



# Pricing & Reimbursement 2018

**First Edition**

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# Reimbursement of Specialty Drugs in the Hospital Inpatient Setting: Are Current Pathways in the USA and Europe Sufficient?

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## Abstract/Synopsis

It has been well established that the growth of specialty pharmaceuticals, which today represent approximately 40% of the United States pharmaceutical market, has been accompanied by greater spending by hospitals on inpatient drugs. (Alliance, 2017) (NORC, 2016). In part, this shift may coincide with greater numbers of hospital and physician-administered therapies for rare and difficult-to-treat diseases. Analyses of US drug spending on inpatient drugs have found that annual spending has increased at up to twice the rate of prescription drugs in some recent years. (NORC, 2016.)

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.

The most common scenario of payment in hospitals, globally, is the use of Diagnosis Related Groups (DRG) to pay a predetermined amount for an entire patient discharge, which reflects 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. (106<sup>th</sup> 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. Other sources have noted the variation and lack of transparency in health technology assessments (HTAs) 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  | <i>Liste en Sus</i> , add-on payment for drugs                       |
| England       | Inpatient/Outpatient: HRGs                                       | High Cost Drugs List, Cancer Drugs Fund                              |
| United States | Medicare: DRGs<br>Commercial: DRGs, Per Diem, Discounted Charges | Medicare: New Technology DRG Payment<br>Commercial: Negotiated rates |

## USA Reimbursement schemes in the 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 approximately 80% of hospitals. 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 selected 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. (106<sup>th</sup> 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 simply requires Medicare to pay additionally for qualified new drugs, it does 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). (CMS, 2001.) CMS deliberately established a high bar for eligibility.

Additional modifications to the statute were implemented under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) which amended the NTAP criteria to include the threshold described below. (Medicare Modernization Act, 2003.) The current eligibility criteria are:

- (1) the technology must be new;
- (2) the 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 service or technology must demonstrate a substantial clinical improvement over existing services or technologies for Medicare beneficiaries. (Centers for Medicare & Medicaid Services, 2018.)

"New" under the CMS rules means within two to three years following market introduction, (Centers for Medicare and Medicaid Services, 2001) and a specific code has been assigned

to identify the service. (Centers for Medicare & Medicaid Services, 2018.) (Centers for Medicare and Medicaid Services, 2001.) Technologies that are substantially similar to older technologies are not considered new.

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, 2018.) Cost thresholds for each MS-DRG are published annually in Table 10 of each year’s IPPS (inpatient payment prospective payment system) final rule.

Determining substantial clinical improvement under the Medicare definition can be somewhat challenging. Technologies are considered eligible if:

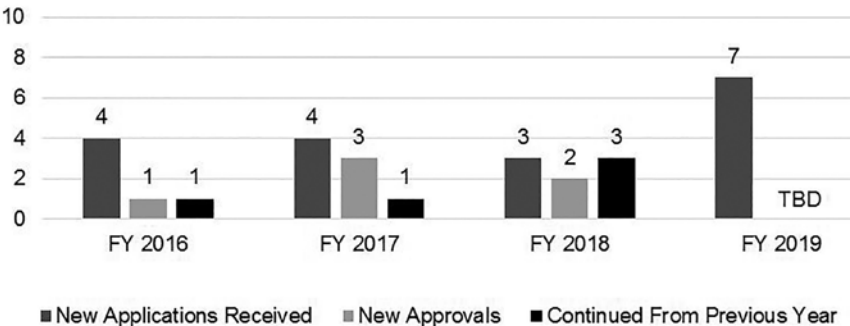
- The drug offers a treatment option for a patient population unresponsive to, or ineligible for, currently available treatments.
- Use of the drug significantly improves clinical outcomes for a patient population as compared to currently available treatments. (Centers for Medicare and Medicaid Services, 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 additional payment is capped at 50% of the additional cost of the technology.
- Cases receive less add-on payment if the case costs less than MS-DRG payment amount plus 50% of the cost of the technology. (Centers for Medicare & Medicaid Services, 2018.)

As the NTAP legislation approaches the end of its second decade, there is some debate as to whether it has had any true impact, with only a very 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.) In 2018, there are five drugs approved for New Technology Add-on Payments. (CMS, 2015.) (AdvaMed, 2016.) (CMS, 2017.)

**Applications and Approvals for New Technology Add-on Drug Payments, United States FY 2016–FY 2018**



The drugs approved for NTAP in FY 2018 are:

- Defitelio® – a treatment for severe hepatic veno-occlusive disease after hematopoietic stem cell transplantation (HSCT). Idarucizumab – for the reversal of anticoagulant effects of dabigatran.
- Vistogard™ – to treat an overdose of certain cancer medicines (capecitabine or fluorouracil).
- ZINPLAVA™ – to reduce recurrence of *Clostridium difficile infection* (CDI).
- Stelara® – for moderate or severe plaque psoriasis.

### 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 April 2014, 36 states rely on DRGs and 10 states use *per diem* rates for inpatient hospital services. The remaining states use other approaches, such as a per stay payment or cost-based reimbursement. (MACPAC, 2016.)

