an efficient result or, at the very least, to be sure of having the most appropriate safeguards.

Market introduction

Market overview: the economic context

The efforts to put its finances back on a sound footing, especially in the last 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 in the past have secured for Italy a strong position in the international ranking (*WHO* ranking for 2000).

Nevertheless, the value of rankings is often relative, since they vary depending on the valuation criteria used. More recent studies (*Gimbe*, 2018) indicate that the Italian SSN has gradually fallen behind the main European countries, also in terms of user "perception" of the quality of the services provided, especially among the weaker sections of the population or in regions with greater economic difficulties.

Specifically, constant cuts in public funding (a reduction of about €28 billion in 10 years) have generated a decrease in the ratio of healthcare spending to GDP from 7% in 2014 to 6.6% in 2018 (Italian Court of Auditors, Report on coordination of public finances, 2019).

In 2017, total pharmaceutical spending amounted to €28.1 billion (€464 *per capita*), of which €19.5 billion was funded by the SSN (€322 *per capita*) and €8.6 billion paid by patients (€142 *per capita*).

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.

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 2018), show that Italy is now the leading EU producer in terms of value of production, ahead even of Germany, and this is due to the growth in exports.

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

The National Health System

Italy currently has 60.59 million citizens who have access to the national healthcare service.

Italy's SSN pays for a large (but not total) share of the Italian pharmaceutical market: it guarantees access to services that, in relation to specific clinical conditions or conditions of risk, are scientifically proven to provide a significant benefit (i.e. added value) in terms of individual or collective health, in relation to the resources employed in their provision.

Therefore the SSN does not include services that do not meet effectiveness and appropriateness requirements; those having such features are included in the mentioned Essential Levels of Assistance (LEA), identified solely and exclusively by the State and subdivided into three main areas: collective healthcare in work environments and daily life; district assistance; and hospital assistance.

With regard to medicines, the State, through the *Agenzia Italiana del Farmaco* (AIFA – https://agenziafarmaco.gov.it), is responsible not only for issuing national marketing authorisations, but also, through the specific Pricing and Reimbursement negotiation procedure, for the selection of drugs to be included in the LEAs, and dispensed with reimbursement by the SSN, therefore including products licensed by the EMA. The list of reimbursable drugs forms the National Pharmaceutical Handbook.

The distribution of drugs to patients is provided essentially through the network of licensed territorial pharmacies both public (n° 1.675) and private (n° 17.656) that are also now open to joint stock companies, who may acquire the ownership. Administration of drugs to patients is also envisaged as an integral part of hospitalisation services. This has significant consequences as regards regional measures of governance introduced to contain expenditure.

Key (public) players

The Legislator defines the legal framework and – at a State level – is responsible for identifying the fundamental principles of the pharmaceutical sector, for determining the LEA that must be uniformly guaranteed throughout the country, and for ruling on governance measures for pharmaceutical access and expenditure.

At a decision-making level there are various players:

- *Ministry of Health*: the central body of the SSN whose main planning functions are exercised by presenting the National Health Plan to the Italian Government, after consultations with the Regions. It is at this level that the LEA are established. The Ministry of Health operates side by side with the Ministry of the Economy, which is responsible for planning and coordinating all questions concerning State funding of the SSN. The Ministry of Health is assisted by the Higher Institute for Health (having technical-administrative responsibilities) and the Higher Health Council (an advisory body). With regard to pharmaceuticals, the Ministry of Health is responsible for licensing advertising for drugs (OTC-SOP) and medical devices.
- *Italian Agency for Medicines (AIFA)*: the national body responsible for pharmaceutical regulation in Italy. This public body operates on an autonomous, transparent and cost-effective basis, under the aegis of the Ministry of Health and the supervision of the Ministry of Health and the Ministry of the Economy. It collaborates with the Regions. For market access, the AIFA manages the pricing and reimbursement procedure with the assistance of the Technical Scientific Committee (TSC), which assesses the added value of drugs, and the Pricing and Reimbursement Committee (PRC), which negotiates the pricing and reimbursement conditions of drugs with the company. The AIFA is responsible for assessing the innovative status of drugs for access to specific benefits (see below) and also manages implementation of measures for the governance of spending (pay-back).
- *Regional drug commissions*: variously named and variously formed scientific commissions operating at regional level, tasked with identifying access for drugs and their availability for hospitals.

Pharmaceutical pricing and reimbursement

General regulatory considerations: Access of drugs on 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"; 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) prescription drugs are listed also (prescription is necessary to buy the drug, but the price is paid by the patient). OTC and SOP are not reimbursed.

Generic (or equivalent) medicines and biosimilars

A number of specific rules apply to generic drugs that are automatically assigned to the same reimbursement class as the related branded drug, without a price negotiation, if the owner company proposes a sale price "of evident interest to the SSN", according to criteria contained in Ministry Decree issued on 4 April 2013 (rebates from 30% to 75% are related to the level of public spending). Negotiation takes place when the proposed price for the generic drug is higher; in this case, the law provides that the rebate shall be at least 20%.

Generic drugs cannot be listed as reimbursed by the SSN before the expiry of the patent or the SPC of the originator even though the pricing and reimbursement have been negotiated (patent linkage).

For drugs listed in class A) not covered by a patent and with the same composition in terms of active ingredients, as well as the same pharmaceutical form, administration route, manner of release, number of unit doses, the SSN reimburses up to an amount equal to the lowest price of the corresponding generic drug available in the normal regional distribution cycle (so-called "reference price"). The purchase of a more expensive equivalent product is possible only at the specific request of the patient and subject to co-payment. The list of all the equivalent class A) drugs with their related reference prices (the "transparency list") is published by the AIFA and periodically reviewed.

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

How patients get the drugs

Patients receive the reimbursed drugs through two channels: retail; and direct distribution. The distinction between the two systems is significant, because it involves a change in price and reimbursement procedures, as well as application of a variety of tools for the governance of public spending.

The retail channel

As a rule, the supply of drugs reimbursed by the SSN is through authorised public or private pharmacies (retail channel), which guarantee full coverage of the entire country, including difficult-to-reach areas. Pharmacies are private entities operating through a concession by the SSN; some pharmacies are held by the municipality. In the retail channel, the drug is purchased by the SSN from a "price list", on the basis of the retail price indicated in the AIFA Act authorising reimbursement. This price includes the "allocated quotas"; namely the remuneration percentages for the players in the distribution chain, wholesalers and pharmacists. The quotas for wholesalers and pharmacists are determined directly by law, with binding minimums; an 8% quota of the producer's margin is expressly envisaged for generic drugs, and may be subject to negotiation (extra discounts) between wholesalers and pharmacists. Pharmacists are required by law to apply additional discounts for the SSN, according to the price category of the drug. These discounts mean that, in practice, the pharmacy margin is regressive; that is, it decreases in percentage terms as the price of the drug increases.

Direct distribution

Directly through their territorial and hospital services, the Regions can guarantee the supply

of drugs required for patients being treated at home, residentially or semi-residentially, as well as drugs for the period immediately after hospitalisation or after an out-patient specialist appointment, for the first full cycle of treatment; this system is known as direct distribution. Drugs for direct distribution are acquired directly by the local health authorities through public tenders, starting from a base price no higher than the ex-factory price negotiated with the AIFA. In this way, thanks to carefully set starting prices and batch organisation, the competition among drug producers enables the SSN to obtain significant reductions on purchase prices. Subsequently, the local health authority dispenses the drug directly to patients through its healthcare facilities, without passing through wholesalers or approved pharmacies.

Distribution on behalf of the local health authority (DPC)

For cost-saving reasons, the Regions have the power to introduce a further form of distribution to patients, known as DPC, whereby the local health authority purchases drugs directly through tenders and subsequently supplies them to patients through the pharmacies (retail channel), which receive a consideration (which is not the same as the allocated quota but a further amount). This form of distribution may be activated only when the particular characteristics of the drugs in question mean that, given the clinical and/or management complexity of the pathology, the patient must make regular visits to the healthcare facility. The aim of this method of distribution is not therefore solely to achieve cost savings, but also to simultaneously guarantee continuity of assistance and monitoring of the suitability of use of specific drugs. When establishing price reimbursement, the AIFA indicates whether or not a drug may be dispensed through direct distribution, including it in a special list known as the Hospital/Territory Continuity Handbook: P-HT. This profile, too, needs to be carefully assessed for the purposes of access.

Early access to drugs

Reimbursed off-label use

The LEAs envisage additional "exceptional" cases of drug provision with costs borne by the SSN, one of which is medicines for "Listed" off-label use. Pursuant to law no. 648/1996, innovative drugs authorised for marketing in other countries but not in Italy, drugs without authorisation but undergoing clinical trials, and drugs to be used for a therapeutic purpose other than the authorised indication, included in a special list drawn up and regularly reviewed by the AIFA, may be distributed with costs borne in full by the SSN. This list ("list 648") also includes, for similar reimbursement purposes, and even if there is a therapeutic alternative among authorised medicines, drugs that may be used for a therapeutic indication other than the authorised indication, provided that said indication is known and complies with research conducted in the national and international medical-scientific community, in accordance with cost-effectiveness and suitability criteria. In this case, the AIFA activates appropriate monitoring tools to protect patient safety and promptly issues the necessary determinations. Requests for inclusion in list 648 may be made by physicians, patient associations, but not by the company that owns the drug.

Compassionate use

In Italy, drugs may be dispensed to patients free of charge on a "compassionate use" basis in these cases: i) as yet unauthorised, undergoing clinical trials and produced in pharmaceutical plants or imported in accordance with the authorisation procedures and current legal requirements; ii) drugs with marketing authorisation for indications other than the authorised ones; and iii) authorised medicines not yet "available" in Italy (the Health Ministry has specified that "unavailable" refers also to cases where the patient is not eligible for

reimbursement due to place in therapy restrictions). In exceptional cases, the AIFA allows compassionate use of medicines whose reimbursement and pricing have already been decided, which, for unforeseen reasons, are not available to patients for a defined period of time. This case applies irrespective of the type of MA (centralised, decentralised, mutual recognition).

Compassionate use may be requested (by physicians): for treatment of patients affected by serious pathologies, rare diseases, rare tumours or diseases placing them in life-threatening conditions; conditions for which no valid therapeutic alternatives are available, or that cannot be included in clinical trials or for therapeutic continuity purposes; and for patients who have already received clinically beneficial treatment under a completed clinical trial.

In the case of compassionate use, provision of the drug free of charge is guaranteed not by the SSN (which does not bear any cost) but directly by the pharmaceutical company (the company is not compelled to adhere to the request). Pharmaceutical companies are entitled to request activation of compassionate-use 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.

AIFA

Criteria for definition of the price and reimbursement

According to the law, all the prices of medicines reimbursed by the SSN must be negotiated between the AIFA and the MA holder, in accordance with the procedures set out in deliberation no. 3/2001 of the inter-ministerial economic planning committee (CIPE) that sets criteria for the negotiation as follows:

- positive cost-effectiveness: the drug is considered useful in the treatment of pathologies for which there is no effective therapy, or delivers a more effective response than other drugs already available for the same *therapeutic indications*;
- a more favourable risk/benefit ratio compared to drugs already available for the same indications;
- assessment of the economic impact on the SSN, also in relation to the market shares achievable in the subsequent 24 months and the projected consumption data;
- per-day therapy cost, compared to other products of similar effectiveness;
- comparison with prices and consumption in other European countries; and
- health technology assessments (HTAs).

For cost-containment reasons, the AIFA may propose reductions in the prices of other drugs on the company price list admitted for reimbursement whose price has not been negotiated. The pharmaceutical company presents its proposals together with proper economic assessments of the product and the industrial context, with reference to investments in production, R&D, exports and a market forecast over a three-year period.

It is possible to arrange Managed Entry Agreements (MEAs); i.e. forms of reimbursement conditional upon the attainment of sales volumes (price-volume agreements, product ceiling, cost-sharing), or reimbursement based on treatment results (risk-sharing, payment by results), or confidential reserved discounts may be applied to the supplies for public health authorities.

The AIFA often insists on setting a cap on expenditure for the drug in an amount negotiated with the company applicable for the validity period of the agreement. Should sales exceed

the cap, the company is obliged to "pay back" the over-expenditure upon request of the AIFA. Usually the cap is fixed for the first access of the drug on to the market as a governance tool. To avoid an automatic renewal of the cap, it is advisable that the company timely address to the AIFA a request to re-negotiate, seeking either to increase the cap or to remove it.

The price negotiated with the AIFA:

- represents the maximum sale price for the SSN, which is then entitled to negotiate further commercial discounts;
- is subject to the addition of margins for wholesalers and pharmacists for sales in the retail channel;
- is valid for 24 months unless otherwise agreed by the parties;
- the agreement is automatically renewed for a further 24 months on the same conditions, should neither party send to the other party a proposed amendment to the conditions at least 90 days before the natural expiry of the contract; or
- should changes arise in the therapeutic indications and/or dosage, such that an increase in the level of usage of the medicine is foreseeable, either party may re-open the negotiation even before the end of the agreed period.

If an agreement is not reached, the drug is listed in class C (payment in full by patients). In this case, the maximum retail price, which is the same throughout Italy, is freely determined by the pharmaceutical company and may be increased only in the month of January of an odd-numbered year. Should the medicine listed in class C be sold to public authorities, however, the pharmaceutical companies are obliged to apply a 50% discount to the retail price.

The 2019 financial law establishes that the AIFA may, before the expiry of the negotiated agreement with the MA holder, re-open the negotiation procedures to re-negotiate the conditions of the existing agreement, "should market changes arise *medio tempore* such as to make an increase in the level of use of the medicine foreseeable or lead to an unfavourable cost-therapy ratio with respect to the alternatives in the national pharmaceutical handbook". This means that amendments may be made to the existing contract at the request of the AIFA (at any time) in the event of market changes. It is up to the AIFA to demonstrate and support the existence of changes constituting the conditions indicated by the law for re-negotiation to be requested. At the time of writing, there are no incidences of the application of this new rule.

In parallel with the negotiation of pricing and reimbursement, the status of innovative drugs may be requested (see below).

The above framework makes the prices of medicines in Italy lower than in other European countries (Farmindustria, *Pharmaceutical Indicators 2018*).

The negotiation procedure

The negotiation procedure is regulated by law. The standard procedure, for general application, has a duration of 180 days (non-mandatory) from filing of the application; the fast-track procedure is completed within 100 days from filing of the application, but applies only to orphan medicines, to other drugs of exceptional therapeutic and social importance listed in a specific AIFA deliberation, and to medicines that may only be used in hospitals or facilities equivalent to hospitals. The fast-track procedure has priority and the reimbursement application may be filed before the issue of the MA, although commencement of the negotiation must be requested within 30 days of issue of the MA, otherwise the AIFA revokes the classification in the C-nn class.

The duration may be extended only once, in the event that additional elements are requested. The procedure may be suspended upon request of the company. During the negotiation, the medicine is automatically listed in the C-nn class and may be marketed without reimbursement by the SSN. The company is entitled to decide whether to sell the drug

immediately or to wait until the reimbursement procedure has been completed. This decision has an impact on the global market access strategy.

During the negotiation, the AIFA obtains opinions from:

- the Technical Scientific Committee (CTS), which provides an opinion on the therapeutic value of the medicine, its innovative content, etc.; and
- the Pricing and Reimbursement Committee (CPR), with regard to economic congruity and definition of the price.

The procedure is concluded with a ruling by the AIFA Director General, which takes effect upon publication in the *Official Gazette*. The same procedure applies to line extensions.

In Italy, the long term of the negotiation procedure represents a weak point for market access.

Remedies in case of delay or failure in the procedure

The deadline of 180 days for the conclusion of the procedure is not mandatory but in case of long-lasting negotiation due to silence/unjustified delay, the company is entitled to write warning letters to the AIFA, and eventually to apply to the Administrative Court to obtain a formal injunction to speed up and conclude the procedure. This remedy is not used in practice, and should be carefully evaluated due to the strong challenge it brings to the course of the negotiation and to the company's reputation.

In case there is failure to reach an agreement and the company is not satisfied with this outcome, it is possible to evaluate if there are arguments to support a judicial action before the Administrative Court. The judicial assessment may only concern the legal compliance of the process (i.e. logic and grounded decisions, transparency of the process) and not the merits of the reasons why the AIFA decided not to reimburse the drug. In practice, the most challenging issues are the price of the drug and its place in therapy.

Policy issues that affect pricing and reimbursement

Sustainable spending and tools of governance

A longer average lifespan, and access to innovative high-cost treatments, make sustainability a major issue. Over the years, additional measures have been introduced in Italy to reduce costs and ensure compliance with the public finance targets agreed with the EU. The question is at the top of the Government's political agenda and is a subject for debate and discussion among industry players with a view to finding solutions that embrace pharmaceutical innovation and financial sustainability.

Below is an overview of the main current tools of governance and the application difficulties encountered in practice.

Pharmaceutical spending limits (for reimbursed drugs only)

The Italian system is today based on a maximum annual spending limit for drugs and mandatory payback of any over-run (in whole or in part) by the pharma companies.

Public pharmaceutical spending may not exceed an overall limit of 14.85% of the national healthcare fund, which is set by law every year. It is subdivided into two main components: agreed spending (*spesa convenzionata*), for drugs distributed through the retail channel, accounting for 7.96% of the healthcare fund; and direct procurement spending for drugs purchased directly by the local health authorities, accounting for 6.89% of the fund.

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.

At the moment, it is not possible to predict the real impact of the new rules on the pharmaceutical companies because the AIFA is still pursuing reimbursement procedures for exceeding the 2018 annual maximum spending limit. It is anyhow essential that every company conducts a full analysis of their position with respect to the portfolio of drugs already on the market or to bemarketed 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 RTHs 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 has 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 proves 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 143% from the first quarter of 2018 to the first quarter of 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:

- periodic review of the National Pharmaceutical Handbook and the adoption of initiatives to attenuate or eliminate price differences between therapeutically equivalent drugs;
- review and update of price negotiation criteria with express incentivisation of the price/volume mechanism (also the State budget law for 2019 has directed to revise the criteria);
- update of the criteria for recognition of the innovative status of applicable drugs (also for price negotiation purposes);
- promotion of the use of equivalent drugs and biosimilars through awareness campaigns;

- the intensification of AIFA therapeutic-equivalence opinions for purchase tenders;
- simplification of the procedures for the issuance of opinions by AIFA committees (CTS-CPR);
- improved exchange of information on the expiry of drug patents, for timely commencement of price re-negotiations;
- the improvement of AIFA monitoring registers; and
- the review of pharmaceutical spending limits.

Other emerging trends

- a focus on customisation of drugs and on Advanced Therapeutic Medicinal Products (and specifically CAR-T) to be balanced with financial sustainability;
- a lively public debate on whether to maintain the possibility of stipulating confidential discounts with the AIFA: the current government aims for absolute costs and price transparency; a possible criticism is the risk of a "reference price" at EU level; and
- raising interest in Patient Support Programs aimed at therapeutic compliance, both from pharma companies developing initiatives and public entities requiring in-tender quotation for specific services to patients. PSPs have played a central role in the ongoing COVID-19 *pandemia*: home delivery of drugs; home administration of therapies; and tools to remotely manage the assistance of patients.

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

In order to face the emergency from the Coronavirus disease (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 the 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 for 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 the AIFA and to the Ethics Committee of the National Institute for Infectious Diseases (INMI) Lazzaro Spallanzani of Rome (which 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 the AIFA and extraordinary meetings of CTS and CPR have been planned to ensure the 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.

Acknowledgment

The authors acknowledge with thanks the contribution of Luigi Selmo to this chapter.

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Japan

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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 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 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 genetically-modified technique, etc., (ii) radioactive pharmaceuticals, (iii) aseptic pharmaceuticals, (iv) any products other than (i), (ii) and (iii), and (v) only the packaging, labelling, and storing of the products set forth in (iii) and (iv).[9] Generally, the Pharmaceuticals and Medical Devices Agency (the "PMDA") designated by the MHLW will conduct an investigation regarding any application for a Licence for Manufacturing.[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 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] 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, however, the MHLW may grant special approval for such item even without certain requirements.[20] On May 7, 2020, such special approval has been 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, 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 such 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 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, though the price paid by the pharmacy shall be considered upon revision of the Drug Price listed in the Drug Price Standard as described below.

Patients pay for any other pharmaceuticals, such as OTC Pharmaceuticals and Pharmaceuticals Requiring Guidance, by themselves.

Application for listing in the Drug Price Standard

The MHLW lists pharmaceuticals in the Drug Price Standard, and the holders of a Marketing Licence of New Pharmaceuticals and generic drugs 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 for 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 basically 50% of the New Pharmaceuticals. If such generic drug is a biosimilar, its Drug Price shall be basically 70% thereof and may be increased by up to 10% depending on sufficiency of the clinical testing. In case such generic drug is an oral medicine and more than 10 of the same generic drugs are newly listed in the Drug Price Standard at the same time, the percentage shall be reduced by 10%.

In case there is any generic drug listed in the Drug Price Standard that is identical to the generic drug newly listed in the Drug Price Standard, the Drug Price of such generic drug shall be the same as such identical generic drug. In case that is any generic drug listed in the Drug Price Standard similar to the generic drug newly listed in the Drug Price Standard, the Drug Price of such generic drug shall be the same as such similar generic drug and the Inter-specification Adjustment shall be applied in order to equalise the ratio of the Drug Price and the active components of such generic drug and that of such similar generic drug.

Revision of the Drug Price

The Weighted Average Market Price Plus Adjustment Range shall be used when revising the Drug Price listed in the Drug Price Standard. Here, the Market Price shall mean the price paid by pharmacies. Such revision is basically made once every year. The MHLW may conduct a necessary survey to ensure the appropriateness of the Drug Price.[59]

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 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 health care 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 health 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 basically increasing. In order to maintain health insurance for elderly people, the 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 2020 or earlier.[61] Therefore, the form of the prescription which a physician or dentist providing health insurance treatment writes 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-mediation in order to hold down the medical expenditure under the health insurance system. Then, the government tries to switch prescription pharmaceuticals to Pharmaceuticals Requiring Guidance, such as pharmaceuticals of which the active component is a histamine-2 receptor antagonist. But there are not so many such pharmaceuticals.

Emerging trends

No new legislation is necessary to modify the Drug Price Standard. The MHLW may 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 make a lot of sales in the large Japanese market, but it costs a lot to have a subsidiary with a Marketing Licence in Japan. If a foreign pharmaceutical company does not have a subsidiary in Japan for some reason, it should execute a licence with a Japanese pharmaceutical company with a Marketing Licence.

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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 (12) and (16), and 77-2 of the Law.
28. Article 14 (5) of the Law.
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), Article 72 (1) of the Health Insurance Act, Article 40 of the National Health Insurance Act, Article 19 of the Rules for Health Insurance-covered Medical Facilities and Medical Practitioners.
50. With certain exceptions.
51. Article 70 (1), Article 72 (1) of the Health Insurance Act, Article 40 of the National Health Insurance Act, Article 9 of Rules for Health Insurance-covered Dispensing Pharmacies and Pharmacists.
52. With certain exceptions.
53. Article 74, Article 76 (2) of the Health Insurance Act, Article 42, Article 45 (2) of the National Health Insurance Act.
54. Article 76 (4), (5) of the Health Insurance Act, Article 45 (4), (5) of the National Health Insurance Act.
55. Article 76 (1), (2) of the Health Insurance Act, Article 45 (1), (2) of the National Health Insurance Act.

56. With certain exceptions.
57. Article 82 (1), 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.

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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 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.

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Korea

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Abstract

In Korea, the pricing and reimbursement of drugs is governed by the National Health Insurance ("NHI") scheme, which is a single-payer system operated by the National Health Insurance Service ("NHIS"). NHI premiums are lower than in other developed countries, leading to relatively high patient co-payment rates and a large number of non-reimbursed (unlisted) products and services. Reducing the financial burden on patients that is caused by these features has long been a government policy objective, and the administration of President Jae-In Moon has rolled out the "Mooncare" initiative under which the government will seek to vastly expand NHI coverage, effectively bringing all therapeutic treatments under the NHI coverage.

Once a pharmaceutical product is approved, companies may apply to the Health Insurance Review and Assessment Service ("HIRA") to have the product listed for reimbursement under NHI. For new drugs, reimbursement listing usually involves a two-step process where: (i) HIRA first decides whether or not the product is eligible for NHI reimbursement by evaluating the product's clinical usefulness and cost-effectiveness; and (ii) the company and 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 and orphan drugs regarding which it is difficult to conduct a pharmacoeconomic ("PE") assessment, the PE assessment is exempted or the company may enter into a risk-sharing agreement ("RSA"). The MRPs of generics and combination drugs is set according to a set formula and reimbursement listing may be completed within three months.

Market introduction/overview

As of 2018, 97.2% of Korean citizens were enrolled in NHI; those who are not enrolled receive subsidies in the form of medical benefit payments from the government. NHI is mostly funded by insurance premiums paid by enrollees, and government subsidies (14%) and health promotion funds generated through the tobacco tax (6%) make up the rest.

Although most Koreans are enrolled under NHI, the benefit they receive is restricted due to relatively high co-payment rates (30% to 60% for outpatients, 20% for inpatients) and the relatively large portion of products and services that are not reimbursed (16.5% as of 2016). Patients pay out of pocket with respect to the co-payments and the non-reimbursed drugs. In order to reduce the financial burden on patients, a reduced co-payment rate of 5% and 10% applies with respect to treatments for cancer and orphan diseases, respectively. The relatively high co-payments and low NHI coverage rate also relate to a lower premium rate, which as of 2020 was 6.67% of monthly income.

The projected population of Korea as of the end of 2020 is 51.78 million and the average age is 42.8 years. As in other developed countries, the population is rapidly ageing – as of 2018, the life expectancy was 82.7 years, higher than the OECD average (80.8 years) and 3.1 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 2018, *per capita* healthcare expenditure was US$3,192, much lower than the OECD average of US$3,994, and total health expenditure as a percentage of GDP was 8.1%, slightly lower than the OECD average of 8.8% (based on health statistics published by the OECD in 2019). 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 needs to submit a certificate of manufacture from the country in which the product is manufactured and a certificate of sale from the countries in which the product has already been approved. The MFDS decides whether to approve the product after reviewing the submitted data, and may conduct an on-site GMP investigation.

The statutory processing period for applications to approve a new drug is 120 days, but the period is tolled when the MFDS requests the dossier to be supplemented.

When requesting the approval of generic drugs, the company must, in principle, submit bioequivalence data to substantiate their efficacy; however, depending on the dosage form or active ingredient, it may be possible to submit physicochemical equivalence data or data from a comparative dissolution test. When seeking the approval of biosimilars, the company must submit quality, non-clinical and clinical compatibility data.

Who is/who are the payer(s)?

The Korean NHI is a social insurance scheme under which the payer is 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 allow 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 set based on formulas set forth in the regulations without PE evaluation and negotiation with NHIS and reimbursement listing takes no longer than three months. Under regulatory amendments that will take 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 proposed regulations that have been pre-announced, HIRA will be required to consult with NHIS on matters such as measures for ensuring steady supply of the generic when setting the MRP for generics.

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 standards, and whether the product is reflected in clinical practice guidelines or mentioned in textbooks for the relevant disease.

If HIRA finds the product to be clinically useful, it then conducts PE analysis to assess whether it is cost-effective compared to treatment alternatives or comparable drugs. When a drug is clinically superior but expensive, the company 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 effective price), or be exempted from having to submit PE data, in which case the "modified price" (ex-factory price, plus domestic distribution margin and VAT) of the product in the A7 countries would be regarded as the benchmark. 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 plans to amend the relevant regulations on PE exemption to allow the NHI listing of certain oncology 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). During this negotiation, the price recommended by HIRA will serve as the *de facto* ceiling. Factors that are taken into account during negotiation include the product's price in OECD and other countries, the MRP of treatment alternatives that are already listed under NHI, the relative prices of the product and treatment alternatives in other countries, and the potential impact on the NHI budget. If the negotiations with NHIS break down, the product would not be listed and the company would need to begin again with the HIRA review stage if it wishes to get the product reimbursed.

Refund/rebate schemes are generally not permitted except for those products that are subject to a 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.

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 "modified price" that takes into account the domestic distribution margin) may also be available depending on the type of the drug. Generally, the supply chain margin will be taken into account when setting the MRP.

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%).

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

In August 2017, the government rolled out the "Plan for Strengthening Coverage of National Health Insurance" (commonly referred to as "Moon Jae-In Care" or "Mooncare" after the current President). One of the key goals of Mooncare is to ultimately bring all therapeutic treatments under NHI coverage.

The government is planning to assess the medical validity of various treatments that are not currently reimbursed under NHI and will expand NHI coverage in phases by 2022, when President Moon's term ends. Although Mooncare could potentially boost sales of certain expensive oncology drugs and orphan drugs, the commercial implications are likely to be mixed for most companies, given the increased pressure on the NHI budget and the likelihood that the government may more proactively employ various price control measures.

Successful market access

Early planning is important in order to 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.

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Market introduction/overview

Setting the scene

The Dutch pricing and reimbursement system is unfortunately not set out in a well-defined set of rules and regulations. Because of this, a better understanding of the Dutch healthcare market and the system 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 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.

Furthermore, 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, affordability and transparency.

The 2019 version of the State of Health in the EU's Country Health Profile on the Netherlands[1] and the 2017 'Facts and Figures' overview by the Dutch Foundation for Pharmaceutical Statistics ("SFK")[2] provides 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.

The healthcare market

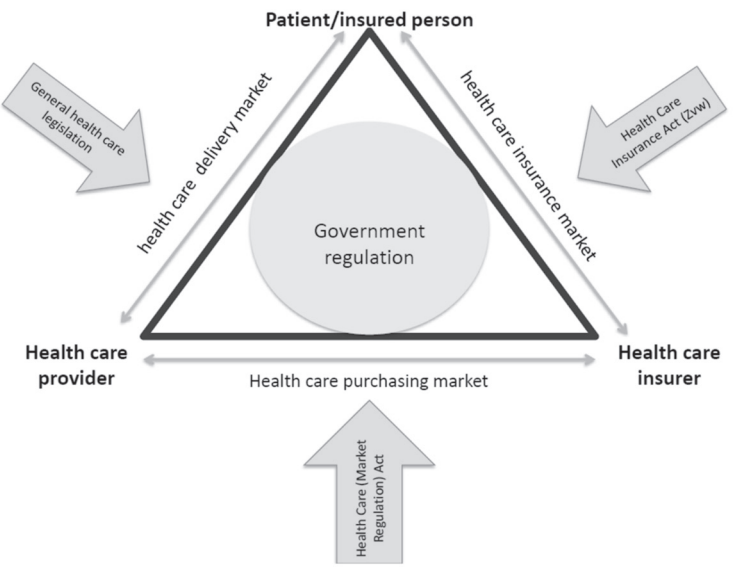
The 2006 reform of the Dutch healthcare system changed the role of the government from direct controller of volumes and prices to rule-setting and overseeing a proper functioning of the markets. The Dutch government is responsible for setting the basic health insurance package ("the basic package"), 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,[3] 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 Belgium, Luxembourg, Austria and Ireland is a member of the cross-country collaboration initiative Beneluxa,[4] 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");[5] the National Healthcare Institute ("*Zorginstituut Nederland*", or "ZIN");[6] the Dutch Healthcare Authority ("*Nederlandse Zorgautoriteit*", or "NZa");[7] and the competition authority the Netherlands Authority for Consumers and Markets ("ACM").[8]

Other important non-government actors are the associations of insurers ("*Zorgverzekeraars Nederland*", or "ZN"),[9] hospitals and other healthcare institutions (NFU,[10] NVZ,[11] ZKN,[12] Actiz),[13] doctors (KNMG,[14] Federatie Medisch Specialisten,[15] etc.), pharmacists (KNMP,[16] NVZA,[17] Netwerk Gespecialiseerde Bereidingsapotheken),[18] patient representatives and industry associations (VIG,[19] BOGIN,[20] HollandBIO).[21]

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. 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",[22] launched a sector inquiry into anti-rheumatic drugs, and submitted a paper for the OECD named "Excessive Pricing in Pharmaceutical Markets".[23] In 2019 the ACM announced[24] 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[25] and an evaluation of the "Guidelines on collective procurement of prescription drugs",[26] 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.[27]

Pharmaceutical pricing and reimbursement

Pricing

The Wgp was introduced in 1996. 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 by the Farmatec unit of the CIBG (a department of the MoH),[28] 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 the MoH introduced a legislative proposal to change the reference countries, by replacing Germany with Norway. According to the MoH, the list prices in Germany (and in particular those for innovative medicinal products) are higher than the European and the Dutch average price level, which would cause the prices in the Netherlands to be higher than the European average price level. The choice for Norway as a reference country was in a large part based on advice by SFK. SFK calculated that replacing Germany with Norway would cause an average price pressure of 7.8% on the prices of medicinal products used for outpatient treatment (in Dutch: "*farmaceutische zorg*", or pharmaceutical care), and estimated that it would cause an average price pressure of 9.9% on the prices of medicinal products used for inpatient treatment in hospitals ("*geneeskundige zorg*", or medical care). 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. In December 2019, the legislative proposal was adopted, 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.

However, the announcement of the first application of the new system as per 1 April 2020 caused quite a lot of unrest in the pharmaceutical market because the maximum prices for many generic products would drop substantially, in some cases even by 30%–70%, causing concerns about the availability of the products on the Dutch market and the sustainability of the maximum prices. This unrest coincided with the start of the COVID-19 crisis, and ultimately the MoH decided not to amend the prices as per 1 April 2020.

The first application of the new system will therefore be as of 1 October 2020. Because of COVID-19 and the fact that the prices for medicinal products in Norway have dropped substantially, *i.a.*, due to the low oil prices (Norway's currency is tied to the value of its most important export product) the MoH has decided to implement certain mitigating measures. Just this one time, the MoH will impose a maximum on the decline in prices of 10%. Furthermore, for products with a yearly turnover below EUR 1 million in the Netherlands, companies can request the MoH to not apply the Wgp. In that case the current Wgp maximum price will continue to apply.

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 is the same for everyone. All residents are required to take out an insurance policy that covers the basic package. 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*").

(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*").[29]

- 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 required, 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: 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*,[30] 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.[31]

(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"[32] 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 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. 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.

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 attempt to negotiate 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 farmacotherapie*" (rational pharmacotherapy). This concerns, *i.a.*, "magistral 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 allowed to give a patient nonetheless a compounded product, e.g. for economic reasons.[33]

(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.[34]

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 ("*Vereniging Innovatieve Geneesmiddelen*", or "VIG") has recently published a guidance document concerning the lock.[35]

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.

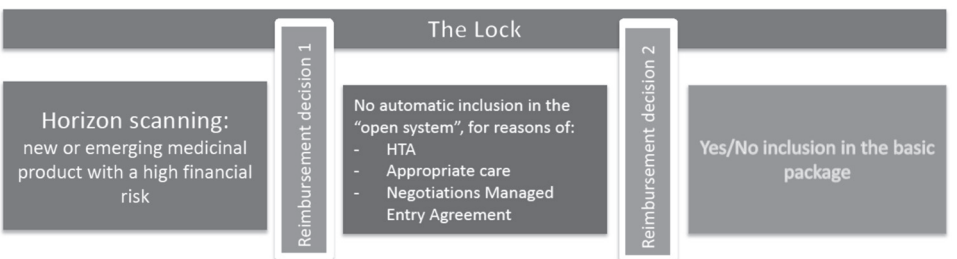
According to the current criteria applied by the MoH, a medicinal product qualifies for the lock chamber if:

- 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*.

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:[36]



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.[37]

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.[38]

Finally, there is an ongoing debate in the Netherlands about the lock chamber 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.

(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.[39] Currently an add-on can only be obtained for authorised medicinal products costing more than EUR 1,000 per year per patient. Furthermore, the product must be listed in the price list of the Z-Index.[40]

An add-on request cannot be submitted by an MA holder. The add-on form[41] must be submitted jointly by (i) one or more hospitals, and (ii) one or more insurers, either directly or through their trade associations.[42] 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:[43]

- A healthcare provider submits the add-on form[44] 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 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.[45]
- 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.[46] 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. In addition,

further to a recent ruling by the CBb concerning replacement compounding in the extramural setting,[47] the NZa recently announced that it will introduce new rules for unauthorised pharmacy preparations in the intramural setting as well.[48]

* * *

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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, food, cosmetics 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, patient access to unauthorised/unlicensed products, regulatory status of borderline products, clinical trials, cross-border healthcare, government transparency and the protection of trade secrets (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 co-founder and honorary member of the Dutch Pharmaceutical Law Association ("VFenR").

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Poland

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Abstract

The following chapter outlines basic information on the Polish healthcare system, in particular the pricing and reimbursement issues.

Market introduction/overview

The Polish pharmaceutical market belongs to the so-called regulated sector, governed by restrictive and detailed pharmaceutical law. Thus, issues such as manufacturing, safety and use of medicinal products or its distribution are governed by very restrictive and specific regulations that are aimed at strengthening control and supervision over the activities of pharmaceutical companies, pharmacies and pharmaceutical wholesalers.

The Polish pharmaceutical market is one of the key sectors of the domestic economy, which notes steady growth. The value of the pharmaceutical sector is currently around 1% of GDP.

The Polish healthcare system is multi-layered and its respective segments are subject to rapid change. The healthcare system is dominated by public financing schemes. Generally, all insured Polish citizens have guaranteed free access to healthcare services. However, the private sector of healthcare services in Poland is predominant and still growing. Uninsured patients are obliged to cover the full costs of medical services. In general, access to public healthcare services is rather difficult.

Pharmaceutical pricing and reimbursement

Reimbursement issues are generally regulated in the Act of 12 May 2011 on Reimbursement of Medicinal Products, Food for Special Nutritional Purposes and Medical Devices, and several regulations laying down more precise requirements and technical rules for the reimbursement process. There are three groups of products that can be covered with reimbursement: (1) medicinal products; (2) medical devices; and (3) food for special nutritional purposes.

Products may be subject to reimbursement if they fulfil the following requirements:

- they are authorised for the market or remain marketed;
- they are available on the Polish market; and
- they have an EAN identification code or another code equivalent to the EAN code.

The reimbursement may also cover medicinal products without market authorisation in Poland, imported in accordance with the conditions and procedures provided for in the Pharmaceutical Law Act dated 6 September 2011, and medicinal products where the clinical data on indications, dosage and method of administration differ from those set forth in the Summary of Product Characteristics.

Whereas, reimbursement shall not cover products:

- in clinical conditions in which the medicine can be effectively replaced by a change in the patient's lifestyle;
- belonging to the Rp availability category, which have a substitute belonging to the OTC category, unless in a given clinical condition they need to be applied for a period longer than 30 days; and
- included on the list of products which cannot be reimbursed.

The costs of reimbursed products are divided between the public payer and the patient, and depend on the reimbursement limit and the co-payment level. The National Health Fund (the public payer) refunds products if they are on an official list of reimbursed products published by the Minister of Health.

The reimbursement approval process is executed by the Minister of Health (MoH). The MoH decides in administrative proceedings which products will be reimbursed and on what terms. Companies are obliged to file reimbursement applications to the MoH. From 1 January 2018, applications may only be submitted electronically in the Reimbursement List System (SOLR) and must, among others, contain: data identifying the product; requested reimbursement conditions; indication of the maximum and minimum net sales price obtained in Poland and other EU countries; proposed price; HTA analysis – clinical, economic, substantiating; and effects on the budget.