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 with 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 (GAO Report on 340b Discounts, 2011). Hence, it may help hospitals offset disproportionately low Medicaid payments for admissions, 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. Alternatively, private payers may reimburse hospitals based on “discounted charges” which help compensate a proportion of the charges per service. In a hospital outpatient context, approximately 54% of commercial lives are reimbursed based on a percentage of charges. (Magellan Rx Management, 2016 Seventh Edition.)

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 of 487%. (Moran Company, 2017.) When compared to the reported costs for those same cases, the authors found the 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 onto the hospital. The net impact of these two very different systems of payment likely means a phenomena of “cost shifting” which occurs regularly 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.<sup>1</sup>

## **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 (*Gemeinsame*

*Bundesausschuss*, or Joint Federal Committee) review prior to local Statutory Health Insurance (SHI) reimbursement for all new drugs. The German Ministry of Health is the highest authority in German healthcare, but the G-BA is the highest authority of the joint self-administration of physicians, hospitals and SHIs. The G-BA has a key role in the 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 IQWiG (Institute for Quality and Efficiency in Health Care), 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 of experts from the industry, physicians' and patients' associations, has a fixed timeframe of six months. (Joint Federal Committee (G-BA), 2017.)

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

### ***Hospital Payment under G-DRGs and NUB Innovation Payment***

The German DRG system (G-DRG) for hospital payment was 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. Hospitals must also follow annual hospital budgets, which are calculated according to the 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 have to fulfil the following criteria (InEK Institute for Remuneration System in the Hospital, 2016 to 2018):

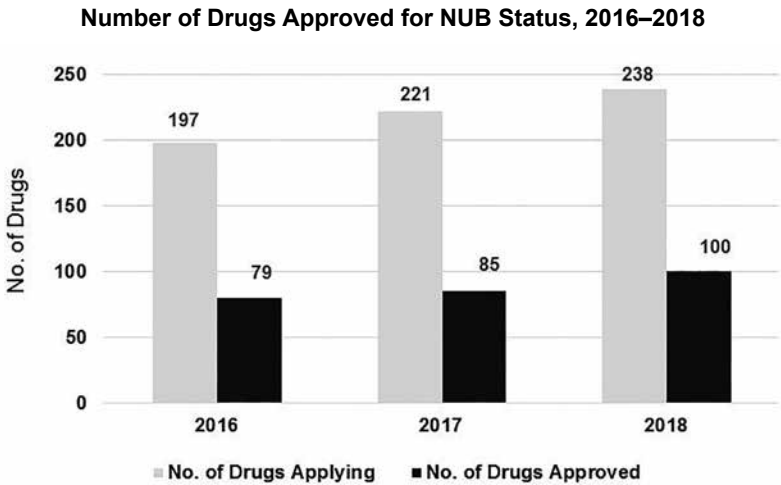
- not properly reimbursed via existing coding and fees;
- have been used for less than four years in German hospitals; and
- cause significant additional costs for the hospital stay.

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 has been an incremental cost of €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.

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. Following the NUB process, InEK then reviews data from “calculation” hospitals to determine the appropriate, long term G-DRG assignment based on the total cost of associated care. Hence, in order for a G-DRG assignment to be possible, a drug must be associated with a specific, definable set of G-DRGs and be used in the right hospitals.

Drug-related NUB applications, as well as approvals, have increased annually as the trend depicted below shows. Overall, applicant drugs from 2016 to 2018 have experienced a 40% success rate.



*(InEK Institute for Remuneration System in the Hospital, 2016 to 2018)*

***ZE Permanent Supplemental Payments***

If drugs do not “fit” into the DRG structure, InEK may consider assigning a 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).

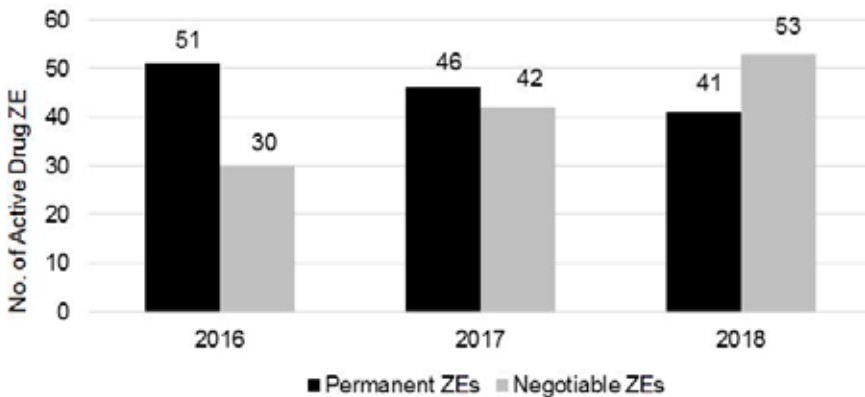
Drugs are eligible for a ZE payment if they involve:

- a clearly defined procedure (with OPS code);
- are used with multiple DRGs without fixed association to any DRG; and
- represent a 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 as part of a list of reimbursable amounts depending on dosage (if applicable) and are reviewed annually.



### InEK ZE Assignments for Inpatient Drugs, 2016–2018



(InEK Institute for Remuneration System in the Hospital, 2016 to 2018)

### The French *Liste en Sus* and Hospital Funding

In France, the High Authority on Health (*Haute Autorité de Santé*, 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 will analyse 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 either “Improvement to Medical Services Rendered” (ASMR) for a product with a direct marketed comparator, or “Medical Services Rendered” (SMR) for novel products. The HAS appraisal assigns an ASMR or SMR rating on a five point scale, where only products with an ASM/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 be likely to 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.