The MoH can also determine in the decision (based on the proposal of an applicant) additional terms of financing the medicinal product from public funds, including indicating the risk-sharing instrument (RSS). The catalogue of possible RSS is open, which does not preclude the use of another measure, provided that it will have an impact on increasing the availability of guaranteed services or reducing the costs of these benefits. The MoH should examine the reimbursement application within 180 days. The MoH issues a reimbursement decision for a period of two or three years, taking into account the following criteria:

1. position of the Economic Committee;
2. recommendation of the President of the Agency for Health Technology Assessment and Tariff System;
3. significance of the clinical condition to which the reimbursement application relates;
4. clinical and practical efficacy;
5. safety;
6. relation between health benefits and health risks;
7. cost to health effects ratio of the previously reimbursed medicines, compared to those covered by the application;
8. price competitiveness;
9. effects on the expenses of the entity obliged to finance services from public funds and the expenses of beneficiaries;
10. presence of an alternative medical technology and its clinical efficacy and safety;
11. reliability and precision of estimates of the criteria referred to in subparagraphs (3) to (10);
12. health priorities; and
13. the additional year-of-life cost threshold adjusted by life quality, set as equal to three times the GDP *per capita*, and if it is impossible to determine this cost – the additional year-of-life cost.

Products for which the pricing and reimbursement decision has been issued are dispensed to the patient up to the amount of the financing limit and for a fee equal to the amount of

the difference between the retail price and the financing limit amount; free of charge, on a flat-rate basis; or for a fee of 30% or 50% of its financing limit.

The reimbursed products fall into one of the following reimbursement categories:

- available at a pharmacy on prescription (in the full scope of registered indications and intended uses, or in an indication determined by a specific clinical condition);
- used as part of a therapeutic programme;
- used in chemotherapy (in the full scope of registered indications and intended uses, or in an indication determined by a specific clinical condition); and
- as part of the provision of guaranteed healthcare services other than indicated above.

The MoH also defines the limit groups of products for which the limit basis is determined. With respect to medicinal products, they are qualified to the same limit group in case of having the same international name or different international name but similar therapeutic action and a similar mechanism of action. The limit basis for a given limit group of medicinal products is constituted by the highest of the lowest wholesale prices for a DDD of a medicinal product which complements 15% of the quantitative volume, counted on the basis of the DDD, sold in a given limit group in the month preceding the announcement of the Reimbursement List by three months.

The main factors determining the price of reimbursed products are: limit basis; retail price (official sales price increased by the official wholesale and retail margin, and VAT payable); and payment rates. Those factors are determined officially by the MoH. Additionally, there are restrictions regarding medicinal products for which there is at least one reimbursed substitute in a given indication. In the case of another substitute reimbursed in the given indication, the official sales price, taking into account the quantity of DDDs in a unit package, shall not be higher than:

- 75% of the official sales price of the only substitute reimbursed in a given indication; or
- the official sales price of a substitute determining the limit basis, or the cheapest substitute if the limit basis in a given limit group is determined by a medication with another active ingredient.

Other factors affecting pricing include: indications; product manufacturing costs; patent protection; size; and profitability of a pharmaceutical company.

Policy issues that affect pricing and reimbursement

In the Polish system, the official sales prices and the official wholesale and retail margins are fixed. In accordance with Polish regulations, in order to provide guaranteed healthcare services, the healthcare provider is obliged to purchase reimbursed products at a price not higher than the official sales price, increased by a margin not higher than the official wholesale margin, and – if the healthcare provider makes a purchase from an entity other than a wholesale trader – at a price not higher than the official sales price.

Also, the healthcare provider is obliged to purchase reimbursed products:

- at a price not higher than the official sales price of a product constituting the limit basis, taking account of the DDD of the medicinal product, the quantity of units of the foodstuff intended for particular nutritional uses in a package, the number of single medical devices or the quantity of medical device units; and
- increased by a margin not higher than the official wholesale margin, and – if the healthcare provider makes a purchase from an entity other than a wholesale trader – at a price not higher than the official sales price.

Politics in Poland has a significant impact on pricing and reimbursement policy. The factors limiting the development of the reimbursed medicinal product market include the transfer

of some drugs used in oncological treatment to the hospital market and falls in drug prices in selected limit groups, most often associated with the appearance of the first counterparts of original medicines in the refund.

Decisions of the MoH regarding the entry – or lack of it – on the list of reimbursed medicinal products are much more important for pharmaceutical companies than economic phenomena. The previous practice of the MoH shows that the RSS are mainly used to reduce public spending while fully controlling the NFZ budget for financing new therapies. Currently RSS are highly required by the MoH. Additionally, political trends in Poland indicate that generic products are more likely to be refunded. Also MoH strives to maintain the lowest prices in the EU.

Emerging trends

The epidemic state in Poland, introduced due to the spread of the COVID-19 virus, has caused extensive legislative activity of the government, which initiated subsequent changes in law aimed at counteracting the epidemic and its effects. Polish government implemented a new law on specific solutions related to the prevention, counteraction and eradication of COVID-19, other infectious diseases and crisis situations caused by them, which introduced significant changes to the entire reimbursement system. The main changes mainly consisted of:

- the list of reimbursed products published by the MoH being in force from 1 March 2020 remains valid until 31 August 2020 – this unfortunately has resulted in a lack of new reimbursement lists and a blockage for new reimbursement proceedings in this period as well as for changes in ongoing reimbursement proceedings;
- an extension of duration of reimbursement decisions which period ends before 1 July 2020 – in consequence of non-publication of two reimbursement lists was an "automatic" extension of reimbursement decisions (including attachments) until 31 August 2020;
- reimbursement decisions which date of entry into force was set for 1 May 2020, were set for 1 September 2020; and
- time limits for proceedings initiated and not completed (1) before 8 March 2020, (2) in the period from 8 March 2020 to 15 August 2020, were suspended until 31 August 2020. However, the MoH may take all actions regarding ongoing proceedings, including issuing of administrative decisions taking into account the applicant's request in full.

Currently, new amendments to the Reimbursement act, which are in the legislative phase, have been introduced. Proposed amendments are likely to significantly change the pricing and reimbursement system for, among others, medicinal products. Proposed changes include long-awaited provisions regarding the fate of reimbursement lists and reimbursement decisions as well as pending proceedings, such as:

- requirement of a mandatory 25% reduction for a risk-sharing instrument in which mechanisms lowering the Official Sales Price were also established;
- imposing new regulation of "effective price" – the effective price determined in the next reimbursement decision cannot be higher than resulting from the previous decision. The effective price has been described as a situation in which the Official Sales Price "per 1 package or per patient" has been reduced under RSS;
- imposing two new drug technologies and new reimbursement applications regarding reimbursement and establishment of an official selling price for drug technology with high clinical value and a high innovation level and time of their examination;
- regulating the rules regarding reimbursement continuation, i.e. indicating the obligation to submit such an application no later than 180 days before the expiry of existing decisions, under pain of leaving the application without consideration;

- exclusion possibility to suspend the proceedings at the request of the applicant. The MoH will be able to suspend proceedings for a period not longer than 90 days only due to the public interest;
- requirements for verification analyses for products and therapies which do not have any substitute reimbursed in a given indication;
- detailed regulations regarding the duration of price negotiations, i.e. price negotiations cannot last longer than 30 days from the first day of negotiations, but they can be divided into a maximum of three rounds. In particularly justified cases, the Economic Commission may adopt a resolution to refer the request to one additional negotiation. In case of reimbursement applications regarding reimbursement and establishment of an official selling price for drug technology with innovation level, the applicant will be asked for price negotiation within one month from submitting the application;
- special financing rules by the President of the Fund of medicinal products or food for special nutritional use used as part of a therapeutic programme for which no subsequent reimbursement decision has been issued, which are available in the territory of the Republic of Poland and there is no alternative reimbursed drug technology;
- providing for the applicant free continuation of treatment to patients who started therapy before the date of the decision has expired in case of medicinal product used as part of a therapeutic programme as a drug technology with a high clinical value for which no subsequent reimbursement decision has been issued after the decision has expired;
- special rules regarding issuing by the MoH a decision on reimbursement and setting the official selling price for drug technology with a high level of innovation, if case if applicant does not submit an application for reimbursement;
- no possibility for the applicant to amend the application after the Economic Committee has adopted a resolution; and
- rules concerning drug technology with high clinical value and a high innovation level.

In case the provisions laid down in the amendment are adopted by the Polish Parliament and signed by the President, they are going to come into force as a rule after 30 days from the date of publication. The amendment also does not implement any transitional provisions, which means that the changes planned and discussed above may apply to all ongoing proceedings. The above-mentioned proposed amendments are unprecedented attempt to amend the Reimbursement Act so extensively without previous public consultations of the Act.

Successful market access

The pressure of minimal reimbursement price policy is still the critical success factor for market access. In general, preparing for various scenarios regarding price negotiations of reimbursed medicinal products is highly recommended.

Due to the current worldwide epidemic state, reimbursement proceedings have been suspended and no changes were made to reimbursement lists until the end of August 2020. However, currently available data indicate that the immediate risk of COVID-19 which will affect the production and supply of innovative drugs in Europe in the short term is very limited.

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Spain

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Abstract

Spain is a very attractive market for pharmaceuticals within the European Union. However, it is also a very regulated market and the decisions are taken by different authorities at different levels. This is why market access can appear complex. In the following chapter we will try to explain the most important rules which must be taken into account in order to understand the process of pricing and reimbursement in Spain.

Market introduction/overview

In 2019, the pharmaceutical market in Spain reached €18.7 billion, of which €7.4 billion corresponds to the hospital market, and €11.3 billion to products dispensed through retail pharmacies. Growth was around 4.3%, with expenditure in hospital products exceeding 7.6% over 2018, whilst growth in retail pharmacies was under 2.5%. In 2020, YTD figures (until March 2020) show a 14.5% increase in the hospital market with respect to the same period of 2019 and a 8.3% increase of the retail market with respect to the same period in 2019.[1]

In the near future, one may expect further increases in the hospital market as a result of the appearance of innovative medicinal products, especially in the area of oncological products and orphan drugs. Further, the unprecedented COVID-19 crisis has increased even further within hospital expenditure (e.g. hospital expenditure in March 2020 is 27.8% higher than in March 2019). Because of this, cost containment measures may appear in various forms, as we shall explain in this chapter.

As in many other EU countries, and according to the Annual Report of the NHS published in December 2019,[2] the Spanish pharmaceutical market is highly dependent on public policies, given that approximately 73% of health expenditure comes from the public sector.

In 2019, Spanish public pharmaceutical expenditure (approx. €18.7 billion)[1] is said to account for approx. 1.5% of the gross domestic product and in 2018 (last data available) public pharmaceutical expenditure accounted for 25.2% of all public healthcare financing (approx. €71.1 billion).[3]

According to data of Farmaindustria (the association of the Spanish innovative pharmaceutical industry), the Spanish pharmaceutical industry is the most productive sector of Spain (double the industry average); it is one of the leaders in exports (exceeding €10.6 billion per year); and by comparison with other sectors in Spain, it has a higher concentration of more stable, qualified and diverse employment (94% of its workers are permanent, 62% have university studies, and 52% are women).

As regards demographics, at the beginning of 2020, 47.1 million inhabitants lived in Spain,

with a gross birth rate of 7.9 births per 1,000 inhabitants and an average maternal age of 32 years. Life expectancy at birth reached 83.2 years. Since 2017, Spain has the classical pyramid of population of a developed country where the number of deaths increases more than the number of births. Data from *Instituto Nacional de Estadística* ("INE")[4] show that steady growth in births may be expected during the next 10 years at rates that may be near 0.5%; but a decline in population of almost 50,000 persons each year. The percentage of the population aged 65 years and over may reach 25% in 2033, and the number of persons that are dependent on others will continue increasing up to almost 60% in 2033.

In relation to the Spanish healthcare system, Article 43 of the Spanish Constitution establishes the right to healthcare as one of the basic principles that must inspire action by all public administrations, and this has been interpreted to recognise universal access to healthcare.[5] However, measures[6] 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.[7]

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 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").[8]

During the year 2017 (last data available), 1,450 presentations of medicinal products were included in the provision of the NHS.[9] 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 which may present a danger, either directly or indirectly (even under normal conditions of use), when they are used without being under medical supervision. The same happens with those medicinal products which are used frequently under abnormal conditions of use, and this may involve, directly or indirectly, a danger to health. Spanish law also sets forth that those medicinal products which contain substances (or preparations based on these substances) whose activity and/or adverse reactions need to be studied in more depth, must also be classified as subject to a medical prescription, and the same happens with those medicinal products which are administered parentally.

AEMPS may also establish some subcategories for medicines that can only be dispensed under medical prescription. This would apply to products subject to a special medical prescription regime, or to medicinal products which can only be dispensed by certain means (such as medicinal products for hospital use). It is also important to note that the MOH may also establish restrictions as regards the prescription, dispensing and financing of some medicinal products within the NHS. These may include the need to go through a special visa procedure before the patient may get a given product under reimbursement by the NHS. Under Spanish law, the regions are not entitled to establish local measures restricting prescription, dispatching or financing of medicines or devices that have been accepted for reimbursement at a national level.

AEMPS may classify as medicinal products which are not subject to medical prescription those that are destined for processes or conditions that do not require an accurate diagnosis, or those whose toxicological, clinical or use evaluation data and route of administration do not require medical prescription, and these medicines will be dispensed by a pharmacist who will inform, advise and instruct about their correct use.

Spanish law also contemplates the classification of medicines between brand medicinal products, generic medicinal products, biologic medicinal products or biosimilar medicinal products.

Article 2 of Spanish Law on Medicinal Products (Royal Legislative-Decree 1/2015) defines generic medicinal products as any medicinal product that has the same qualitative and quantitative composition in active ingredients and the same pharmaceutical form, and whose bioequivalence with the reference medicine has been demonstrated by adequate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active ingredient will be considered the same active ingredient, unless they have considerably different properties in terms of safety and/or efficacy. Biosimilar products are not defined under Spanish law, although there exist provisions under which all biological products are considered 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 which is competent to rule on reimbursement. As explained, the reimbursement process then starts *ex officio*. The General Directorate of Pharmacy and Medical Devices shall send a letter to the MAH or to its local representative, informing it that the process has begun and granting the company a period between 10 and 15 working days to make any submission it deems convenient on the reimbursement of the product.

Under the law, the process to decide on pricing and reimbursement may take up to 180 days. Furthermore, the authorities usually request additional information, and these requests may stop the clock of the procedure. In practice, companies may well expect the reimbursement approval to run for a minimum of six months. Sometimes, we have seen procedures take up to a year.

Who influences the decision?

The most important decision-maker in the reimbursement process is the central government. AEMPS has a very important role when issuing its therapeutic position report, and the MOH, through the General Directorate for Pharmacy and the ICPM, decides on reimbursement and then on price. In theory, the General Directorate for Pharmacy is the first to decide on whether the product is reimbursed or not; and the ICPM then decides on the maximum reimbursed price. In practice, however, the two procedures run in parallel and overlap, because the decision of the General Directorate for Pharmacy regarding reimbursement is also based on the price that the ICPM would set for the product.

The General Directorate for Pharmacy, on the other hand, takes care of process management, preparing the rulings that the ICPM shall adopt; it is also the *de facto* leader of the negotiations with the MAH, and coordinates the work done by evaluation teams who handle the dossiers prior to the meeting of the ICPM.

It is also very important to note that authorities of the Autonomous Regions have a very important role in this decision, because they are the ones funding the dispensing of the product to the patient. This is also why three of the Autonomous Regions are members (on a rotating basis) of the ICPM. At present, representatives of all other Autonomous Regions may participate as observers at all ICPM meetings. On the other hand, whilst the central Spanish legislature and government have exclusive competence to enact legislation on medicinal products, the Constitutional Court has established in several cases[10] 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 AEMPS shall prepare, and on the opinion of the Advisory Committee on Pharmaceutical Coverage. Any studies that the MAH may present may also be considered.
c) The innovation of the product; whether it provides an indisputable therapeutic advance for altering the course of an illness or easing the course of such illness; and its prognostics, results or contribution to the NHS.
d) The contribution of the product to Spain's gross domestic product. This is awkward because it could indicate that local manufacturing or development operations have an influence on pricing and reimbursement; something which would be totally contrary to EU law principles.
e) The return mechanisms which may be proposed by the marketing authorisation holder (discounts, price reviews). This is the result of the increasing relevance that risk-sharing schemes are having in Spanish practice nowadays; many companies, especially for high-budgetary-impact products, are required to offer specific arrangements to obtain reimbursement. These may be in various forms, including caps on the number of units that will be reimbursed by the NHS and chargebacks in the event that some established therapeutic results are not achieved.

The medicines which are directly excluded from the pharmaceutical provision are: those which are not subject to medical prescription; those medicinal products which are not addressed at healing a concrete illness; and products which are considered cosmetics, dietetics, mineral waters, elixirs, dentifrices and other similar products. Spanish law also specifies that those medicinal products which are indicated for syndromes or illnesses of minor severity, and those which do not respond to current therapeutic needs, shall also be excluded from the pharmaceutical provision.

What is the relationship between pricing and reimbursement?

Under Spanish law, the ICPM determines the maximum price for the units of the products that are reimbursed by the Spanish NHS. The MOH will also take note of the so-called "Notified Price". The notified price is the price at which the MAH intends to market the product if it is not reimbursed by the NHS. This may apply to products that are not eligible for reimbursement and also to units of reimbursed products that are marketed outside the NHS (i.e. private patients or products that wholesalers may parallel-export from Spain to other EU Member States). The MOH, when receiving notice of the notified price, may only oppose it on the grounds of protecting public interest. 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[11] 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 case a similar product is commercialised in the Spanish market, the authorities may use it in order to determine the price. The price of any competing product inside Spain will undoubtedly serve as a reference for the MOH when discussing the price of a new product.

What is the process to appeal a decision?

Companies may file an administrative appeal against the decision taken by the ICPM once this is notified. The appeal must be filed within one month of the date on which the decision is considered to have been notified. These decisions are notified electronically, and companies have a period of 10 days to download the notice once they receive the alert that it is ready to be downloaded.

If the administrative appeal is rejected, the company may file a court action seeking a declaration that the ICPM acted wrongly. However, in pricing and reimbursement cases, the chances of a court action being successful are rather limited, given that the MOH has wide discretionary powers on these matters. In general, companies have more chances of being successful at the administrative appeal level if they are able to provide evidence of some major mistake in the administrative decision.

The administrative appeal does not suspend the application of the decision taken by the ICPM. The suspension may be requested when filing the administrative appeal and this request must be answered within one month. In this case, failure to respond by the MOH acts in favour of the appellant, because in such event the suspension is deemed to have been granted. Afterwards, however, the MOH may lift such suspension when deciding on the substance of the appeal. In order for the suspension request to have any chance of success, the applicant must provide evidence that the immediate entry into force of the decision of the ICPM will result in irreparable harm. The threshold is thus rather high; and this is why we normally consider that the chances of succeeding in a request for suspension are rather low.

One issue which often arises when dealing with administrative procedures in Spain refers to the general climate, and to whether companies that may be strict enforcing their rights, and even filing administrative or court appeals, may suffer some sort of negative reaction by the MOH. Our opinion, based on over 20 years of experience dealing with these matters, is that neither AEMPS, nor the MOH nor the ICPM penalises companies for defending their position – provided this is done under general good faith principles. In some cases, special diplomacy may need to be exerted to ensure that the position of the company is not misinterpreted – it is important to play fair – but in general terms, this is not something to be too concerned about.

Reference pricing

It is also very important to bear in mind that in Spain the public financing of medicines is subject to a reference price system. Once a generic version of a medicinal product is approved, or even in other circumstances if no generic exists in Spain but the main active ingredient of a product has been generally available in the EU for the last 10 years, the MOH may make it subject to a reference price, which will apply to all financed product presentations containing the same active ingredient and identical administration route.

The reference price is the maximum price which the Spanish authorities will pay for these products when they are prescribed and dispatched through an official prescription at a pharmacy, and such price is fixed on the value represented by the lowest cost of the treatment per day of the presentations of the medicinal products included in each group. The reference price system, as an instrument designed to guarantee the sustainability of the public pharmaceutical provision, uses the appearance on the market of competing products for a certain active ingredient to establish a maximum price for the dose necessary for a day of treatment with this active ingredient, which is the maximum price that the NHS will satisfy when the presentations with this active ingredient are dispensed or administered to the patient charged to public funds.