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

- SMR (*Service Medical Rendu*) reviews are written for drugs that are brand new or indications that do not yet have a standard treatment protocol.
- ASMR (*Amélioration de Service Medical Rendu*) reviews are written for drugs that are improvements on existing medications or variations on existing treatments. (HAS Haute Autorité De Santé, 2014.)

Either review 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.

The process of adoption at a hospital level is driven by an internal technology appraisal committee and may take six 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 vs. new protocol.

Price negotiations are more substantial in public than in private hospitals. Typically, there is very little price negotiation with private hospitals, where acquisition prices are close to the published tariffs.

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 diagnosis-related group type of classification among 700 *Groupes Homogènes de Maladies* (GHM), which have severity adjustment for comorbidities. A nationally fixed tariff (*Groupe Homogènes 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 (ICD10) and procedures (CCAM) codes.

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

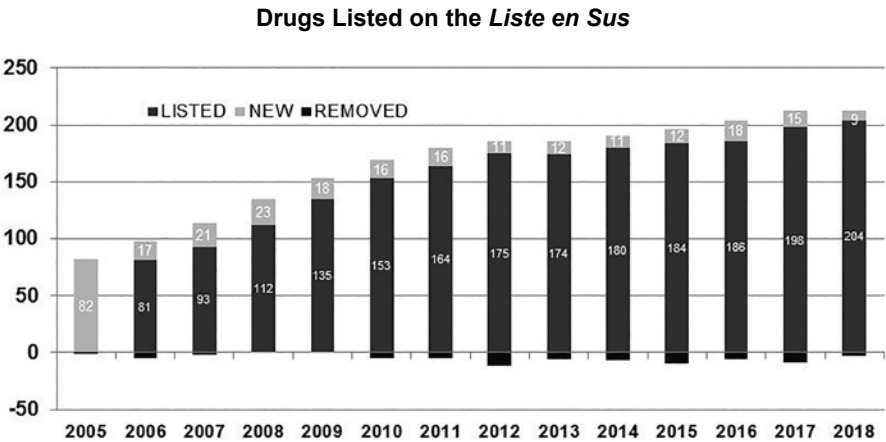
Unlike the US and German temporary add on payments, the *Liste en Sus* technically does not have a time limitation and some products can remain listed for years.

The *Liste en Sus* mostly includes anticancer, anti-inflammatory, auto-immune and immunoglobulin drugs and 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.

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 in 2018 there are 210 products eligible. However, from 2011 to 2018 the number of listed drugs increased only slightly.



*(Liste en Sus, 2018.)*

**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.

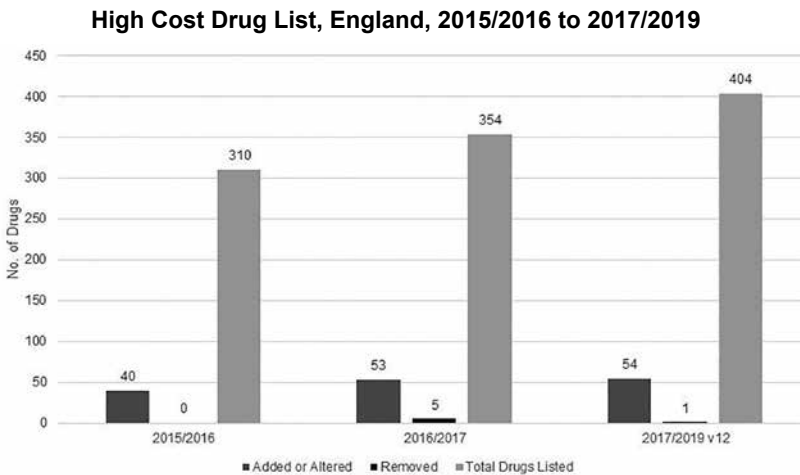
High-cost drugs and devices account for around 25% of expenditures on specialised care in England. To ensure that providers and commissioners of health services can deliver the best value of care to patients, NHS England is continuing to implement measures introduced in recent years which are designed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

In England, drug add-on payments are either negotiated locally with Clinical Commissioning Groups (CCGs) or designated nationally for specialised services. The High Cost Drugs List in the NHS is intended for specialised products, whose use is concentrated in a relatively small number of centres. 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 Drugs list have historically been:

- the drug and its expected associated costs of care are disproportionately high-cost compared to the other expected costs of care within the HRG, which would affect fair reimbursement;
- there is, or is expected to be, more than £1.5 million spent or 600 cases in England *per annum*; and
- 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.)

*Cont'd overleaf*



- In the 2015/2016 time period, a total of 310 drugs were listed, 40 were added or altered, (NHS England and Monitor, 2014).
- For the 2016/17 list, 53 were added or altered (Monitor and NHS England, 2016), and five were removed, leaving a total of 354 drugs listed.
- For 2017/2018, 54 drugs were newly added or altered to the inpatient High Cost Drugs List. Only one drug was removed. There are 404 drugs listed. (NHS Improvement and NHS England, 2017.)
- As of April 2018, three drugs were removed from the High Cost Drugs List, and 16 new drugs were added. (NHS England, 2018.)

Though it is encouraged, prior NICE appraisal is not a requirement for listing on the High Cost Drugs list.

NHS England recommends payments for high-cost drugs excluded from National Tariff are 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 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 annual budget for the CDF increased annually in the initial years, but the programme 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 with a new appraisal approach enacted. (NHS England.) The expanded role of NICE followed criticism of overspending on drugs with low therapeutic benefit. 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 (National Institute for Health and Care Excellence, 2014), but with additional specific amendments for the Cancer Drug Fund. (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”.
- 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 will have to agree to the expenditure control mechanism. (NHS England, 2016.)

The CDF budget is currently fixed at £340 million. (NHS England Cancer Drugs Fund Team, 2016.) Currently 97 drugs (including drugs listed more than once for variations in indication) are listed. (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 patients via higher markups on other prescribed products. But in mostly single payer environments, such as Britain or Germany, no such cost shifting is possible.

Some systems have maintained special pathways for funding cancer drugs, specifically, which has to some extent created a safe harbour in some markets, but 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.

\* \* \*

## Endnote

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# Angola

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## Abstract

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

## Market Introduction/Overview

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

After almost four decades of conflict, ending in 2002, Angola experienced fast economic growth mainly driven by its oil industry. The sharp decline in oil prices since mid-2014 and a weak growth of the non-oil sector significantly impacted the economy and social services, resulting in a reduction of public revenues, severe tax and external imbalances (including forex shortages). Exports dropped by more than half, and the external accounts moved from surplus to deficit. On top of this, this led to the devaluation of the Angolan Kwanza. The negative impact on Angola's economy threatens the recent economic and social development progresses, notably the long-term target of improving human development outcomes. Public spending on health has decreased since 2014 (however, this was already low compared to international standards), compromising previous increases in health expenditure by the public sector.

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

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

## Pharmaceutical Pricing and Reimbursement

### Regulatory classification

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

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

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

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

Generics and biosimilar medicines do not yet have a legal definition. However, the law does define “therapeutic equivalents” to the reference product. The law establishes that the Ministry of Health should promote generic substitution in pharmacies, and that medicines should be purchased at the best available price. Additionally, it is stated that generics should benefit from simpler and cheaper registration procedures. However, all these aspects reflect legal intentions, the law – or any regulation – not providing for any specific regime. Government plans also set out that the acquisition of generics is a priority.

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

Most of medicines are purchased by the State. Reimbursement of pharmaceutical products has not yet been regulated, despite several indications that this is a public policy priority that should advance soon.

As for medical prescription, the foundation of the regime has been laid, but additional regulation is required to define which medicines are subject to medical prescription.

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

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

- (i) raise direct or indirect risks when used without medical supervision;
- (ii) are, or can be, sizably used for a different purpose than intended, and such purpose poses a direct or indirect risk to public health;
- (iii) contain substances, or combinations that include substances, with sensitive side effects; and

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

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

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

- (i) antibiotics, including antituberculous medicines and 3<sup>rd</sup> generation antibiotics;
- (ii) Misoprostol;
- (iii) Sildenafil, Tadalafil and Vardenafil; and
- (iv) narcotic and psychotropic medicines.

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

#### Who is/Who are the payer(s)?

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

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

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

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

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

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

The prices are not set linearly.

The General Framework for National Pharmaceutical Policy foresees the creation of a Commission for Price Regulation with the purpose of creating or changing the laws and regulations applicable to the pricing of pharmaceutical products. Even though the law dates from 2010, this Commission has not been created so far. Because of the delay in creating or changing these laws and regulations, a Law dated from 1974 is still in force, but is considered inapplicable due to it being incompatible with inflation and overall market evolution.

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

No regulation is foreseen regarding hospital medicines. For this reason, prices are determined by the outcome of public procurement procedures, launched to purchase hospital medicines. Tender award procedures for medicinal products are launched by a Centralized Medicine Purchase Authority (“CECOMA”). CECOMA is a public authority, working under the supervision of the Ministry of Health that is in charge of developing and managing the system of purchase, distribution, and maintenance of goods for the National Health Service. In other words, CECOMA purchases and stores medicines and carries out their distribution to the health facilities all over the country. Prior to the acquisition, CECOMA submits an inventory with the available stock to said health facilities who prepare an annual estimate of their needs. Based on the information provided, CECOMA then proceeds to contact local and international suppliers, and launches tender procedures to award supply contracts that correspond to the identified needs. Each healthcare facility should provide their estimates within the budget that is allocated to them and allocated to each healthcare facility. In the call for tenders, CECOMA should determine the maximum price it is willing to pay for a certain product. While the maximum price should be decided by CECOMA, the product’s final sale price should result from the tender procedure, and will depend on whether there is competition in the tender.

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

#### Issues that affect pricing

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

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

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

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

### **Policy Issues that Affect Pricing and Reimbursement**

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

There is a clear need for improvement of quality of primary healthcare service delivery, notably for underprivileged groups and rural areas. The quality failures are mainly due to a defective health system, e.g. dysfunctional health posts and hospitals, outdated classifications

of healthcare professionals, lack of trained staff, restricted number of individuals with appropriate academic background, lack of incentives linked to performance (outputs or service quality), work delays and absence, etc. In addition, the health system is exposed to disease outbursts. Epidemiologic surveillance system detected several epidemics since 2013, namely: yellow fever; malaria; measles; human and animal rabies; cholera diarrhea (bloody stool and viral); dengue fever; and chikungunya. Some of these occurrences are a sign of feeble vaccination coverage.