In general terms, when a medicinal product is included in the reference price system, one may expect a reduction between 40% and 50% in the price of the reference/s product/s (the price of generics are likely to be within this range).

In 2018, Spanish courts had to rule on various cases where plaintiffs argued that the MOH was inadequately including, in the same reference price group, products that did not have the same active ingredient. In the majority of these cases, the issue was whether products, having as their active ingredient different salts or esters, should be considered the same for reference price purposes. The courts ruled that if the MOH wished to include all these products in the same reference price group, it should provide evidence that the differences between the various salts or esters included in the same group did not have enough significance from an efficacy or safety perspective.

On another note, in 2018, the Spanish MOH took special measures to protect some products that could be impacted by reductions of their reference price in cases where such reduction could result in the products not being available anymore.

Between 2019–2020, Spanish courts have 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.[12] 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 done 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. The resolution of the appeal is still pending. Our opinion is that this ruling 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.

Other judgments in this first group mainly confirm the regime applicable on this matter until 2019 and do not provide for a significant modification of the same. These judgments refer to aspects such as the determination of the identity between two active ingredients (e.g. the active ingredient identified in the SmPC prevails over the ATC Classification System and, therefore, if the MOH wishes to include two medicinal products in the same reference price group on the basis of the ATC 5 Classification System, the MOH must provide sufficient evidence that the active ingredients of the two products are the same) or the specific regime of pediatric products for reference pricing purposes (e.g. for a product to be deemed a pediatric product and, therefore, subject to specific rules regarding its inclusion in reference price groups, it is required that such product "covers exclusively pediatric indications", and not simply that the product is "mostly used in pediatric population").

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.[13] 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.

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.

From May 2019 until February 2020 (last period with available information),[14] the ICPM has reviewed the price of 75 products. Such reviews ended with 23 price increases and 52 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 1090/2015, in these situations the product may be available for patients under the rules that apply to products for which a valid MA exists in Spain but which are not commercially available.

These rules allow access to the product if the prescribing doctor, under his/her own responsibility, considers that the use of such product is indispensable for the treatment of an individual patient because no other equivalent product is available in Spain. An equivalent product is one having the same composition and the same pharmaceutical form. The patient – or the patient's representative – must consent in writing 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).

What happens with products for which reimbursement is denied?

Up to very recently, there was consensus in Spain in the sense that if the MOH decided to deny reimbursement, the MAH could still place the product 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.[15] 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.

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 2019–2020, 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 2019–2020, 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). 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.

On another note, it is important to mention that it is common practice in Spain that contracting bodies do not publish information about supply agreements that they may negotiate individually with companies when there is no invitation to tender because there is no competition in a given market. In these cases, where the supply agreement is entered into following the process known as "negotiated procedures without prior publication of a contract notice", it is common that the agreement is not published at all. We cannot exclude that this administrative practice changes in the future because, as a matter of law, even these agreements should be publicised. But for the time being, this is where things stand.

It is also relevant to mention that during 2019–2020, 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[16] 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[17] 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.

Finally, with respect to the position of the Spanish Courts, we can say that the judgments published in the period 2019–2020 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 two most recent rulings regarding access to price and reimbursement rulings (April 2020) and disclosure of supply prices offered to hospitals (May 2020) 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.

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 31 December 2019, and recently extended until 30 June 2020. This extension, has been published[18] in the Spanish Official Journal on 10 March 2020 and contemplates that Farmaindustria and the Government will

"collaborate in a new agreement with the objective, among others, of reflecting in it the implication of all entities involved in the sustainability of the SNS and of the rationalisation of public pharmaceutical expenditure, in such a manner that its provisions apply to the full year 2020 replacing the existing ones". Therefore, the future and terms of the Farmaindustria Agreement are currently very open; and negotiations regarding this matter are ongoing.

With respect 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 approx. €97 million. Regarding 2019, no definitive data are currently available, but we can anticipate that, considering the GDP growth of such year, the claw-back payment will probably be higher than the one for 2018. 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.

Finally, we can not finish this section without mentioning the impact of the unprecedented crisis generated by COVID-19. In the context of this crisis, we expect the Spanish government to request the pharma sector (and maybe also other industries who supply products to the NHS) to further contribute to the sustainability of the NHS. Under Spanish law, the Government may resort to legal instruments imposing taxes, claw-back payments or similar monetary obligations to companies, and in our opinion, it is likely to do so. This is what happened in 2010, when the Government approved Royal Decree-Law 4/2010 imposing a quarterly claw-back payment of 2% on sales for companies selling over €3 million, and Royal Decree-Law 8/2010 imposing a compulsory 7.5% discount on sales made to hospitals for original products not subject to generic competition or reference pricing (4% for orphan drugs and 15% for products over 10 years old not subject to generic competition).

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[19]

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.

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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Sweden

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Abstract

This chapter provides an overview of the model for pricing and reimbursement of pharmaceutical products in Sweden, including brief notes on reimbursement of medical devices.

In 2002, Sweden abandoned the reference price system for pharmaceutical reimbursement used since the 1990s, which is still widely adopted in European countries, and 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 pharmaceutical products. The main features of the value-based model are the use of cost-effectiveness analysis for determining the reimbursement status of pharmaceuticals, and mandatory substitution for the lowest-cost generic alternative. The use of cost-effectiveness analysis in reimbursement decisions aims to relate and balance the reimbursement price with the social value of the product, 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 subsidised out-patient pharmaceutical products included in the reimbursement scheme are formally financed by the regions but are covered by government grants. Patients only pay a limited part of the price for such pharmaceuticals and a patient's maximum costs during a year are subject to high-cost protection.

Market introduction/overview

Swedish healthcare is a shared responsibility of the state, 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 elderly, immigration constitutes the largest demographic change and primarily increases the population that is of working age.

Manufacturing of medicinal products and medical devices is one of the largest industries in Sweden, and is accorded a high priority by the Swedish Government, and for 2020 Sweden continues to be the EU innovation leader according to the European Innovation Scoreboard. During 2019, the Swedish pharmaceutical market had a turnover of SEK 50.4 billion, an increase of 6% compared to 2018. In 2019, close to 212 million pharmaceutical packages were sold in Sweden. Approximately 50% of these packages were prescription pharmaceutical products, while approximately 44% were non-prescription pharmaceutical products.

The Swedish pharmacy market was deregulated in 2009. Since then, the number of pharmacies has increased by almost 500. Currently, there are over 1,400 outpatient pharmacies in Sweden. The industry is dominated by five pharmacy chains and there are just over 30 companies with one or a few pharmacies. In addition to out-patient pharmacies, there are hospital pharmacies, dose-dispensing pharmacies and distance pharmacies.

Since the deregulation, pharmacies have increased their opening hours. This, as well as the emergence of e-commerce, has contributed to improved accessibility than before the deregulation.

Pharmaceutical pricing and reimbursement

Regulatory classification

Legal framework

Being an EU Member State, Sweden's legal framework for pharmaceutical products is to a large extent based on relevant EU directives and subject to EU regulations. The national legislative basis for regulatory issues (including marketing authorisation and substitutability), supervision and enforcement of pharmaceutical products in Sweden is primarily stipulated in the Medicinal Products Act (2015:315) (Sw. *läkemedelslagen*) and the Medicinal Products Ordinance (2015:458) (Sw. *läkemedelsförordningen*) and, for medical devices, in the Medical Devices Act (1993:584) (Sw. *lag om medicintekniska produkter*) and the Medical Devices Ordinance (1993:876) (Sw. *förordning om medicintekniska produkter*). The Medicinal 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 (Sw. *Läkemedelsverket*) (MPA).

Notably, on 26 May 2017, the new EU regulations on medical devices entered into force within the European Union; Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices. However, the new rules will only apply after a transitional period of three years after entry into force for the regulation on medical devices (which was initially intended to enter into force on 26 May 2020, but was postponed by the European Parliament and the Council of the EU until 26 May 2021 as a result of the COVID-19 pandemic), and five years after entry into force for the regulation on in vitro diagnostic medical devices (spring 2022).

The legal framework concerning the granting of marketing authorisation of a pharmaceutical product differs from the framework concerning pricing and reimbursement. While the former is based on EU rules as described above, the latter is substantially regulated at a national Swedish level, with little influence by the EU.

The Swedish Dental and Pharmaceutical Benefits Agency (Sw. *Tandvårds- och läkemedelsförmånsverket*) (TLV), which is an expert state agency, decides to what extent a

pharmaceutical product shall be reimbursed, according to the Pharmaceutical Benefits Act (2002:160) (Sw. *lag om läkemedelsförmåner m.m.*) (PBA) and the Pharmaceutical Benefits Ordinance (2002:687) (Sw. *förordning om läkemedelsförmåner m.m.*) (PBO). TLV also issues regulations and general advice.

In addition, Sweden has a system for substitution of generically equivalent medicinal products. The MPA (and/or the European Medicines Agency) approves all medicinal products, including generics and parallel imported products, with regard to their quality, safety and efficacy. The MPA decides which medicinal products shall be substitutable at the pharmacies and publishes a list of groups that includes such products.

The basic principles for substitution are that products that have the same active substance in the same amount, and are otherwise medically equivalent, shall be substituted. Only products that are included in the benefits scheme may be substituted. The system demands that pharmacies dispense the least expensive generic product available to the patient, regardless of the prescribed product, unless the prescribing doctor has opposed substitution for medical reasons in writing. The patient may also refuse substitution if he or she is willing to pay the difference between the prescribed medicine and the generic alternative. The system was introduced in 2002 and has resulted in several court cases regarding the MPA's decisions on the equivalence of different medicinal products.

Prescription vs. requisition

Pricing and reimbursement procedure and regulation of pharmaceutical products primarily depends on whether the specific product is a *prescription pharmaceutical* or a *requisition pharmaceutical*.

Prescription is the case when a pharmaceutical product is prescribed to a patient and based on which a pharmacy may provide the specific pharmaceutical product to the patient. The price of prescription pharmaceuticals included in the reimbursement scheme is determined by TLV, while the pricing of prescription pharmaceuticals outside this system can be set freely (see below).

Requisition, on the other hand, means the requisition of pharmaceutical products by and to healthcare professionals, to be administered to patients in institutional or non-institutional healthcare. Institutional care refers to treatment given to patients in a hospital or other type of institution, and non-institutional care refers to any other treatment of a patient that is not defined as institutional. Requisition pharmaceutical products are procured and priced pursuant to public procurement procedures carried out by the Swedish regions.

It is possible for a specific pharmaceutical product to be subject to both prescription and requisition. In such case, two different systems of regulation will apply – which can lead to different pricing of the same product.

Prescription-only vs. non-prescription pharmaceuticals

Pursuant to Chapter 4 of the Medicinal Products Act, a pharmaceutical product will, in connection with being granted marketing authorisation, be classified either as a prescription only or a non-prescription pharmaceutical product. The MPA will decide the classification for the pharmaceutical product depending on its intended use and characteristics. A prescription-only pharmaceutical product must be subject to either the prescription or requisition regulation in order to reach the patient. Non-prescription pharmaceuticals, on the other hand, are not required to be subject to either the prescription or requisition regulation; however, nothing prevents non-prescription drugs from being prescribed or requisitioned.

Products eligible for reimbursement

Pharmaceutical products prescribed for certain purposes and to a specified group of people

may be covered by the pharmaceutical reimbursement scheme in accordance with the PBA. The general rule is that only prescription-only pharmaceutical products are eligible for reimbursement, as set forth in Section 15 of the PBA. However, pursuant to Section 17 of the same act, and further by the PBO, TLV has been authorised to issue regulations regarding the prerequisites for non-prescription pharmaceutical products being eligible for reimbursement. According to the TLV regulation TLVFS 2003:2 (regarding non-prescription pharmaceutical products in accordance with PBA) (last amended by TLVFS 2012:3), non-prescription pharmaceuticals are eligible for reimbursement. In addition to pharmaceuticals, there are also other products that are eligible for reimbursement.

As stipulated in Section 18 of the PBA, only some medical devices are eligible. Medical devices eligible for reimbursement, called consumables, only includes products used: (i) in connection with stoma; (ii) to induce a pharmaceutical product into the human body; and (iii) for self-monitoring of medication. Stoma-consumables are covered by the same rules regarding reimbursement as pharmaceutical products in general, while consumables used to induce pharmaceuticals, and for self-monitoring of medication, are entirely reimbursed and are free of charge for the patient.

Even food may, under certain circumstances, be eligible for reimbursement. According to Section 20 of the PBA and as further regulated in Sections 6 and 7 of the PBO, foods that have been prescribed to a child (aged below 16) may be reimbursed provided that the child suffers from any of the specific conditions stipulated in the PBO.

Who is/are the payers?

Pricing of medicinal products that are included in the reimbursement system is regulated and the cost of such medicinal products dispensed in pharmacies to patients is to a large extent subsidised by the state. The patient pays some of the costs for subsidised prescription pharmaceuticals, but according to the PBA, a patient's maximum costs are subject to high-cost protection valid for 12 months at a time starting from the date of the first purchase. As at the time 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 medicinal products and medical devices included in the reimbursement scheme. The purpose of this is to reduce inequality of children's health between groups in society with different financial conditions. Also, prescribed contraceptive drugs included in the reimbursement scheme are free for all women under the age of 21.

As stated above, the prices for requisition pharmaceutical products used in institutional and non-institutional healthcare are negotiated in public procurement processes, and the patient only pays the standard patient fee that applies for the healthcare treatment concerned.

Most non-prescription (over-the-counter) medicinal products are not subject to regulated pricing and are not reimbursed by the state. As a result, such medicinal products purchased in pharmacies (or other authorised retail stores) are typically paid for entirely by the end customer.

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

TLV decides to what extent a medicinal product shall be reimbursed, according to the PBA. For a medicinal product to be covered by the reimbursement scheme, a written application

shall be submitted to TLV. The company applying for reimbursement is responsible for demonstrating that the medicinal product meets the applicable legal requirements. In the application, the applicant shall state the requested price of the product and provide reasoning and adequate documentation to support the requested price (see below how the price is determined), e.g. a health economic analysis.

An application is granted if the pharmaceutical product is eligible for reimbursement and all the material requirements in the PBA are fulfilled, and if TLV finds that the requested price is justified in consideration of the value that the medicinal product brings to society in terms of improved health (i.e. it is cost-effective and brings marginal benefit to the market).

Medical devices that are eligible for reimbursement are subject to the same reimbursement rules as medicinal products, as long as the devices are to be used by patients and prescribed by a physician. However, the rules regarding substitution of medicinal products do not apply to medical devices.

Decisions made by the MPA, TLV and other governmental authorities can be appealed to the Swedish Administrative Courts. The Administrative Procedures Act (1971:291) (Sw. *förvaltningsprocesslagen*) governs the procedure of such appeals. Decisions and judgments from the Administrative Courts may, in most cases subject to granting of leave to appeal, be appealed to one of the Administrative Courts of Appeal, whose decisions and judgments may further be appealed to the Supreme Administrative Court. Proceedings in the administrative court system are primarily conducted in writing, but oral hearings are possible if requested by a party or if the court finds it appropriate.

Appeals of decisions by authorities (e.g. the MPA and TLV) are submitted directly by the company to the authority. The main rule is that an appeal must be submitted so that it is received by the authority no later than three weeks from the date on which the appellant received the decision, or it may be inadmissible. Only if the authority does not amend its original decision as claimed by the appellant, will the appeal be forwarded to the relevant Administrative Court. If all formal requirements of appeal are fulfilled, and the appeal is not dismissed on formal grounds, the Administrative Courts are authorised to assess an appealed decision in its entirety. The main possible outcomes are, depending on the circumstances in each case, either: rejection of the appeal; material change of the appealed decision; or referral of the case back to the authority for reassessment in accordance with any statements of reason from the court. It is possible to claim that the court should issue an interlocutory order regarding the appellant's claims (in full or in part), to be in effect during the court proceedings.

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

The main rule is that only prescription-only pharmaceutical products may be included in the pharmaceutical reimbursement scheme. In general, all pharmaceuticals, including over-the-counter pharmaceuticals, may be reimbursed and included in the reimbursement scheme, provided that the conditions stipulated in the PBA are fulfilled. According to the PBA, the requirements for a prescription-only pharmaceutical product to be included in the reimbursement scheme are that: (i) the costs of using the pharmaceutical product appear reasonable from a medical, humanitarian and socioeconomic perspective; and (ii) there are no other available pharmaceutical products or treatments, which, when balancing the intended effect and potential harm, are deemed to be significantly more suitable.

TLV shall determine whether the price requested by the applicant is reasonable by making a total assessment, taking into consideration three ethical principles of healthcare that are included in the HSL to guide priority-setting in the health service. These ethical principles are:

(i) the human dignity principle, which implies that the care should be given with respect to the equality of all human beings and with consideration of the individual's dignity;

(ii) the needs and solidarity principle, which entails that the person with the greatest need for healthcare shall be given priority; and
(iii) the cost-effectiveness principle, which means that one should strive towards a reasonable relationship between cost and effect, measured in improved health and an increased quality of life, when considering different activities and measures.

A decision on reimbursement is thus based on value, which is often described in terms as applying "value-based pricing of pharmaceuticals". In actual fact, prices can be freely set under a value-based ceiling price. There are few countries that apply the value-based pricing of pharmaceuticals. Instead, most EU countries apply international reference pricing in some form.

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

There are no additional provisions specifying the criteria that TLV applies when taking a decision on a subsidy and price, at the legislative level. Instead, the idea is that TLV provides more detailed guidance through regulations and general advice. The administrative courts also continuously develop legal precedent on the conditions for determining subsidy and price.

In order to estimate the cost for the use of the pharmaceutical product, TLV requires information regarding the relevant patient group and volume; for instance, the number of patients that will need the pharmaceutical product and for how long. Furthermore, TLV considers whether there is a risk that the pharmaceutical product is used outside a potential limitation of the subsidy – which, in that case, risks being a usage that is not cost-effective. TLV has developed a practice on how to apply the criteria for subsidy and pricing. In 2003, TLV issued general guidelines (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 product, and describes how TLV believes that a health-economic analysis should be conducted. The guidelines are worth considering in the planning and implementation of health economics studies to be used in upcoming applications for subsidy and pricing.

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

There are various pricing procedures for pharmaceutical products; for example, through decisions by TLV, the 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 above "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, which is one of several factors considered when TLV makes decisions on price and reimbursement. Risk-sharing through managed entry agreements has become an increasingly valuable tool to manage uncertainties for certain new pharmaceutical products. Furthermore, they may ensure cost-effectiveness and reduce the increasing costs for new pharmaceuticals. Consequently, the discussions between regions, pharmaceutical companies and TLV can enable the use of such pharmaceuticals, even when there is significant uncertainty concerning their medical effect and cost effectiveness. Furthermore, the pharmacies have a right of negotiation, which means that they may use prices other than those determined by TLV, for some pharmaceutical products, mainly parallel imported pharmaceutical products.

The pricing of non-prescription (over-the-counter) pharmaceutical products can be set freely. The patient pays the entire cost for these medicinal products. Prices are regulated for non-prescription drugs that are included in the reimbursement system, and the patient makes a co-payment. It should be noted that most over-the-counter pharmaceutical products are not included in the reimbursement system. The reason is that pharmaceutical companies usually do not apply for reimbursement for over-the-counter pharmaceuticals, since pharmaceutical products outside the reimbursement scheme are unregulated and subject to free pricing.

The MPA decides which medicinal products that shall be substituted at the pharmacies and publishes a list of groups that includes such products. Only products that are reimbursed may be substituted. Sweden also has a 'product of the month' system for substitutable products. The product of the month within the groups of substitutable products is decided by TLV and appointed through a monthly auction. The substitution is mandatory and consequently, the pharmacies are obligated to dispense the least expensive pharmaceutical product included in the reimbursement scheme that is available on the market, regardless of the prescribed product.

In-patient care

The prices for in-patient care (hospitals) medicinal products are negotiated in the county council's public procurement processes, which are regulated by the Swedish Public Procurement Act (2016:1145) (Sw. *lagen om offentlig upphandling*). The patient only pays the patient fee that applies for the in-patient treatment concerned, and except for such flat fee, the entire price of pharmaceutical products used in in-patient case is reimbursed by the regions. Pharmaceutical products used in in-patient care are not covered by the national reimbursement scheme and there is no nationwide reimbursement list for in-patient pharmaceuticals, since regions decide on which treatments to use and finance them at the regional level.

Issues that affect pricing

Generic substitution

As stated above, the MPA approves all medicinal products with regard to their quality, safety and efficacy, and the MPA also decides which medicinal products shall be substituted at the pharmacies and publishes a list of groups that includes such products. The basic principles for substitution are that the products have the same active substance in the same amount, and are otherwise medically equivalent. Only products that are reimbursed can be substituted. As of June 2020, the PBA was amended to enable substitution also of prescribed pharmaceuticals that are not included in the reimbursement scheme, if there is an equivalent pharmaceutical in the reimbursement scheme. This means that pharmacies are obligated to dispense the least expensive pharmaceutical product included in the reimbursement scheme that is available

on the market – regardless of what product is prescribed. Physicians and pharmacists at the pharmacies may only prohibit substitution on medical grounds, as stipulated in Section 21 of the PBA. The purpose of this substitution system is to safeguard the lowest possible cost for both the patient as well as the society.

Ceiling prices

Generic substitution leads to lower prices due to competitive market forces, which may result in significant price differences between generic substitutes arising. In this situation, TLV may decrease the maximum accepted selling price within the reimbursement scheme by setting a lower ceiling price for substitutable pharmaceuticals. This is most relevant for the branded original pharmaceutical product that has lost its patent protection.

Each month, TLV analyses prices and sales volumes in order to find groups where the criteria for setting a ceiling price are met. When the prices of a group of substitutable generic pharmaceuticals have dropped by at least 70% of the price that the pharmaceuticals had before generic competition arose, and when generic competition has been ongoing for at least four months, TLV sets a ceiling price. The ceiling price may not enter into force until at least six months after the introduction of generic competition within the substitution group.

The new fixed ceiling price is normally 35% of the highest price in the relevant substitution group when generic competition arose. Setting the ceiling price in this way thus reduces the differences in price between substitutable generic pharmaceuticals within the reimbursement scheme, but it also has the effect of further decreasing costs in addition to the cost-decreasing effect of generic substitution itself, by forcing a lower price of original pharmaceuticals within the reimbursement scheme. After TLV has determined a ceiling price, pharmaceutical companies have the options of either applying for a new price that meets the set ceiling, or withdrawing from the reimbursement scheme.

Price reduction after 15 years

As of November 2014, certain rules apply for the pricing of some older drugs (see TLV's regulation TLVFS 2014:9, last amended by HSLF-FS 2018:30). The change is based on changes in the PBA and means that TLV will reduce the price of pharmaceutical products by 7.5% when they are older than 15 years. The 15-year threshold is determined based on the date of first marketing authorisation in each relevant so-called substance/form group. This means that TLV can decide to reduce the price of pharmaceutical products that have recently been approved for reimbursement, if the first marketing authorisation in the same substance/form group is older than 15 years. TLV's decisions to reduce the price can be appealed to the administrative courts (see section "What is the process for securing reimbursement for a new pharmaceutical product?").

The first price reductions under the new rules came into effect on 1 January 2015. The intention is to contribute to a more cost-effective use of pharmaceuticals in Sweden. The changes were initiated by an agreement on lowering the prices of some older medicinal products, between the Swedish Government and the trade organisation for the Swedish research-based pharmaceutical industry (LIF) in 2013.

Policy issues that affect pricing and reimbursement

According to Statistics Sweden, the population in Sweden will continue to increase within all age groups. The percentage increase is greater in the older age groups. In addition to the increasing number of elderly, immigration constitutes the largest demographic change and primarily increases the population that is of working age.

A recently reported public inquiry appointed by the Swedish Government (see further "Emerging trends" below), *inter alia*, concluded that shared resources available for financing pharmaceuticals are insufficient to meet all needs and therefore priorities must be set. As the population grows, gets older and suffers from more chronic diseases, while innovation within the pharmaceutical industry increases and drugs become more expensive, the need for priorities will also increase. These issues are likely to affect pricing and reimbursement policy, at least in the long term.

Emerging trends

The Swedish Government has a major focus on the pricing and reimbursement of pharmaceutical products and in 2016 the Government appointed a public inquiry to investigate and analyse the current system of funding, subsidising and pricing of pharmaceutical products. It is the first review since 1998, when the cost responsibility for pharmaceutical products benefits passed from the state to the 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, 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 between the regions' negotiation delegation, TLV and the pharmaceutical company in question, as well as managed entry agreements for pharmaceutical products covered by the reimbursement scheme, were introduced. The idea of the three-party negotiations is to give companies yet another opportunity to receive reimbursement for their products, if they do not receive reimbursement immediately, as well as facilitate access to new, innovative treatment options for patients while maintaining a general price control and reduction for the society. The three-party negotiations typically involve discussions concerning risk-sharing between the companies and TLV, e.g. by considering the possibility of granting reimbursement only for a limited amount of time. The three-party negotiation model has so far been tested and used in connection with the introduction of new pharmaceutical products as well as in the case of established drugs, such as particularly costly medicines and biological drugs for which the patent has expired. The public inquiry report mentioned above (SOU 2018:89) proposes a few changes and

clarifications of the three-party negotiation process, including that the framework for such negotiations should be regulated by law. Managed entry agreements are used to an increasing extent and now encompass products with a total annual turnover of approximately SEK 4 billion. More than half of the sales of newly introduced unique drugs are covered by managed entry agreements. The public inquiry report mentioned above (SOU 2018:89) proposes changes to the organisation for managed entry agreements, including, e.g. introduction of a new 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 substitution of prescribed pharmaceuticals not included in the benefits scheme, to equivalent medicinal products that are included in the benefits 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.

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.

If an application for listing in the reimbursement scheme is rejected by TLV, the company may consider attempting to enter into three-party negotiations with the regions' negotiation delegation and TLV in order to get another opportunity for reimbursement of its products. For such a negotiation process to be successful, it is beneficial to understand the different factors that will be considered by the regions and TLV. As an alternative, or if the three-party negotiation fails, companies may also appeal the rejected decision to have the case tried by the administrative courts, or set about putting the drug on the market without reimbursement (an option that is always available) or resubmit the application to TLV (e.g. including a more comprehensive health economic analysis) for a second-round evaluation.

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Switzerland

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Abstract

Every resident in Switzerland is mandatorily obliged to be covered by basic healthcare insurance which provides for a wide range of services. Persons with lower incomes are, in principle, granted reductions on the premiums payable for such basic healthcare insurance. Thus, every resident in Switzerland is granted access to affordable healthcare.

In general, therapeutic products are only reimbursed if they are listed on the so-called specialty list. In order to be listed thereon, a medicinal product must be admitted by the competent Swiss authority, and 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 2018, healthcare costs amounted in total to 81.9 billion Swiss francs (provisional result). Compared to the general domestic product ("**GDP**"), healthcare spending represented 11.9% in 2018 (provisional result). Every resident in Switzerland paid on average 802 Swiss francs per month (provisional result) for the healthcare system in 2018 (*cf.* https://www.bfs.admin; last visited on 3 May 2020). The corresponding numbers for 2019 are not yet available.

In 2019, the total value of goods and services exported from Switzerland amounted to 312 billion Swiss francs (provisional result), whereas the value of imported goods and services amounted to 276 billion Swiss francs (provisional result). A positive balance of 36 billion Swiss francs (provisional result) in favour of Switzerland resulted therefrom. The most important part of Switzerland's exports were chemical and pharmaceutical products, which constituted 36.7% of the exports (115 billion Swiss francs). Chemical and pharmaceutical products further constituted the second-largest group of imported products (19.1% of the imports, respectively 53 billion Swiss francs). It must be noted that all numbers stated above are provisional results (*cf.* Key figures 2019, available under the following link: https://www.ezv.admin.ch; last visited on 3 May 2020).

According to the Association of research-based pharmaceutical companies in Switzerland ("**Interpharma**"), in 2018, reimbursable therapeutic products represented approximately 84.4% of the total pharmaceutical market. This corresponds to 68% of all packs of therapeutic products sold in 2018 in Switzerland. Most of these reimbursable therapeutic products' packs were prescription-only products (*cf.* Interpharma, Pharmaceutical Market Switzerland, 2019, p.24).

Over 496,200 people in Switzerland worked in the healthcare industry and the pharmaceutical sector in 2017. This corresponds to approximately one in 12 of the working population (*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 2018, 281 hospitals and maternity units (37,956 beds) and 1,566 homes for elderly and care (92,309 residents per 31 December) were registered in Switzerland (*cf.* https://www.admin.bfs.ch; last visited on 3 May 2020). The density of general practitioners is, however, relatively low compared to other countries. The same applies with respect to pharmacies, whose density is comparatively low, as in certain cantons doctors are permitted to dispense medicines themselves (*cf.* Interpharma, Healthcare Switzerland, 2018, p.18). Contrary to certain countries, such as the USA, most therapeutic products cannot be sold via supermarkets.

Switzerland is one of the world's leading players in the domain of biomedical research and technology. Given the high importance of the pharmaceutical market, the Swiss Federal Council has endeavoured to strengthen the international position of Switzerland with several initiatives, such as the "Masterplan for the promotion of biomedical research and technology" of 2013 (for further information, *cf.* 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 60 approved non-profit insurance providers currently offer basic mandatory insurance and optional loss of earnings 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.

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 3 May 2020).

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 3 May 2020).

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 3 May 2020).

The hospitalisation ratio per 1,000 residents was 117.8 in 2018, while infant mortality stood at 3.3‰, in 2018 (*cf.* "Health – Pocket Statistics 2019" available under the link: https://www.bfs.admin.ch; last visited on 3 May 2020).

The most common causes of death in Switzerland are cardiovascular diseases (approx. 32% of the deaths in 2016) and cancer (approx. 26% of the deaths in 2016). According to the Swiss Cancer Report 2015 published by the FSO, cancer has become a chronic illness. In 2015, 317,000 people in Switzerland were living with a cancer diagnosis. This is twice as many as 25 years ago. Every year, approximately 17,000 people living in Switzerland die from the consequences of cancer. Pursuant to said report, it is expected that around 40% of the Swiss population will be diagnosed with cancer at any point in their lifetime. The main reason for this increase is due to the fact that the population is getting older. However, in comparison to the other European countries, Swiss incidence rates are still average for men and even low for women, except for melanoma, which have a high incidence rate in Switzerland (nevertheless, mortality rates for melanoma are very low). As regards survival rates across all types of cancer, Switzerland's five-year survival rates are among the highest in Europe (*cf.* for more details, Swiss Cancer Report 2015 of the FSO, available under the link: https://www.bfs.admin.ch; last visited on 3 May 2020).

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 3 May 2020).

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 recently 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, composition and possible side effects of the therapeutic product in question (article 33 OBHI). Finally, a therapeutic product is deemed economically efficient if the indicated therapeutic effect is reached most cost-efficiently (article 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 Germany, Denmark, Great Britain, Netherlands, France, Austria, Belgium, Finland and Sweden (so-called *Auslandpreisvergleich*); and on the other hand, on an assessment with respect to other therapeutic products (so-called *therapeutischer Quervergleich*). As regards the comparison with other therapeutic products, the FOPH examines the efficiency and costs of the therapeutic product in question compared with other drugs used for the treatment of the same disease (article 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 2018 is expected to reach the age of 81.7 (men) or 85.4 (women) (*cf.* https://www.bfs.admin.ch; last visited on 3 May 2020). 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, 15.3% lived in retirement homes per 31 December 2018 and 28.9% needed care at home, and that the total costs of retirement homes alone amounted to 10.357 million Swiss francs in 2018 (*cf.* https://www.bfs.admin.ch; last visited on 3 May 2020), the costs for healthcare will most presumably further rise.

As already discussed herein above, the most common causes of death in Switzerland are cardiovascular diseases and cancer (*cf.* above, "Incidence and prevalence of disease", in "Market introduction/overview"). Since the costs of certain therapeutic products for the treatment of cancer are very high, a further increase of healthcare costs is to be expected in this respect too.

The extremely high costs for the healthcare system and, in particular, the financing of these costs are currently a highly controversial political topic in Switzerland (*cf.* also above, "Size, demographics" in "Market introduction/overview"). Also, costs and benefits of very expensive treatments, in particular when carried out with regard to old persons, are debated increasingly vehemently.

Prohibition of benefits and kick-back

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). 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 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 which employ them, to solicit, be promised or accept any undue advantage for themselves or for the benefit of a third party. Further, it is forbidden 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) a 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 2022 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 entering into force of 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 aims at improving the population's access to therapeutic products and the conditions for biomedical research and industry. The Federal Council transferred the dispatch on the revision of the TPA to the Parliament on 7 November 2012, which accepted the core elements of the Federal Council's draft, amended part of it, and adopted the revised TPA on 18 March 2016.

Certain provisions entered into force on 1 January 2018. With regard to the remaining implementing provisions, a consultation process was conducted in 2017. Thereupon, the

revised provisions of the TPA and the corresponding ordinances entered into force on 1 January 2019 and 1 January 2020, respectively.

Further, Switzerland is adapting 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 has recently been deferred by one year. As Switzerland aims to achieve equivalence with the EU legislation, the entry into force of the revised Swiss medical device legislation has also been deferred by one year, to 26 May 2021.

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

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Abstract

The UK has a large and complex healthcare system, under which the National Health Service ("NHS") funds the vast majority of medicines prescribed to patients.

The complexities of the system mean there is no single pathway to NHS reimbursement for a medicinal product, nor a universal reimbursement list. If and how the NHS funds a product often depends on the setting in which the NHS uses it. However, guidance from the National Institute for Health and Care Excellence ("NICE") plays an important role in determining whether the NHS will support the use of a product. The UK has price control policies for branded medicines but, in general, leaves the price of generic products open to market forces.

NHS drug expenditure continues to increase, albeit growth rates vary significantly depending on product type. Reasons for this include a growing and ageing population, with specific needs, as well as the launch of costlier high-tech and rare disease medicines into the UK. Although the Government has increased funding for the NHS, particularly in response to COVID-19, there continues to be significant downward pressure on drug budgets. 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. As such, the landscape for pricing and reimbursement is increasingly multi-layered. Commercial negotiations with the NHS and procurement initiatives often have a significant effect on the actual selling price of a product.

Market overview

The UK comprises four constituent nations: England; Wales; Scotland; and Northern Ireland. The UK has a population of approximately 66.4 million people, with the vast majority (approximately 55.9 million) resident in England. There is a well-developed healthcare market in the UK, dominated by a large and sophisticated public healthcare system, the NHS. The NHS is almost entirely state-funded and mostly free to patients at the point of need.

When considering pricing and reimbursement in the NHS, it is important to keep two points in mind. Firstly, the structure and organisation of the NHS varies across the four nations of the UK, though many key concepts are similar. For the sake of simplicity, this chapter focuses primarily on the NHS in England, which is by far the largest market. Secondly, the way the NHS pays for medicines differs considerably between those supplied in "primary care" (i.e., prescribed by General Practitioners or other community prescribers and dispensed in a community pharmacy or by a dispensing doctor) and "secondary care" (i.e., in hospitals, clinics and similar settings). This distinction is relevant throughout this chapter.

In England, the NHS spent an estimated £18.9 billion on medicines in 2018/19, without taking discounts into account. That represents a 4.1% increase on the prior year and is broadly

consistent with an average 5% annual growth rate since 2010/11. That growth is almost entirely attributable to medicines dispensed in hospital settings (i.e., secondary care), the cost of which has more than doubled since 2010/11. In 2018/19, spending on hospital medicines accounted for 53.7% of NHS's total expenditure on medicines, which is an increase of 11.1% on the previous year.

By contrast, spending on medicines in primary care fell by 2.8% in 2018/19. The gross amount spent has broadly remained the same since 2010/11, despite the fact that the volume of medicines dispensed in primary care has risen by an average of 3% each year. This demonstrates the downward pressure on prices for medicines that are mainly dispensed by community pharmacies to non-hospitalised patients.

Historically, the NHS in England spends approximately three-quarters of its drugs budget on branded products.

Pharmaceutical pricing and reimbursement

Regulatory classification

Classification of medicinal products

The Human Medicines Regulations 2012 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) the Medicines and Healthcare products Regulatory Agency ("MHRA") or the European Commission has allocated the product to a particular category.

In principle, NHS reimbursement is available to all three classes of medicines. However, the NHS increasingly focuses its expenditure on POMs and to that end, 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 shrinking 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. Prescribers in secondary care settings usually only deviate from these policies for clinically justified reasons, such as an individual patient's exceptional circumstances or requirements.

In both primary and secondary care settings, guidelines issued by NICE play an important

role in determining whether the NHS funds a product and, in practice, whether clinicians would prescribe the product to NHS patients (see section, "How is the reimbursement amount set?" below, which discusses NICE guidelines).

Who is/are the payer(s)?

The NHS ultimately funds the vast majority of POMs supplied to patients in the UK. In England only, it recovers a small fraction of its costs through flat-rate prescription charges, payable 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:

- The NHS has responsibility for commissioning primary care in England, though these days there are many Clinical Commissioning Groups ("CCGs") (discussed further below) co-commission primary care services with the NHS. The reimbursement mechanism in primary care is largely centralised under the Community Pharmacy Contractual Framework. Essentially, contractors who dispense products in primary care will receive a fixed reimbursement price for a particular product.
- Commissioning in secondary care is effectively the responsibility of approximately 200 local CCGs.[6] CCGs receive funding from the NHS and it is for them to obtain value for money in terms of the products and services they make available.
- 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), though it works closely with other actors such as Public Health England to fulfil these duties.

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 can focus on the use of products during the epidemic. 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 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).

From April 2019, NICE charges companies up to £126,000 for conducting technology appraisals.

NICE assessment

NICE evaluates whether the NHS should fund products or treatments (which NICE refers to as "technologies") based on clinical and cost-effectiveness assessments. In summer 2019, NICE began the process of reviewing its methodologies, including how it conducts health technology appraisals. NICE intends to implement a new system by summer 2021, with the aim of applying common principles to reviewing drugs, medical devices and diagnostics. 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 in order to receive a positive recommendation.

NICE's Budget Impact Test

Introduced in April 2017, the "Budget Impact Test" is an additional step for NICE assessments. Any product that NICE has assessed to be cost-effective but is likely to cost the NHS more than £20 million in any of the first three years of its use must be subject to further negotiations between the supplier and 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 Voluntary Scheme (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 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 12 pieces of final guidance in more than six 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, 79 new oncology drugs treating 160 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 ("Voluntary Scheme"); or the so-called "Statutory Scheme".

Voluntary Scheme

As the name suggests, the Voluntary Scheme is an opt-in arrangement, agreed between the innovative pharmaceutical industry body, the Association of the British Pharmaceutical Industry ("ABPI") and the Department of Health. In one form or other, the Voluntary Scheme has been running in the UK since 1957. The current scheme came into effect on 1 January 2019 and will run for five years.

The Voluntary Scheme contains complex arrangements for price and profit control. Below are some key features:

- The Voluntary Scheme aims to cap increases in the amount the NHS spends on branded medicines, which companies that have opted into the Scheme ("Members") supply, to 2% growth *per annum*. To stay within this cap, Members must pay the Department of Health a fixed percentage of their net sales of branded medicines supplied to the NHS ("Scheme Payments"), with certain exceptions. Scheme Payments are designed to offset anticipated growth above the agreed 2% limit. 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 5.9% of net sales for 2020 (the figure was 9.6% in 2019 and the original prediction for 2020 was 14.2%).
- Members who are small companies (i.e., essentially, those whose sales of branded products to the NHS total less than £5 million in the previous year) are exempt from

making Scheme Payments. For medium-sized companies (i.e., essentially, those whose sales of branded products to the NHS total between £5 million and £25 million in the previous year), the first £5 million of sales may be exempt from Scheme Payments.