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

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

### Emerging Trends

Angola has not enacted a coherent and comprehensive regulatory system. The existing legal framework is clearly insufficient and is not applicable to a great extent. Legal and administrative reforms are patently necessary, and apparently imminent.

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

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

- (i) rehabilitating and expanding public healthcare infrastructure and capacity, especially for rural and underserved urban populations;
- (ii) expanding the training of healthcare professionals; and
- (iii) preventing diseases.

The Plan also foresees the transition of the health system from a government financed model to a system that resorts to diversified revenue streams. Considering the country’s current stage of development, and according to the World Health Organization (“WHO”), however, primary healthcare will continue to rely on public and external financial resources.

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

- (i) supporting local production of medicines;
- (ii) building a National Lab for Quality Control;
- (iii) further developing the List (the National List of Essential Medicines);
- (iv) preparing a National Form of Medicines and Therapeutic Guides, as an important tool to support the rational use of medicines; and
- (v) developing the legal and technical framework of traditional medicines.

Presidential Decrees of 2010 establish that an increase in local manufacturing of basic

primary pharmaceuticals as a government priority. The self-sufficiency of the national market is deemed as the ideal scenario, and thus as the ultimate goal.

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

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

Reimbursement of medicines is also mentioned as a priority. At the current stage of development, the Government considers that reimbursement is a “human rights” issue, and that it materialises the principle of the State burdening a significant share of health costs.

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

- (i) definition and reorganisation of the National Health System and the National Health Service;
- (ii) increase of coverage and rational organisation of healthcare services (with a reference system between health centres, hospitals, and polyvalent hospitals);
- (iii) lowering mother and child mortality rates;
- (iv) lowering the death rate for chronic and most prevalent diseases (malaria, tuberculosis, trypanosomiasis, measles, tetanus, meningitis, and poliomyelitis);
- (v) coordination of public and private sectors and traditional medicine;
- (vi) standardisation, organisation and financing of healthcare services; and
- (vii) promotion of scientific investigation.

### **Successful Market Access**

Considering the structural lack of regulation and the unpredictability of the market, cooperation with the competent authorities plays a significant role. Interested parties should try to anticipate market and regulatory trends and ensure that their products are approved and placed in the market according to the authorities’ interpretation of applicable laws. Interested parties should also consider adjusting their portfolio or business plan to cater the most pressing needs of the Angolan population. Given the scarcity of resources and the system’s level of maturity, it is natural that successful market access should depend on the product being used to treat or prevent a disease whose treatment or prevention is deemed as a priority. Local collaboration can also help to accelerate or clarify procedures that can be particularly lengthy or bureaucratic if they are managed remotely.

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# Australia

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## Abstract

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

## Market Introduction/Overview

Australia is a nation with a population of approximately 25 million people.<sup>1</sup> It is a generally healthy nation, with life expectancies in the top five of OECD nations. Australians have access to a Government-subsidised system of universal healthcare, which includes subsidised access to many medicines through the Pharmaceutical Benefits Scheme (**PBS**).

Like many western countries, Australia is experiencing an ageing of its population. The median age of the Australian population, as at June 2016, was 37.2 years, compared to 36.7 years in June 2006. The Australian population is also growing – population growth in the 12 months leading up to September 2017 was 1.6%, a slightly higher rate of growth than the average for the previous three years. Roughly two-thirds of the population growth is attributable to immigration and one-third to natural increases.

While Australia is a generally healthy nation, it faces many of the problems typical of western countries in which life expectancy has been extended and diet and lifestyle factors play a significant role in affecting health. The following snapshot of Australian health is taken from the Australian Institute for Health and Welfare's report on Australia's Health for 2016:<sup>2</sup>

- in 2016 nearly 10 million Australians were aged 45 or older;
- the life expectancy of a person born in 2014 is 80.3 years for a male and 84.4 years for a female;
- in 2013 the leading cause of death in Australia was coronary heart disease (although 2013 was also the first year in which deaths from all forms of cancer (narrowly) exceeded deaths from all cardiovascular disease combined);
- chronic disease is becoming increasingly common. This is attributable to a combination of the ageing of the population and a change in lifestyle factors which contribute to chronic disease. The five risk factors which make the highest contribution to chronic disease in Australia are tobacco use, high body mass, high alcohol use, physical inactivity and high blood pressure. In 2014–2015, 63% of Australian adults were estimated to be overweight or obese; and

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

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

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

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

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

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

The total Commonwealth health budget for 2017–2018 was approximately AU\$68 billion. Of that amount, approximately AU\$11 billion is allocated to the PBS.<sup>3</sup> The PBS is the third-largest item in the health budget after Medicare (AU\$ 23 billion) and aged care (AU\$ 11.5 billion). However, it should be noted that the budget allocation of AU\$11 billion for the Pharmaceutical Benefits Scheme 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, having grown to that size from AU\$194 million in 2011–2012.<sup>4</sup>

## 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 Pharmaceutical Benefits Scheme (**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.<sup>5</sup> 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.<sup>6</sup>

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.<sup>7</sup>

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 dependents, 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-subsidised 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.