- Importantly, not all branded medicines supplied by Members are subject to Scheme Payments. Medicines containing new active substances sold to the NHS within 36 months of their marketing authorisation are outside the net of Scheme Payments. However, sales of those products will still contribute to calculating expenditure grown across the scheme.
- The Voluntary Scheme also contains pricing controls. A Member may not increase the list price of a product without the prior approval of the Department of Health, which (amongst other things) requires a justification for the increase and an assessment of the Member's profits. In order to avoid stifling innovation, Members have the freedom to set the list price of medicines containing new active substances launched in the UK within 36 months of the grant of a marketing authorisation. However, this still requires a Member to confirm that its intended selling arrangements to the NHS will take cost-effectiveness into account. In other words, very high prices would go hand in hand with significant NHS discounts.

As part of the Voluntary Scheme agreement, 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.

Statutory Scheme

Manufacturers or suppliers of branded medicines to the NHS who do not participate in the Voluntary Scheme are, by default, subject to the so-called "Statutory Scheme" (per sections 262–264 of the NHS Act 2006).

The Government revised the Statutory Scheme significantly in 2018 through the Branded Health Service Medicines (Costs) Regulations 2018 (the "2018 Regulations"). The 2018 Regulations came into force on 1 April 2018 and were subject to further 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 7.4% for 2020 and will be 10.9% for 2021 and subsequent calendar years. The percentages for 2020 onwards are approximately half of those the initial version of the scheme predicted.
- 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 Voluntary Scheme applies, the Statutory Scheme will encompass all biologic medicines supplied to the NHS, including biosimilars.

The revisions to the Statutory Scheme bring it more closely in line with the Voluntary Scheme, though there are some differences. Arguably, pricing arrangements for products

containing new active substances are more straightforward under the Voluntary Scheme than the alternative. Importantly, 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 NHS in England increasingly takes a joined-up approach to procurement and medicines optimisation. For example, the NHS has established several national and regional procurement groups to co-ordinate and support medicines procurement, sharing information and expertise. Similar groups exist to align local formularies and prescribing policies to the most cost-effective options available, which can stimulate companies to offer keener prices to remain locally recommended or on a preferred formulary.

As in most other markets, competition from generic and biosimilar products also affects the price of innovator products on the market. The NHS' policy, for some time, has been to encourage clinicians to prescribe most products by their International Non-proprietary Name ("INN") to encourage generic prescribing and dispensing. Many NHS organisations (such as CCGs or Hospital Trusts) also run programmes to switch patients from innovative to generic or biosimilar products. These factors mean that once generic or biosimilar products enter the market, suppliers of innovative products can rapidly lose market share unless they reduce prices. Note, that in general 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 three years, the NHS has experienced severe shortages in the supply of certain generic medicines. Reportedly, this is the result of Brexit-related uncertainty and a variety of other supply-side issues. These shortages have led to price increases and the NHS has, in some cases, reflected this by offering a higher reimbursement amount in the Drug Tariff, often on a temporary or *ad hoc* basis.

Policy issues that affect pricing and reimbursement

The NHS' medicines policies aim to balance a number of interests, including:

- obtaining value for money for taxpayers;
- ensuring there is equitable access to treatment for NHS patients; and
- stimulating innovation in the life sciences industry by reimbursing new products that demonstrate clinical and cost-effectiveness.

However, demographic change, an increase in spending on prescription medicines, and budgetary pressure, make it increasingly difficult to maintain this balance.

The UK's population is growing as well as becoming older. The Office for National Statistics projects the UK's population to increase from approximately 66.4 million people in 2018 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 and diabetes.

As noted above, the volume and cost of drugs used in and/or reimbursed by the NHS is on a steady upward trajectory. Population and demographic changes are major contributing factors. Another reason is an increase in high-cost innovative medicines 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 Government claws-back from the industry under both schemes has fallen in 2020 from early projections, which suggests the rising cost of branded medicines is now better controlled. 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, at various levels (including, for example, the approach the NHS takes to deliver best-value). We discuss some of the key trends below:

- The NHS is committed to speeding-up access to promising technologies in specific, priority treatment areas. The NHS's Accelerated Access Collaborative ("AAC") identifies game-changing innovations and provides their manufacturers with strategic support to ensure rapid uptake within the NHS. Recently, the AAC identified tumour-agnostic oncology and histopathology-independent drugs and advanced therapy medicinal products ("ATMPs") as a particular area of interest.

- Although a review process is underway, NICE's cost-effectiveness criteria and Budget Impact Test are currently relatively rigid and have remained so for several years. In effect, this means that companies (particularly of high-cost drugs) are increasingly having to negotiate agreements with the NHS (e.g., through Managed Access Agreements or Patient Access Schemes), by which a positive NICE recommendation becomes possible. Usually, that involves significant discounts from the product's list price.
- There is growing evidence of the NHS exercising its strengthened mandate to negotiate bespoke, confidential pricing and access deals with pharmaceutical companies either alongside or outside the parameters of a NICE appraisal. For example, in October 2019, the NHS concluded long-running discussions by agreeing a deal with Vertex Pharmaceuticals to enable NHS funding for three cystic fibrosis products licensed in the UK.
- Co-ordinated procurement has emerged as a key tool for the NHS to achieve best-value in purchasing medicines for hospital or specialist settings. Depending on the therapeutic area, the NHS co-ordinates tendering centrally, often resulting in Framework Agreements awarded at the regional (or even supra-regional) level. 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. The co-ordinated approach has led to medicines procurement litigation and this is likely to be a growing trend. 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. For example, NHS-organised Regional Medicines Optimisation Committees also provide targeted guidance to CCGs and clinicians about savings associated with switching to biosimilars. The overall aim is to switch 90% of new patients and 80% of existing patients to the cheapest available biological product within three to 12 months of its UK launch. Similarly, in some therapeutic areas, the NHS publishes internal "reference prices" that limit the amount that an NHS hospital receives from central NHS funding if the hospital purchases products that exceed the relevant reference price.
- Linked to this is the growing tendency for the NHS to support using unlicensed products (or licensed products off-label) for reasons of cost. Historically, the NHS respected the principle of using licensed products within their label wherever possible, which is consistent with the MHRA's position and professional guidelines for doctors. Similarly, NICE's position is that it cannot positively recommend unlicensed products or off-label use of licensed medicines in an assessment (though it sometimes takes this into account for cost-comparison purposes). Despite this, the NHS has in certain high-profile cases advocated using lower-cost, unlicensed or off-label products. This is highly controversial, having been the subject of High Court and recent Court of Appeal litigation in respect of reformulated bevacixumab for intra-ocular use.
- NHS organisations continue to seek increasing amounts of information from internal and external sources about product pricing (e.g., discounts). The Health Service Medical Supplies (Costs) Act 2017 gives the Secretary of State wide-ranging powers to demand a variety of information from all stages in the medicines supply chain. Anecdotally, the NHS expects more transparency from companies to help it achieve better value for money, particularly in areas where there has traditionally been price opacity (e.g., generics). Similarly, there is a growing expectation that NHS bodies that enter into

commercial agreements with suppliers will share this information within the NHS with a view to deriving the best value nationally.

- The industry continues to face scrutiny from the UK Competition and Markets Authority ("CMA"). In particular, the CMA has investigated alleged anti-competitive agreements and conduct and suspected excessive and unfair pricing. Largely, this concerns allegations that manufacturers of generic products have inappropriately increased prices of products for which there is no meaningful competition.
- Although the UK has formally exited the EU, there continues to be uncertainty as to EU/UK relations following the end of the so-called "Withdrawal Period" on 31 December 2020. These uncertainties have had an indirect effect on availability of medicines. The UK has implemented measures to outlaw exporting or stock-piling certain medicines (largely generics and products where there is significant parallel trade), designed to alleviate shortages and price-volatility. In the longer term, and subject to ongoing EU/UK negotiations, this could have knock-on effects in the mainstream branded products market (particularly combined with Serious Shortage Protocol rules).

  The long-term impact of COVID-19 on the NHS and the medicines landscape is unknown. The Government is committed to providing significant additional resources to the NHS and supporting life-sciences companies. However, this is principally to manage the current health crisis and may not be sustainable in the longer term, particularly as the UK enters into a deep forecasted recession. One could not rule out drastic changes in the medicines pricing and reimbursement environment in future.

Successful market entry

Formulating a successful strategy for market entry will depend on the type of product in question and its place in the NHS' complex architecture. The following are some general points to consider:

- **NICE appraisal**. A company should investigate whether its product will be subject to a NICE appraisal and if so, whether it could meet NICE's cost-effectiveness criteria. The company could also explore qualifying for HST status or the Cancer Drugs Fund. For high-cost products, the company should consider the possibility of offering a Patient Access Scheme.
- **Specialised commissioning categories**. Falling within the scope of Specialised Services, Highly Specialised Services, the Cancer Drugs Fund or benefitting from Accelerated Access Collaborative Support would increase the likelihood of a high-cost product receiving NHS funding.
- **Appreciating the NHS' approach to commissioning and procurement**. It is critically important to appreciate the NHS' multi-layered approach to medicines pricing and purchasing. In particular, that achieving a list price and a NICE recommendation are not always determinative of the price that the NHS will pay for a product. The NHS can seek to achieve value through a variety of mechanisms, including tendering and direct negotiations with the industry. Companies should therefore consider their pricing and discount strategy in a holistic way. This is particularly important if a product's main use is in secondary care.
- **Understanding NHS prescribing policies**. In the UK, market penetration is often a greater concern for companies than market entry. The NHS' prescribing policies (both local and national) have a significant impact on the uptake of a new product. Understanding these is therefore important.

Endnotes

1. Regulation 5 of the Human Medicines Regulations 2012.
2. See also Regulation 220 of the Human Medicines Regulations 2012.
3. "Conditions for which over the counter items should not routinely be prescribed in primary care: Guidance for CCGs" NHS, 29 March 2018.
4. Schedule 1 to the NHS (General Medical Services Contracts) (Prescription of Drugs, etc.) Regulations 2004.
5. Schedule 2 to the NHS (General Medical Services Contracts) (Prescription of Drugs, etc.) Regulations 2004.
6. Pursuant to the Health and Social Care Act 2012.
7. Regulations 7(2)-(3) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 (SI 2013/259) and as set out in the NHS Constitution.

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Abstract

The 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 the net price reflecting the actual amount of money received.

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 coverage is more prevalent than public health insurance coverage, covering 67.3% of the population.[1] Most private insurance is offered through employers under favorable tax policies, 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 health insurance coverage at all. In 2018, the latest year for which coverage data is available, the U.S. population of 324 million had coverage as follows:

- 217.8 million received coverage under private plans, including 178.4 million through employment-based plans;
- 57.7 million received coverage under Medicare;
- 57.8 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
- 27.5 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]

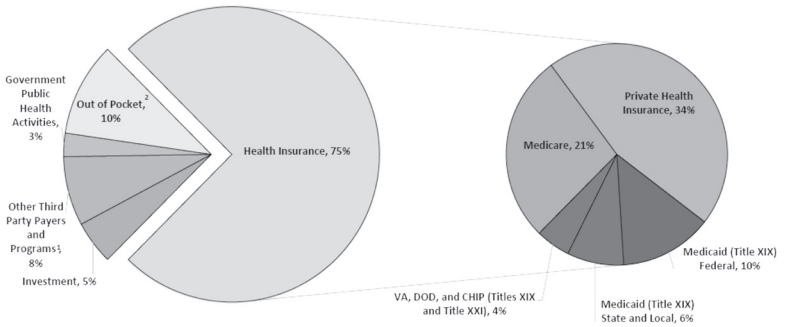
Although many developed nations choose to provide health care under a universal or single payer system, the U.S. has elected to use a multiple payer model combined with government- and privately-run safety net programs and mandatory access to emergency care for all residents.[4] In addition to funding Medicaid and other programs aimed at vulnerable populations, the federal government requires drug manufacturers to provide outpatient drugs to 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] The health care sector accounts for 24% of all government spending and is one of the largest categories of consumer spending overall, accounting for 8.1% of consumer expenditures.[7]

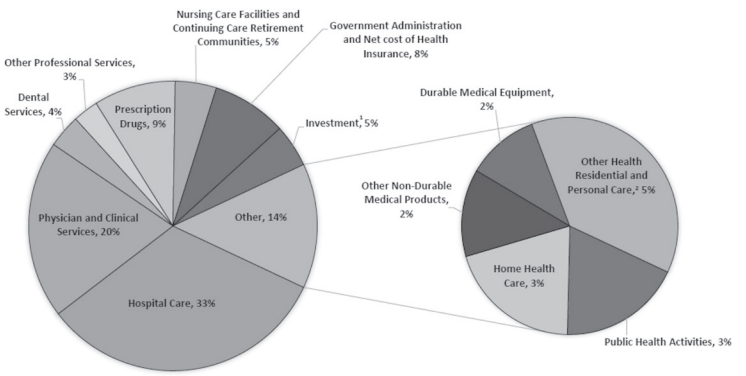
In 2018 alone, the U.S. spent approximately $3.6 trillion on health care.[8] Figures 1 and 2 show how health care spending breaks down across payers and services, as estimated by the Centers for Medicare & Medicaid Services ("CMS").

Figure 1: The nation's health dollar – where it came from[9]



[1] Includes worksite health care, other private revenues, Indian Health Service, workers' 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.

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.

As shown in Figure 2, CMS estimates that prescription drugs account for approximately 9% of health care spending. Some sources estimate that the percentage of spending on prescription drugs is actually higher – 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.[11]

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 2019, the federal government recovered over $3 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 – $2.6 billion related to health care cases, including those involving drug and medical device manufacturers, managed care providers, hospitals, pharmacies, hospice organizations, laboratories, and physicians.[12] 2019 was the tenth consecutive year in which civil health care fraud recoveries exceeded $2 billion.[13] 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.[14] 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

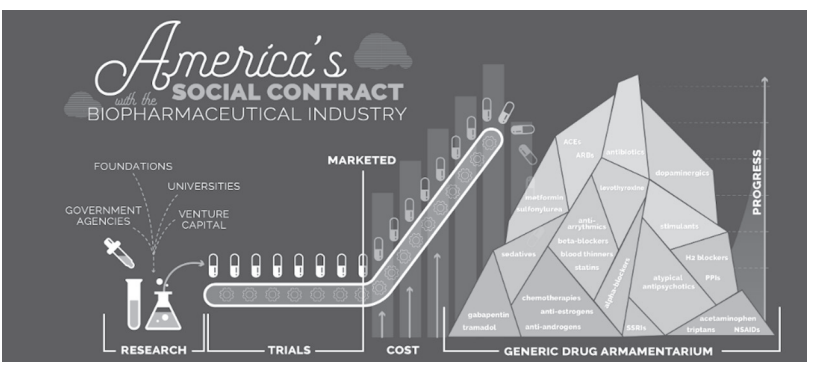
The high list price of prescription drugs in the U.S. is frequently discussed in the press and public discourse. Yet, the headlines often fail to capture both the types of drugs driving health care expenditures and the intricacies of the drug supply chain that create a significantly lower net price for a given drug product.

Branded versus generic drugs

Approximately nine out of 10 prescriptions filled are for inexpensive generic drugs.[15] 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.[16] 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.

Figure 3: America's social contract with the Biopharmaceutical Industry[17]



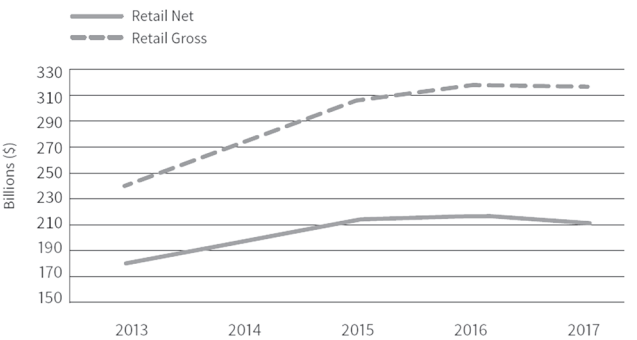
A small subset of branded drugs known as "specialty drugs" are a principal driver of prescription drug prices and expenditures. Medicare defines specialty drugs as pharmaceuticals costing $670 or more per month,[18] and other payers look at factors beyond price, designating products as specialty drugs if they (a) are novel therapies, (b) require social handling, monitoring, or administration, or (c) are used to treat rare conditions.[19] Specialty drugs account for approximately 2% of prescriptions but almost half of prescription drug spending.[20] Further, specialty share of net prescription drug spending increased from 26.2% in 2009 to 49.5% in 2018.[21] 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.[22] 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 of 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 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.[23]

List price versus net price

Figure 4, reproduced from the Trump Administration's "Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs", 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.

Figure 4: List price *vs.* net price[24]



Source: Medicine Use and Spending in the U.S; A Review of 2017 and Outlook to 2022, April 19, 2018

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.[25] The prevalence of additional fees, such as administrative and service fees required by PBMs, may also impact pricing considerations.

Global comparisons

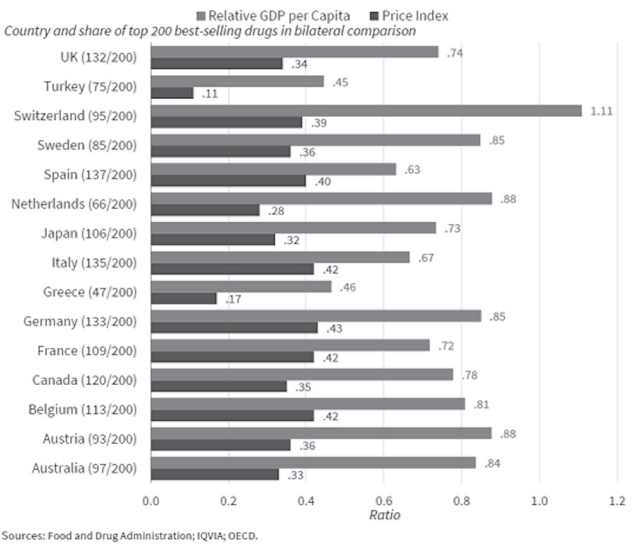
Health care spending in the U.S. far outpaces international averages. In 2018, national health care spending constituted 16.9% of GDP (in comparison to the Organisation for Economic Co-operation and Development ("OECD") average of 8.8%), totaling about $10,586 *per capita* (in comparison to the OECD average of $5,287).[26]

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".[27]

Figure 5: Foreign-U.S. price index for 200 top-selling prescriptions and relative GDP *per Capita* for selected nations, 2017[28]



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.[29] Currently, there are over 20,000 prescription drugs approved for marketing in the U.S., as well as 400 FDA-licensed biologics products.[30]

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").[31] 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.[32] FDA may also approve generic versions of an approved drug product as well as biological products that are biosimilar to a reference product.[33] 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".[34] In 2019, FDA approved 70 new drugs and biological products, 107 first-time generic drugs, and 10 biosimilar products.[35]

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 the 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.[36] 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.[37] 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).[38] 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.[39]

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.[40] In addition to priority review, other programs may be available to help expedite the development and review of drugs intended to address unmet medical need in the treatment of serious or life-threatening diseases or conditions, including: breakthrough therapy designation; fast track designation; and accelerated approval.[41]

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.[42] During that time, FDA cannot accept for review any NDA or ANDA or a drug containing the same active moiety.[43] 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.[44] Other incentives are also available, such as priority review vouchers for drugs treating neglected tropical diseases, rare pediatric diseases, and medical countermeasures.[45]

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,[46] 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.[47]

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.[48]

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.[49]

Average Wholesale Price ("AWP"). The list price of a drug from a wholesaler to a pharmacy.[50]

Best Price. The lowest available price offered by the manufacturer to any wholesaler, retailer, or provider, excluding certain government programs.[51]

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.[52]

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.[53] It has since been expanded to cover individuals with disabilities or end-stage renal disease. The Medicare program, along with Medicaid and certain other federal health care programs, is administered by CMS.

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".[54]

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.[55] 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.[56] MACs make coverage determination on a case-by-case basis or as local coverage determinations ("LCDs") or pursuant to national coverage determinations ("NCDs").[57]
- 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.[58] 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.[59] All individuals entitled to Part A may voluntarily enroll and obtain Part B benefits for a monthly premium.[60] 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.[61] Parts A and B, together, constitute "original Medicare".[62]
- 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.[63] 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.[64] 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.[65] All MA plans, except PFFS plans, must offer options that include coverage for prescription drugs ("MA-PDs").[66] MA-PDs generally must comply with Part D requirements, 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.[67] 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.[68] Part D plans must be reviewed and approved by CMS.[69]

ii. Coverage and reimbursement methodology

As a preliminary matter, drug products must be approved by the FDA in order to be reimbursed by Medicare. Parts A and B, however, generally 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".[70] 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.[71]

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.[72] 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.[73]

Under Part D, the private plan sponsors administering the PDP and MA-PD benefits determine which prescription drug products are covered. The plan sponsors develop 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.[74] 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.[75] 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,[76] and must cover "substantially all" immunosuppressant (for prophylaxis of organ transplant rejection), antidepressants, antipsychotics, anticonvulsants, antiretrovirals, and antineoplastics.[77]

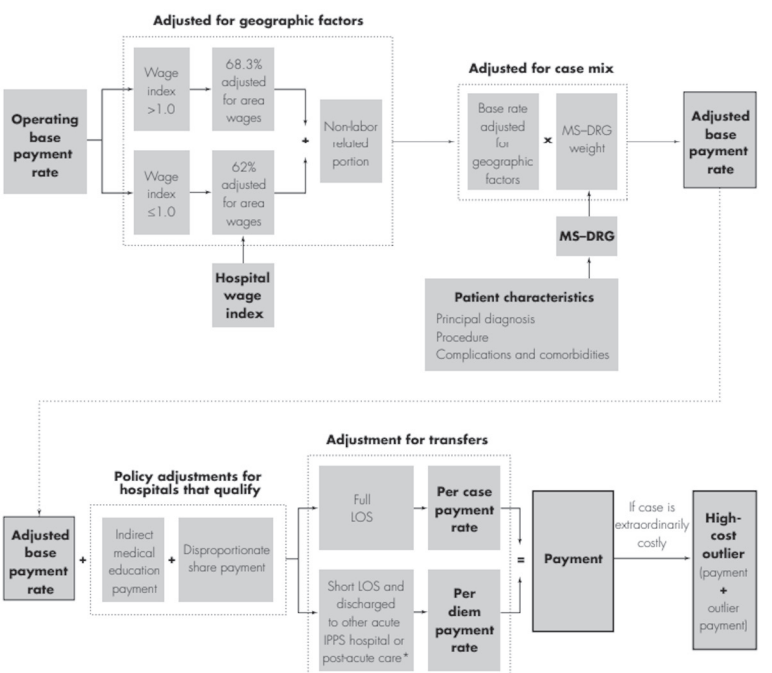
Part A reimbursement

Reimbursement for most acute care hospital services under Part A is determined using the inpatient prospective payment system ("IPPS") based on diagnosis-related groups. The IPPS was established by Congress through the Social Security Amendments of 1983.[78] 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.[79]

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.[80] Second, a weighting factor is associated with the diagnosis related group ("DRG") to which the beneficiary is assigned, to account for the resources required to treat the beneficiary.[81] 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.[82] 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.[83]

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.[84]

Figure 6: Acute inpatient prospective payment system for Fiscal Year 2020[85]



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 received 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.[86] 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.[87]

The current reimbursement methodology for most Part B drugs was established by the MMA.[88] Under this methodology, reimbursement payments for Part B drugs are generally calculated based on the ASP, which the manufacturer reports to CMS.[89] 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.[90]

Manufacturers report ASP on a quarterly basis. Certain manufacturers, such as those with Medicaid rebate agreements, are obligated to report ASP data,[91] while other manufacturers voluntarily report ASP data or WAC data.[92] Reimbursement rates are updated quarterly; however, the rates are calculated using the reported ASP from two quarters ago.[93]

Reimbursement for Part B drugs administered in the physician office setting is statutorily set at 106% of ASP, referred to as "ASP+6".[94] Beneficiaries are generally responsible for 20% of the cost of drug products under Part B.[95] 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.[96]

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").[97] 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.[98]

Part C reimbursement

Medicare Advantage 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

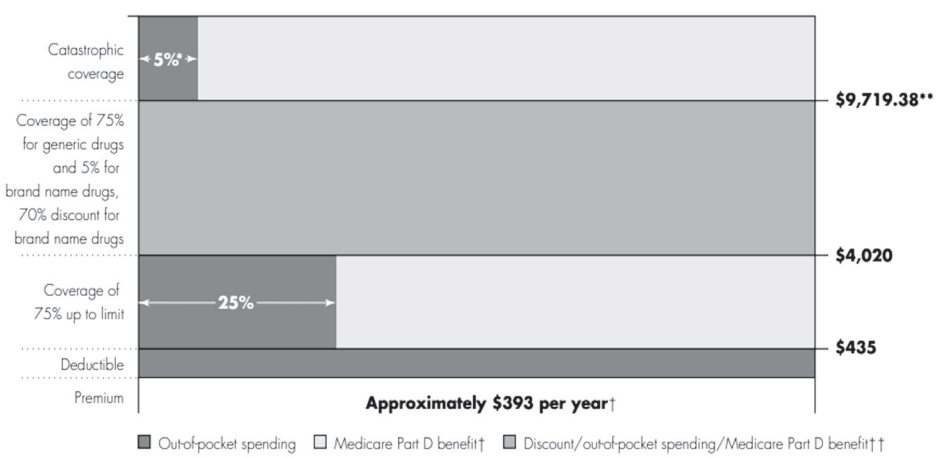
amount, plus a rebate based on the difference between the bid and the benchmark that is passed on to the beneficiaries. However, if the bid is equal to or greater than the benchmark, the benchmark will be the reimbursement payment and beneficiaries are required to pay an additional premium based on the difference between the bid and the benchmark.[99]

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.[100]

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.[101] In 2020, the standard benefit included a $435 deductible and 25% coinsurance for the cost of drug products between $435 and $4,020. Beneficiaries then enter the coverage gap, referred to as the "doughnut hole", until they reach the catastrophic limit and out-of-pocket threshold of $6,350. After reaching the catastrophic limit, beneficiaries pay the higher of either a 5% coinsurance or a set amount per prescription.[102] 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.[103] As of 2020, the doughnut hole is closed, meaning beneficiaries are responsible for only the 25% coinsurance until they reach the catastrophic limit.[104]

Figure 7: Standard drug benefit in 2020[105]



Note: Benefit structure applicable to an enrollee who has no supplementary drug coverage.

Cost sharing above the out-of-pocket ("OOP") threshold is the greater of either 5% coinsurance or a copay of $3.60 for generic drugs, or $8.95 for brand name drugs.

Equivalent to $6.350 in OOP spending: $435 (deductible) + $896.25 (25% cost sharing for generic drugs, 25% cost sharing for brand name drugs, and 70% manufacturer discount for brand name drugs in the "coverage gap"). The amount of total covered drug spending at which a beneficiary meets the annual OOP threshold depends on the mix of brand name and generic drugs that the individual fills during the coverage gap. The estimated amount of total drug expenses at the annual OOP threshold for 2020 ($9,719.38) is for an individual not receiving Part D's low-income subsidy ("LIS") who has no other sources of supplemental coverage.

There is a base beneficiary premium of about $393 per year, which is 25.5% of expected Medicare Part D benefits

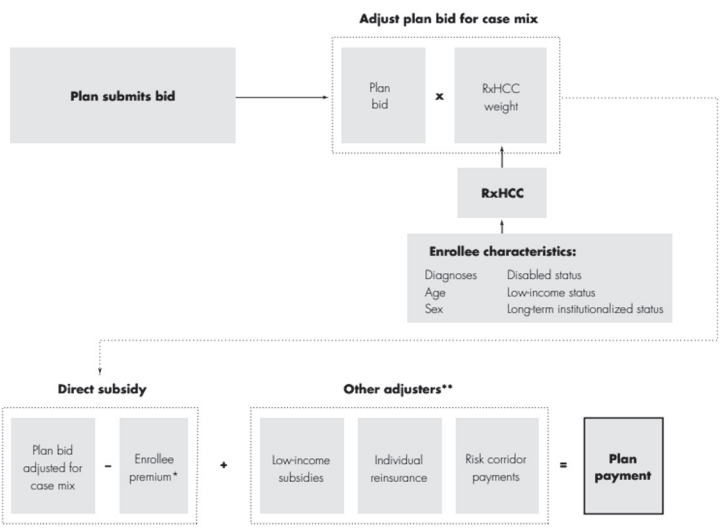
per person, but the actual premiums that beneficiaries pay vary by plan. Federal subsidies pay for the remainder of covered Part D benefits.

In 2020, cost sharing for drugs filled during the coverage gap will be 25% for generic drugs (the remaining 75% will be picked up by the Part D benefit) and about 25% for brand name drugs. The actual cost sharing amount for brand name drugs will depend on the dispensing fee charged by a plan since the 5% covered by the Part D benefit applies to both the ingredient and the dispensing fee, while the 70% manufacturer discount applies only to the ingredient cost.

Part D reimbursement payments made to both 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. CMS also pays additional subsidies for low-income beneficiaries and reinsurance subsidies to cover the costs of beneficiaries with high prescription drug expenses.[106]

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.[107] 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.[108]

Figure 8: Part D payment system[109]



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-oncome 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 indivudals 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.[110] 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.[111]

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.[112]

i. Benefit designs

Medicaid coverage includes a range of benefit options, including primary care, preventative care, and long-term care services and supports. Medicaid beneficiaries may receive benefits through a fee-for-service system or a managed care system, depending on which systems are offered by the state. Through the fee-for-service 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.[113]

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.[114] 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.[115] Further, some state Medicaid programs also provide coverage for OTC drug products.[116]

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.[117]

ii. Coverage and reimbursement methodology

Pursuant to the Medicaid Drug Rebate Program ("MDRP"),[118] 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.[119] 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.[120]

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.[121]

Fee-for-service 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.[122] 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").[123] 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.[124]

Medicaid managed care plans also reimburse pharmacies for drug products dispensed to beneficiaries. Like payments made by fee-for-service 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.[125] 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.[126]

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 fee-for-service 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 fee-for-service Medicaid programs must comply with federal and state requirements for drug reimbursement.[127] Concerns regarding the lack of transparency for PBMs have led some states to consider disclosure requirements for PBMs.[128]

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.[129] 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.[130] 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.[131] 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.[132]

Pursuant to the MDRP, as discussed above, a drug product is covered by Medicaid only if the manufacturer enters into a Medicaid rebate agreement.[133] 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.[134] 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[135]

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 providers that primarily serve low-income and uninsured individuals (frequently referred to as "safety net providers").[136] 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.[137] 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) to cover entities (defined by statute 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").[138]

The ceiling price is calculated quarterly using MDRP figures (AMP minus the Unit Rebate Amount) 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. This exclusion is not limited to sales under the 340B Program but applies to *all* sales to a covered entity, including commercial sales. Consequently, one of the critiques of the program is that a gap exists between the prices hospitals pay to acquire 340B drugs and the price at which payers reimburse those drugs.[139]

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 using only one contract pharmacy, leading to growth in 340B dispensing.[140] In addition, hospital acquisition of oncology practices has driven increased 340B profitability for hospitals.[141] 340B spending has increased significantly in recent years, rising from $5.3 billion in 2010 to $24.3 billion in 2018.[142]

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".[143] In litigation challenging this change in reimbursement, the U.S. District Court ruled that HHS exceeded its statutory authority by reducing the reimbursement rate in this manner,[144] but the case is currently on appeal before the U.S. Court of Appeals for the District of Columbia.

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.[145] 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.[146] 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.[147] 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").[148] Additionally, individual and group plans are also available for purchase outside of the Health Insurance Marketplaces.[149]

Private plans typically include medical and pharmacy benefits. Drugs used with 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 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.[150] 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 insurance plans, in exchange for preferred formulary placement. Discounts generally come in the form of rebates. PBMs retain these rebates and pass

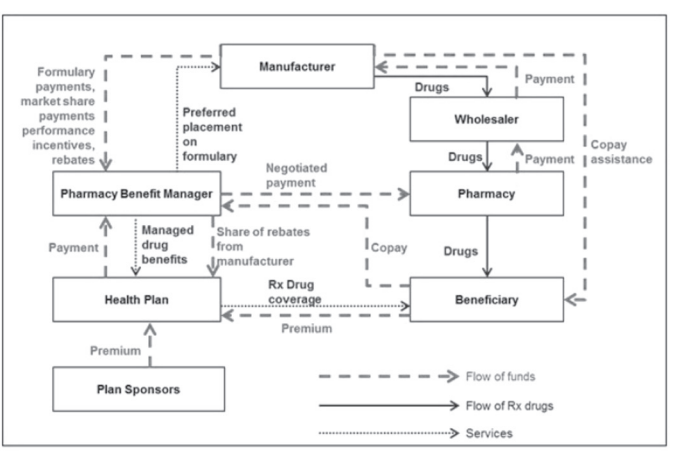
along some portion of the manufacturer price concession under a blended effective rate for an employer's or plan's branded drug spend. Rebate agreements between PBMs and manufacturers often contain price protection provisions that require the manufacturer to pay additional concessions to the payer or 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.

- **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.

The rebates paid to PBMs have come under recent criticism, including from the Trump administration, which views rebates as a key driver of increased drug costs.[151] In 2019, the administration proposed a rule that would have eliminated traditional retrospective rebates from government drug plans to PBMs in favor of point of sale discounts at the pharmacy counter that provided patients with a portion of the manufacturer's price concessions.[152] However, this rule has since been withdrawn.

Figure 10 illustrates the flow of funds, prescription drugs, and services for non-specialty drugs covered under private insurance and purchased in a retail setting.

Figure 10: The Flow of Funds in the Pharmaceutical Distribution System[153]



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 – currently control the majority of the market, together totaling an estimated

71% of Medicaid and Medicare Part D beneficiaries and 86% of the private market.[154] 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 the PBMs generally consider vertical integration to be to the benefit of patients,[155] 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).[156] 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,[157] 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 copays (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 time of prescribing, in order to better align the physician's decisions with the lowest cost option for the patient, employer, or health system.[158]
- **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.[159] At least one state, Oklahoma, prohibits pharmacists from substituting pharmaceutical products without the consent of both the prescriber and the patient.[160]
- **Cost sharing/copay 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 copay assistance. Under accumulator programs, the plan does not allow the value of manufacturer copay assistance to count toward the beneficiary's deductible or out-of-pocket maximum, so that once the copay 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 copay obligation with available copay assistance from manufacturers (i.e., by dividing the annual maximum benefit to set monthly copay amounts for beneficiaries). Manufacturer assistance applies to the beneficiary's copay obligation but not toward the beneficiary's deductible or out-of-pocket maximum. 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.[161] Certain states have recently proposed legislation to limit these benefit design programs. 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 copay assistance from manufacturers toward a patient's cost-sharing obligations.[162] In some instances, the accumulator prohibition only applies if there is no generic version of the prescription medication available or the patient has received permission to take the name brand drug through prior authorization, step therapy, or an issuer's appeals process.[163] This is a rapidly evolving area with significant variation at the PBM, plan, and manufacturer level.
- **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 Outcomes Based Contracts ("OBCs") and Performance Based Risk Sharing Agreements ("PBRSAs").[164] To date, Medicaid's "best price" requirement represents a key challenge to adopting such value-based arrangements, 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. Manufacturers and payers must also comply with the federal Anti-Kickback Statute ("AKS"), which 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.[165] Statutory and regulatory safe harbors protect certain arrangements from AKS liability, including qualifying discount and warranty arrangements,[166] but it is unclear how enforcement agencies would apply these safe harbors to value-based contracting arrangements. VBC arrangements 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 labeling. FDA guidance expressly permitting the communication of health care

economic information ("HCEI") consistent with approved labeling lowers the risk related to such communications, and FDA has stated explicitly that it does not regulate contract terms for value-based arrangements.[167]

- **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 nongovernmental 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.[168] ICER's assessments evaluate two concepts: long-term value for money; and short-term affordability.[169] 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.[170] 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.[171] ICER has 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.[172]

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 copay assistance (i.e. copay 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 copays and deductibles.[173] Although free drug programs for financially needy patients have historically not raised extensive concerns under anti-kickback laws, the Office of Inspector General ("OIG"), which is tasked with identifying and combating waste, fraud, and abuse within HHS, has articulated concerns with PAPs related to Medicare Part D.[174] For example, PAPs and copay coupons may increase costs to the federal government under Medicare Part D because cost-sharing subsidies for Part D-covered drugs count toward patients' true out-of-pocket expenses ("TrOOP") and will therefore 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.[175] 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.[176] The OIG has also scrutinized charitable organizations that are not truly independent from manufacturer donors.[177] 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.[178]

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[179] – 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.[180] 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.[181] State Medicaid programs mandate coverage of off-label uses where the drug is listed in CMS-recognized compendia.[182] 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.[183] 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.[184] 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).[185]

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;[186] intermediate-size patient population expanded access INDs;[187] and treatment INDs for widespread use.[188] 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".[189] 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,[190] the federal Right to Try Act was signed into law in 2018 to permit access to investigational drugs.[191] 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.[192] Manufacturers have discretion over whether to make their products available to patients who qualify for access under the law.

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.

According to one study, the cost to develop a new prescription drug that gains marketing approval was estimated to be $2.6 billion as of 2013.[193] 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 research and development ("R&D"), the cost of total development increases to nearly $2.9 billion.[194] 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 health technology assessment information, and testing on comparator drugs to accommodate payer demands for comparative effectiveness data.[195]

The cost of this development appears to fall disproportionately on the U.S., where drug prices far outpace prices in other countries. For example, a recent HHS report found that drug acquisition costs in the U.S. exceed those in Europe, Canada, and Japan.[196] Among the 27 drug products included in HHS's analysis, acquisition costs in the U.S. for Medicare Part B drugs were 1.8 times higher than in comparator countries.[197] Other analyses indicate that this price disparity may be even higher. For example, a study conducted by the Johns Hopkins Bloomberg School of Public Health found that prices for 79 brand-name prescription drugs averaged 3.2 to 4.1 times higher in the U.S. compared with other countries.[198]

The CEA recently 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".[199] 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.[200] 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".[201] By contrast, "[r]educing foreign price controls would increase profits and innovation, thereby leading to greater competition and lower prices for U.S. patients".[202]

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. (see discussion below), to exercising trade policy tools to combat drug pricing practices in foreign markets.[203] Additionally, states are actively considering proposals that would address drug pricing practices by a variety of mechanisms.

Transparency in setting drug prices

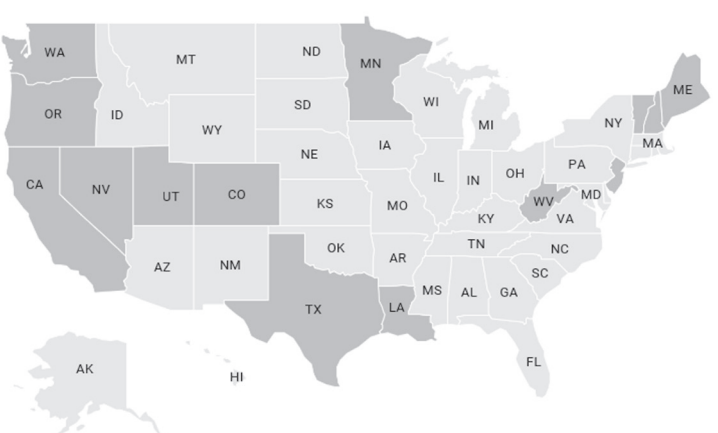
A number of states have enacted laws requiring drug price reporting by manufacturers, payers, PBMs, and other entities. These laws are designed to incentivize manufacturers to lower drug prices by requiring them to report information about launch prices and price increases, as well as their justification for how drug prices are set.