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. Negotiations are in progress between the Commonwealth and industry in relation to the implementation of certain recommendations of the review.

### 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<sup>8</sup> 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<sup>9</sup> except as follows:

- A patient co-payment which from 1 January 2018 is up to AU\$39.50 or AU\$6.50 if the patient has a concession card for most PBS medicines. Pharmacists may (voluntarily) choose to discount the PBS patient co-payment by up to AU\$1.00 for some medicines. The amount of the co-payment is adjusted annually on 1 January in accordance with the Consumer Price Index (**CPI**).<sup>10</sup>
- 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\$4.45) and an additional fee for ready prepared items (currently AU\$1.21). Neither of these fees can be added to increase the amount payable by the patient above the co-payment amount.
- Some brands of medicines have a price premium or brand premium. This is an additional amount which represents the difference between the price at which the sponsor is prepared to sell and the price which the Government is prepared to subsidise. Government policy is to only allow such arrangements in limited circumstances, typically where an innovator medicine and one or more generic brands of the same drug are listed on the Schedule.

The legislation also provides for a “Safety Net”. If a patient’s prescriptions exceed the relevant Safety Net Threshold for a calendar year, general patients pay for further PBS prescriptions at the concessional co-payment rate, and concessional patients will receive PBS prescriptions at no additional charge for the remainder of the year. Current Safety Net thresholds (as at 1 January 2018) are AU\$384 for concession card holders and AU\$1,521.80 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, a medicine must be approved for supply in Australia before it can be listed on the Schedule. For prescription medicines, these must be registered 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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>13</sup> Furthermore, if a medicine is substantially more costly than alternative therapies, the PBAC may not recommend its listing unless the PBAC is satisfied that the medicine for some patients provides a significant improvement in efficacy or reduction in toxicity of the alternative therapies.<sup>14</sup>

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**).<sup>15</sup> The PBAC Guidelines identify five quantitative factors which influence PBAC decision-making:<sup>16</sup>

- (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 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 1.2, January 2018),<sup>17</sup> which provides further detailed information about the processes, procedures, timelines and documents required. 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, (if positive) negotiation and agreement on 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.<sup>18</sup> 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.<sup>19</sup> The reviewer's findings are not binding on the PBAC.

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

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

Once a pharmaceutical benefit is listed on the PBS, a set of quite complex arrangements set out the way in which the reimbursement is paid. In general terms, the Schedule specifies the price which may be charged by the sponsor for the medicine (the Approved Ex-Manufacturer Price, or AEMP). However, the Commonwealth subsidy is paid to the pharmacist who dispenses the medicine. The subsidy (called the Commonwealth price) is therefore the AEMP plus mark-ups and associated fees charged by the wholesaler and pharmacist. Those mark ups and fees are controlled. For community pharmacy, the current Sixth Community Pharmacy Agreement between the Commonwealth and The Pharmacy Guild of Australia set out how the Commonwealth price is set.<sup>20</sup> 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.<sup>21</sup> 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.<sup>22</sup> 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.<sup>23</sup> 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 5<sup>th</sup>, 10<sup>th</sup> and 15<sup>th</sup> anniversary of listing for drugs on the F1 formulary (5%, 10% and 5%, respectively),<sup>24</sup> subject to a Ministerial discretion;
- statutory price reductions on the first listing of a bioequivalent or biosimilar brand of a pharmaceutical item (currently 16%, but will increase to 25% on 1 October 2018, with the addition of a Ministerial discretion);<sup>25</sup> 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<sup>26</sup> 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.<sup>27</sup>

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.<sup>28</sup>

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

### **Policy Issues That Affect Pricing and Reimbursement**

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

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

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

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

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

#### **Statutory Price Reductions and Strategic Agreements**

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



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

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

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

The first such agreement was a Memorandum of Understanding entered into between Medicines Australia and the Commonwealth in 2010 with a four-year term.<sup>29</sup> The Memorandum of Understanding was generally thought to have been effective in achieving cost control on PBS expenditure,<sup>30</sup> but questions were raised about whether it had been effective in providing industry with policy certainty.

In 2015, the Generic Medicines Industry Association Entered into a Strategic Agreement with the Commonwealth with a five-year term.<sup>31</sup> It 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 in addition 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.<sup>32</sup> This Strategic Agreement provides for a substantial change to the way in which the statutory price reduction regime operates (including increased price reductions). However, it also introduces 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 industry has 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 2018.

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

### Rebates

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

This has resulted in a dramatic growth in rebates over the last decade (see section “Market Introduction/Overview” above) to the extent that the size of the rebates is about 25% of the

total PBS budget and close to half of the amount of that budget attributable to the price charged by sponsors for their products. In recent years, the listing of non-interferon Hepatitis C medicines appears to have more than doubled the total value of rebates payable by industry. For sponsors this creates a problem because the perceived cost of their products to Government is much greater than the actual cost. Medicines Australia has made submissions to the Commonwealth seeking explicit recognition of rebates in the way the PBS budget is presented.

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

For these reasons the Commonwealth has proposed restructuring the PBS payments system so that for high-cost drugs a net subsidy amount would be paid directly to the sponsor rather than to the pharmacist. It is proposing to run a pilot programme commencing 1 July 2018. 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.