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,[204] whereas Oregon requires reporting for price increases exceeding 10% of WAC.[205] Both 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.[206] Oregon requires manufacturers to report this information to a state government agency,[207] whereas California also requires manufacturers to provide advance notice to certain purchasers.[208] Oregon also requires the submission of non-public information.[209] States that have collected such information have also begun publishing reports of the drug pricing information received from manufacturers, and relevant state agencies often send follow-up requests for information if initial submissions are deemed vague or incomplete. Failure to comply with state disclosure requirements can lead to significant penalties. For example, in late 2019 and early 2020, California fined more than a dozen manufacturers a total of $17.5 million for failing to report information required under the state drug pricing transparency law.[210]

States also 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 (e.g., Connecticut).[211] Manufacturers of the drugs identified by the board are required to report certain information about the drugs' costs and pricing. Reporting requirements in some states apply only to certain types of drugs. For example, Nevada's drug price transparency law initially applied only to certain drug products essential for diabetes treatment.[212] In 2019, Nevada expanded the law to apply to drugs essential for asthma treatment as well.[213]

Although state laws requiring drug price reporting are proliferating, a number of these laws have been subject to legal challenges or struck down by the courts.[214]

Figure 11: State drug pricing transparency laws[215]



Emerging trends

International Pricing Index ("IPI") model for Medicare Part B

Given that Medicare Part B covers many of the highest cost drug products, on October 25, 2018, the Trump administration released an Advance Notice of Proposed Rulemaking ("ANPRM") on a proposal to tie Medicare Part B reimbursement rates to an international pricing index ("IPI").[216] Under this model, the following changes would apply for qualifying drug products and participants in Medicare Part B:

- CMS would contract with private-sector entities to serve as vendors that would negotiate drug acquisition prices with manufacturers. These vendors would then supply health care providers with the drugs to provide to patients and submit claims to Medicare for reimbursement.
- CMS would reimburse vendors based on a "Target Price", which would be calculated based on the drug's average price in fourteen "economically-similar" countries: Austria; Belgium; Canada; Czech Republic; Denmark; Finland; France; Germany; Greece; Ireland; Italy; Japan; the Netherlands; and the United Kingdom. HHS has stated that the Target Price would equal 126% of the average international price.[217] If the drug's ASP is lower than the Target Price, then reimbursement would be set at ASP.
- CMS would pay health care providers a flat fee based on the historical 6% add-on payment the providers typically would have received under the "buy-and-bill" system. Providers would also continue to receive an administrative fee.

The IPI Model would initially focus on Part B single-source drugs, biologicals, and biosimilars, as well as drugs that are technically multi-source but have only a single manufacturer. The IPI Model proposes to include 50% of all Medicare Part B spend based on physician practices and hospital outpatient departments ("HOPDs") in select geographic regions to participate in the IPI Model. The remaining practices and HOPDs would continue to operate under the existing "buy-and-bill" system.

Although the Trump administration originally proposed to follow this ANPRM with a proposed rule in 2019 with implementation planned for 2020, the proposed rule has not yet been issued. It is unclear when the proposed rule might be released or whether the proposed rule will meaningfully differ from the ANPRM (e.g., by expanding to Part D drugs). Critics argue the IPI model would inappropriately tie reimbursement to faulty health technology assessments conducted in other jurisdictions and adversely impact pharmaceutical innovation in the U.S. Legal challenges to the rule are anticipated.

The Administration's proposal follows prior efforts to overhaul the reimbursement structure under Medicare Part B. In 2006, as required by the 2003 Medicare Modernization Act, CMS launched the Competitive Acquisition Program ("CAP") as an alternative to the buy-and-bill system. Under CAP, providers could acquire certain Part B drugs through third-party vendors.[218] CAP was suspended in 2008 after facing significant implementation challenges. Additionally, in March 2016, CMS proposed the "Part B Drug Payment Model", which would have changed the 6% add-on to 2.5% plus a flat fee, with phased-in value-based purchasing payment structures.[219] CMS withdrew this proposal due to "complexity of the issues".[220]

Other proposals related to drug pricing

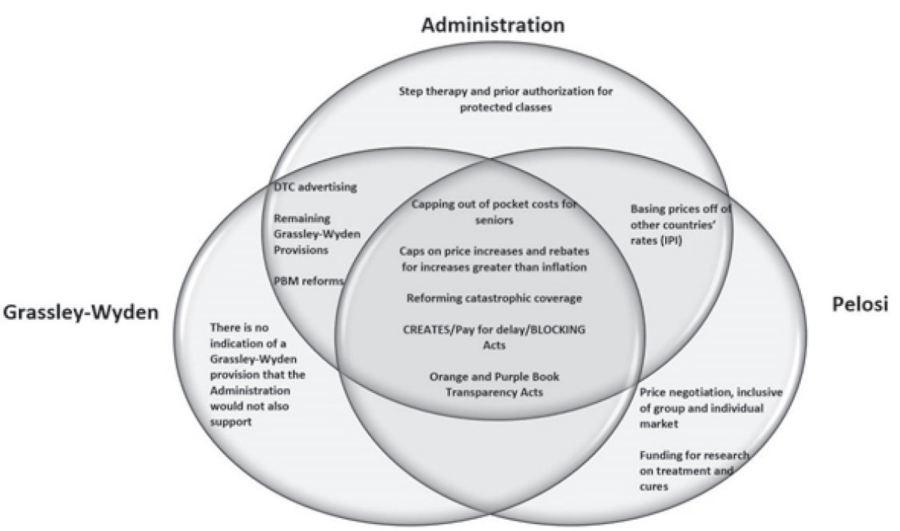
Several legislative proposals also contemplate significant reform to Medicare and Medicaid reimbursement based on international reference pricing or other mechanisms. For example, the Prescription Drug Pricing Reduction Act ("PDPRA") of 2019 (also known as the Grassley-Wyden bill) is a bipartisan bill in the U.S. Senate that proposes to: (a) penalize

manufacturers for price increases above inflation on Medicare Part B and Part D drugs by requiring manufacturers to pay additional rebates to Medicare if they increase their relevant prices (Average Sales Price in Part B, list price in Part D) more rapidly than the inflation rate; (b) cap patients' out-of-pocket costs in Part D (starting at $3,100 in 2022) and redesign the responsibilities within the benefit structure to incentivize plans to negotiate prices; (c) adjust incentives under Part B by reducing payments for new single-source drugs from 106% to 103% of WAC, among other changes; (d) exclude authorized generics from the calculation of Average Manufacturer Price in Medicaid; (e) improve information disclosure, including with respect to ASP reporting and drug pricing/rebates; and (f) create easier process for state Medicaid programs to engage in risk-sharing value-based agreements with manufacturers. The CBO estimates beneficiaries will save $27 billion in OOP over a 10-year period from Part D redesign and inflation-rebate policies (approximately $20 billion and $7 billion, respectively).[221]

The Lower Drug Costs Now Act of 2019 (also known as the Pelosi bill) is a partisan bill with 106 Democratic co-sponsors in the U.S. House of Representatives. In addition to including an out-of-pocket cap for Medicare Part D drugs and limiting price increases to the inflation rate like the Grassley-Wyden bill above, the bill would: (a) allow the HHS secretary to directly negotiate prices on the 250 drugs posing the greatest total cost to Medicare and the U.S. health system that do not have at least two competitors (includes some insulins, cancer treatments and specialty drugs); (b) set the maximum price for the negotiated prices at 1.2 times the average price of the drug in six foreign countries (Australia, Canada, France, Germany, Japan, and the United Kingdom); and (c) steeply fine drug companies if they don't participate in the negotiation process or abide by the agreed-on price.[222]

In addition to supporting the IPI Model, the Trump Administration has advanced several proposals both consistent with and inconsistent with potential legislation. Figure 12 illustrates the commonalities and differences among these proposals.

Figure 12: Comparing legislative and executive proposals[223]



Democratic frontrunner Joe Biden's platform largely aligns with the House bill.[224] Thus, regardless of who wins the 2020 election, drug pricing issues are likely to remain at the forefront of national politics. The COVID-19 pandemic has also brought forth proposals for pricing control and march-in rights with respect to COVID-19 treatments.[225]

Status and future of the Affordable Care Act

In 2010, the U.S. Congress enacted the ACA,[226] which was the most significant regulatory overhaul and expansion of coverage since the creation of Medicare and Medicaid in 1965. The ACA implemented numerous reforms aimed at making affordable health insurance available to more people and decreasing the rate of uninsured Americans. For example, the ACA:

- required most individuals to purchase insurance (the so-called "Individual Mandate");
- expanded Medicaid eligibility to individuals with incomes up to 138% of the FPL for individuals under age 65;
- prevented insurers from denying coverage to individuals with pre-existing conditions;
- created health insurance exchanges through which individuals could buy insurance and provided premium and cost-sharing subsidies to households with incomes between 100% and 400% of the FPL;
- required employers of a certain size to offer health insurance to their employees; and
- mandated that all individual and small group plans cover certain "essential health benefits", including prescription drugs.[227]

Since the ACA was enacted in 2010, an additional 20 million Americans have gained health insurance.[228] However, the Act remains highly controversial. Republican legislators have worked to "repeal and replace" the ACA, most notably with the American Healthcare Act ("AHCA") in 2017, which failed in the Senate and thus was not enacted.[229] Since taking office, the Trump administration also has introduced regulations relaxing the essential health benefit requirements[230] and issued Executive Orders delaying or attempting to forestall the implementation of other ACA provisions.[231] The Tax Cuts and Jobs Act of 2017 effectively eliminated the individual mandate by reducing the tax penalty that the ACA imposed on individuals who refused to purchase health insurance to zero.[232]

The ACA also has faced constitutional challenges, including two petitions currently pending before the Supreme Court.[233] In 2012, the U.S. Supreme Court upheld the constitutionality of the individual mandate, holding that the penalty imposed on individuals who do not buy health insurance is a tax and thereby permissible under Congress's power to "lay and collect taxes".[234] Following the passage of the Tax Cuts and Jobs Act of 2017, a group of states and individuals challenged the mandate on the grounds that, because the tax penalty is now zero, it is not a tax and therefore the mandate is not constitutional.[235] These plaintiffs also argue that, because the mandate is such an integral part of the ACA, the entire Act should be invalidated. In March 2020, the Supreme Court agreed to review a decision by the U.S. Court of Appeals for the Fifth Circuit[236] on the constitutionality of the mandate and to review the constitutionality of the ACA overall. The Justices will hear oral arguments during the Court's next term, which begins in October 2020.[237]

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 Anti-Kickback Statute, False Claims Act, and other federal and state laws.[238]

Accordingly, drug manufacturers and investors funding development of investigational 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, conducing 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.

* * *

Endnotes

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54. *Id.* § 1395y(a)(1)(A).
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59. *Id.* § 1395k(a).
60. 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.
61. *Id.* § 1395kk-1.
62. *Id.* §§ 1395j-1395w-6.
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66. 42 U.S.C. § 1395w-131.
67. *Id.* § 1395w-101.
68. *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. 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).
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73. 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).
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90. *Id.* § 1395w-3a(c)(1).
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101. 42 U.S.C. § 1395w-102(a).
102. 42 C.F.R. § 423.104.
103. The Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 3301-3315, 124 Stat. 119, 461-80 (2010).
104. 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.
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113. 42 U.S.C. §§ 1396b(m), 1395mm(a)(1).
114. *Id.* §§ 1396a, 1396u-7.
115. *Id.* §§ 1396a(a)(54), 1396u-7(b)(2)(A).
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118. *See generally id.* § 1396r-8.
119. *Id.* § 1396r-8(a)-(b).
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121. 42 C.F.R. § 447.53.
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144. *American Hosp. Ass'n v. Azar*, 385 F. Supp. 3d. 1 (D.D.C. 2019).
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147. 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/.
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155. *See, e.g.*, *id.*; *see also* Statement of Steve Miller, M.D. Executive Vice President & Chief Clinical Officer Cigna Corporation, Drug Pricing in America: A Prescription for Change, Part III: Hearing Before the S. Comm. on Finance, 116th Cong. (Apr. 9, 2019), https://www.finance.senate.gov/imo/media/doc/Cigna%20ExpressScripts%20Testimony%20of%20Steven%20Miller%20MD.pdf ("The 2018 Cigna Value of Integration Study shows that clients with Cigna medical, pharmacy, and behavioral benefits reduce annual medical costs by an average of $645 for each person with an identified health improvement opportunity—savings that can increase to nearly $10,000 for individuals with certain chronic conditions.").
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157. *Id.*

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160. *Id.*
161. Patient Protection and Affordable Care Act; HHS Notice of Benefit and Payment Parameters for 2021; Notice Requirement for Non-Federal Governmental Plans, 85 Fed. Reg. 29164 (May 14, 2020) (revising 42 C.F.R. § 156.130).
162. *See, e.g.*, H.B. 2166, 54th Leg., 1st Sess. (Ariz. 2019); H.B. 465, 101st G.A. (Ill. 2019); S.B. 1596, 2019 Sess. (Va. 2019); H.B. 2770, 2019 Sess. (W. Va. 2019).
163. H.B. 2166, 54th Leg., 1st Sess. (Ariz. 2019).
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171. *Current and New Approaches to Making Drugs More Affordable*, CVS Health (Aug. 2018), https://cvshealth.com/sites/default/files/cvs-health-current-and-new-approaches-to-making-drugs-more-affordable.pdf.
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176. *Id.* at 70,626.
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181. Ctrs. for Medicare & Medicaid Servs., *Medicare Benefit Policy Manual*, ch. 15, § 50.4.2, https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c15.pdf (last revised July 12, 2019). Cancer drugs must be covered-off label if listed in one of five compendia—AFHS-DI, DrugDex, the NCCN, Clinical Pharmacology, and Lexi-Drugs. Contractors are also permitted to rely on peer-reviewed research published in one of 26 specified journals. *Id*. § 50.4.5.
182. 42 U.S.C. § 1396r-8 (stating that the program shall assess data on drug use against predetermined standards consistent with AFHS-DI, DrugDex, and a third compendium that is no longer published).
183. *See*, *e.g.*, N.Y. Ins. Law § 3221 (requiring payers to cover drugs prescribed for a different type of cancer than the type for which it was approved, provided that the drug has been recognized in AHFS-DI, NCCN, DrugDex, Clinical Pharmacology, or other authoritative compendia as identified by HHS or CMS or recommended by review article or editorial comment in a major peer reviewed professional journal, unless the drug has been determined to be contraindicated for the specific type of cancer for which it is being prescribed); Md. Ins. § 15-804 (prohibiting the exclusion of a coverage if the off-label use is recognized for treatment in "any of the standard reference compendia or in the medical literature").
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188. 21 C.F.R. § 312.320.
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191. Right to Try Act of 2017, Pub. L. No. 115-176, 132 Stat. 1372 (2018) (codified at 21 U.S.C. § 360bbb-0).
192. 21 U.S.C. § 360bbb-0; *Right to Try*, U.S. Food & Drug Admin., https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try (content

current as of Jan. 14, 2020). An eligible investigational drug is one (a) for which For which a Phase 1 clinical trial has been completed, (b) that hat has not been approved or licensed by the FDA for any use, (c) for which an application has been filed with FDA or is under investigation in a clinical trial that is intended to form the primary basis of a claim of effectiveness in support of FDA approval and is the subject of an active IND application, and (d) for which active development or production is ongoing, and has not been discontinued by the manufacturer or placed on clinical hold by the FDA. *Id.*

193. Joseph DiMasi, *et al.*, *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. of Health Econ. 20–33 (2016), https://www.sciencedirect.com/science/article/abs/pii/S0167629616000291?via%3Dihub.
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197. *Id.*
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200. *Id.*
201. *Id.* at 20.
202. *Id.* at 2.
203. For instance, in the 2015 Bipartisan Trade Priorities Act, Congress directed the Administration "to achieve the elimination of government measures such as price controls and reference pricing which deny full market access for United States products". Bipartisan Congressional Trade Priorities and Accountability Act of 2015, Pub. L. No. 114-26, § 102(b)(7)(F), 129 Stat. 320, 326 (2015); *see also* House Ways and Means Committee Report, Bipartisan Congressional Trade Priorities and Accountability Act of 2015, H.R. Rep. 114-100 (2015).
204. S.B. 17, 2017–2018 Reg. Sess. (Cal. 2017).
205. H.B. 4005, 79th Leg., 2018 Sess. (Or. 2018); H.B. 2658, 80th Leg., 2019 Sess. (Or. 2019).
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210. E. Silverman, *California fines more than a dozen drug makers for not providing drug pricing data*, STAT+ (Apr. 28, 2020), https://www.statnews.com/pharmalot/2020/04/28/california-drug-prices-transparency-nevada/.
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212. S.B. 539, 79th Sess. (Nev. 2017).
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Nevada); *Ass'n for Accessible Medicines v. Frosh*, No. 17-2166 (4th Cir. 2018) (striking down H.B. 631 in Maryland).

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219. Medicare Program; Part B Drug Payment Model, 81 Fed. Reg. 13,229, 13,229-61 (Mar. 11, 2016).
220. Medicare Program; Part B Drug Payment Model; Withdrawal, 82 Fed. Reg. 41,618, 41,618 (Oct. 4, 2017).
221. Prescription Drug Pricing Reduction Act of 2019, S. 2543, 116th Cong. (2019-2020).
222. Elijah E. Cummings Lower Drug Costs Now Act, H.R. 3, 116th Cong. (2019-2020).
223. John Wilkerson & Rachel Cohrs, *Pelosi's Medicare Price Bargaining Bill Triggers Political Maneuvering*, InsideHealthPolicy (Sept. 23, 2019), https://insidehealthpolicy.com/inside-drug-pricing-regimen/pelosi%E2%80%99s-medicare-price-bargaining-bill-triggers-political-maneuvering.
224. *Health Care*, Biden for President, https://joebiden.com/healthcare/.
225. *See*, *e.g.*, Michael Liu *et al.*, *March-In Rights And Compulsory Licensing—Safety Nets For Access To A COVID-19 Vaccine*, Health Affairs (May 6, 2020), https://www.healthaffairs.org/do/10.1377/hblog20200501.798711/full/.
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231. Exec. Order No. 13,813, 82 Fed. Reg. 48,385 (Oct. 17, 2017); Exec. Order No. 13,765, 82 Fed. Reg. 8,351 (Jan. 24, 2017).
232. Pub. L. No. 115-97, § 11081, 131 Stat. 2054, 2092 (2017).
233. *Texas v. California*, No. 19-1019, https://www.supremecourt.gov/docket/docketfiles/html/public/19-1019.html; *California v. Texas*, No. 19-840, https://www.supremecourt.gov/docket/docketfiles/html/public/19-840.html.

234. *NFIB v. Sebelius*, 567 U.S. 519 (2012). The Court struck down provisions that would have withheld federal funds from states that refused to expand their Medicaid programs. To date, 37 states (including the District of Columbia) have adopted Medicaid expansion, while 14 states have not adopted expansion. *See Status of State Action on the Medicaid Expansion Decision*, Kaiser Family Found. (Apr. 27, 2020), https://www.kff.org/health-reform/state-indicator/state-activity-around-expanding-medicaid-under-the-affordable-care-act/.
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236. *Texas v. United States*, 945 F.3d 355 (5th Cir. 2019) (holding that the individual mandate is unconstitutional but remanding to the lower court to consider whether the mandate is severable from the ACA).
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238. *See, e.g.*, Press Release, *Justice Department Recovers over $3 Billion from False Claims Act Cases in Fiscal Year 2019*, U.S. Dep't of Justice (Jan. 9, 2020), https://www.justice.gov/opa/pr/justice-department-recovers-over-3-billion-false-claims-act-cases-fiscal-year-2019 ("The Department of Justice obtained more than $3 billion in settlements and judgments from civil cases involving fraud and false claims against the government in the fiscal year ending Sept. 30, 2019 . . . $2.6 billion relates to matters that involved the health care industry, including drug and medical device manufacturers, managed care providers, hospitals, pharmacies, hospice organizations, laboratories, and physicians.").

Acknowledgments

The authors would like to acknowledge the significant contributions of Stefanie Doebler, Jennifer Plitsch, Beth Braiterman, and Tara Carrier.

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