#### 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%.<sup>33</sup> The PBAC's rigid meeting schedule exacerbates the problem because it means that if a submission is rejected by the PBAC it is usually a minimum of four months and more commonly eight months before the medicine can return to the PBAC.

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

### **Emerging Trends**

As described in "Policy Issues That Affect Pricing and Reimbursement", "Statutory Price Reductions and Strategic Agreements" above, a Strategic Agreement was signed by Medicines Australia and the Commonwealth, with a five-year term. That Strategic Agreement is the basis for legislative change, which is still coming into effect (some parts commence in October 2018). The purpose of this Strategic Agreement is to give some certainty to the prescription medicines industry and the Government and, particularly around pricing, we expect the industry is hopeful that there will be some stability around pricing mechanisms over the next five years. However, 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 topic of rebates and a potential new structure for the reimbursement of (at least) high-cost medicines is currently under debate both in the context of the PBS and the LSDP. Predictions about the form and timing of such changes are premature.

## Successful Market Access

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

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

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

\* \* \*

## Endnotes

1. Unless otherwise indicated, data presented in this introduction and overview are sourced from the Australian Bureau of Statistics ([www.abs.gov.au](http://www.abs.gov.au)).
2. <https://www.aihw.gov.au/reports/australias-health/australias-health-2016/contents/summary>.
3. Health Portfolio Budget Statements 2017–2018, Budget Related Paper No 1.10, May 2017 [http://www.health.gov.au/internet/budget/publishing.nsf/Content/2017-2018\\_Health\\_PBS\\_sup4/\\$File/2017-18\\_Health\\_PBS\\_Complete.pdf](http://www.health.gov.au/internet/budget/publishing.nsf/Content/2017-2018_Health_PBS_sup4/$File/2017-18_Health_PBS_Complete.pdf).
4. 2018–2019 Medicines Australia Federal Budget Submission (<https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/02/2018-2019-MA-Federal-Budget-Submission.pdf>).
5. <http://www.pbs.gov.au/info/about-the-pbs>.
6. Section 3, *Therapeutic Goods Act* 1989 (Cth) – “medicine”.
7. Sections 84 “PBS prescriber”, 88–90 of the National Health Act. The Schedule of Pharmaceutical Benefits identifies which items are able to be prescribed by which type of PBS prescriber (e.g. dentists and optometrists cannot prescribe general PBS items but have access to a separate Dental Schedule or Optometrical Schedule (respectively)).
8. Currently, Belgium, Finland, Ireland, Italy, Malta, the Netherlands, New Zealand, Norway, Slovenia, Sweden and the United Kingdom.
9. 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).

10. [http://www.pbs.gov.au/info/about-the-pbs#What\\_are\\_the\\_current\\_patient\\_fees\\_and\\_charges](http://www.pbs.gov.au/info/about-the-pbs#What_are_the_current_patient_fees_and_charges).
11. Section 85 of the National Health Act.
12. Section 101 of the National Health Act sets out the functions of the PBAC.
13. Section 101(3A) of the National Health Act.
14. Section 101(3B) of the National Health Act. Section 100 of the National Health Act also empowers the Minister to make special arrangements for, or in relation to, providing that an adequate supply of pharmaceutical benefits will be available to persons living in isolated areas, who are receiving treatment in circumstances where pharmaceutical benefits are inadequate for that treatment or if the pharmaceutical benefits can be more conveniently or efficiently supplied under those arrangements. Examples include the Efficient Funding of Chemotherapy program, Highly Specialised Drugs Program and IVF Program (<https://www.pbs.gov.au/browse/section100>).
15. <https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf>.
16. Page 4, PBAC Guidelines.
17. <http://www.pbs.gov.au/industry/listing/procedure-guidance/files/procedure-guidance-listing-medicines-on-the-pbs.pdf>.
18. Section 85AB of the National Health Act.
19. <http://www.pbs.gov.au/info/general/independent-review/independent-review-pbs-info-for-applicants>.
20. <https://www.guild.org.au/resources/6cpa>.
21. Section 85AD of the National Health Act.
22. Page 60, PBAC Guidelines.
23. Section 85E of the National Health Act empowers the Minister to enter into such deeds on behalf of the Commonwealth.
24. Sections 99ACF, 99ACHA, 99ACJ, 99ACK of the National Health Act.
25. Section 99ACB of the National Health Act, and to be amended by National Health Amendment (Pharmaceutical Benefits – Budget and Other Measures) Act 2018.
26. Part 7, Division 2 – Subdivision B (sections 71–81) of the National Health (Pharmaceutical Benefits) Regulations 2017 (Cth).
27. Section 103(2)(a) of the National Health Act.
28. Section 103(2A) of the National Health Act.
29. <http://www.pbs.gov.au/info/industry/useful-resources/memorandum>.
30. 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>.
31. [https://www.gbma.com.au/wp-content/uploads/2015/09/GMiA\\_StrategicAgreement\\_SignedCommonwealthandGMiA\\_-150524\\_FINAL.pdf](https://www.gbma.com.au/wp-content/uploads/2015/09/GMiA_StrategicAgreement_SignedCommonwealthandGMiA_-150524_FINAL.pdf).
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# Austria

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## Abstract

Austria has one of the best healthcare systems in the world, and access to medical services can be considered exemplary in international terms. The principle of statutory health insurance, combined with the co-insurance of children and non-working partners, ensures that 99% of the entire population enjoy health insurance coverage. At the same time, the high rates of cost increases in recent years and the way in which competences for various parts of the healthcare system are divided represent great challenges.

Thus, as in other EU-countries, cutting health spending is a high priority. One of the measures towards reducing spending for medicinal products was the introduction of a new Reimbursement Code (which is a positive list as defined in the EU Transparency Directive) (*Erstattungskodex*) with effect as of 1 January 2005, which has been amended regularly since to further cut costs. Under applicable Austrian national insurance laws and the Reimbursement Code, the National Health Insurance Association is responsible for deciding whether a medicinal product shall be reimbursed. Eligibility criteria for reimbursement are based on pharmacological evaluation, medical-therapeutic evaluation and a health-economic evaluation. Only products listed in the Reimbursement Code are reimbursed by the national health insurance system and products are listed in one of four different boxes of the Reimbursement Code: red; dark yellow; light yellow; and green. Reimbursement of a product listed in the red or dark yellow box is generally subject to approval by a chief consulting physician employed by the Association. For certain products, a documentation system applies, these are listed in the light yellow box. Medicinal products listed in the green box can be prescribed freely.

## Market Introduction/Overview

### Market

#### **General Information**

Austria is a democratic republic. Austria is a federal state made up of nine provinces, which are organised in districts and municipalities (*Gemeinden*). Austria has been a Member State of the European Union since 1995 and adopted the Euro as its currency in 2002.

This federal structure of the country affects the Austrian healthcare system. Through the multitude of decision-makers (federal, state, municipality, social insurance carriers), healthcare financing is not regulated from one source, but rather depends on multiple sources of financing (including taxes, social insurance premiums through social insurance, federal, state, municipality, etc.). Agreement among those players is essential due to fragmented responsibilities.

With a gross domestic product (GDP) of EUR 41,970 *per capita*, Austria is one of the richest countries in the world.

### **Population of Austria**

The population of Austria in 2017 was 8,773,686. The principle of statutory insurance, combined with the co-insurance of children and non-working partners, ensure that 99% of the entire population enjoy health insurance coverage by one of the 21 social insurance institutions (status 2017), in addition to 15 special healthcare institutions.

### **Diseases and Diagnosis in Austria**

Illnesses of the respiratory system and of the musculoskeletal system are the main causes for notifications of sickness in Austria. Diseases of the respiratory system together with diseases of the musculoskeletal system represent the cause for approximately 43% of the notifications of illness. Together, cardiac diseases, cardiovascular diseases and cancer cause seven of 10 deaths. Considering the growth of the population and its continuous ageing, mortality has decreased by 18% over the past decade. In particular, mortality from cardiovascular diseases has been declining.

The most common discharge diagnosis in Austria is malignant neoplasms (80% cancer) for women and diseases of the circulatory system in the case of men. The latter is also the most frequent cause of death in Austria, followed by cancer and respiratory diseases.

### **The Austrian Social Insurance System**

The Austrian social insurance system is based on the principles of compulsory insurance, solidarity and self-governance (*Selbstverwaltung*) and is primarily funded through insurance contributions. It includes the branches of health, accident and pension insurance and consists of 21 social security institutions with the National Health Insurance Association (*Hauptverband der österreichischen Sozialversicherungsträger* – hereinafter referred to as “**Association**”) as their umbrella organisation. The present Austrian government has announced a reduction of the 21 institutions to approximately five, but there is quite some uncertainty that this fundamental reform will indeed be implemented.

Healthcare is based on a social insurance model that guarantees all inhabitants equitable access to high-quality health services – irrespective of their age, sex, origin, social status or income.

Patients have four different levels of healthcare providers at their disposal: (i) Physicians (general practitioners and specialists), dispensing or non-dispensing as well as primary care centres; (ii) hospitals and out-patient wards; (iii) pharmacies; and (iv) other medical/therapeutic services.

The Austrian healthcare system is characterised by a high density of easily accessible healthcare facilities. In 2011, a total of 273 hospitals with about 64,000 beds were available for in-patient care. At that point in time about 23,000 physicians and more than 85,000 other healthcare professionals were employed in hospitals. About 80% of the 85,000 other healthcare professionals worked in nursing care.

### **Competition**

With 823 companies active in biotechnology, pharma or the medical device business, Life Sciences are an important and constantly growing part of Austria’s economy. The Life Sciences industry in Austria is fully diversified and Life Sciences are an important pillar in the Austrian economy.

The strong economic development of the Life Sciences sector is also supported by a

dense network of internationally renowned research and teaching expertise. A total of 55 institutions are fully dedicated to Life Sciences research and have significant activities in this field. Besides high-quality research, the academic institutions also provide the sector with well-trained people, representing a strong pillar in the country's educational system. In 2014, the total number of Life Sciences students at universities and universities of applied science accounted to more than 59,000.

The top 20 largest Pharma companies in Austria especially focus on cancer and immune medicines to increase turnover. These segments generated EUR 94.1 billion in 2014. The second-largest cash cow for the industry – however, with decreasing importance – are medicinal products for cardiovascular diseases and metabolic diseases. However, the largest jump in turnover was recorded by those companies that sell medicinal products against infectious diseases.

### **Access to the Market**

Pharmaceutical wholesale is regulated by law in Austria such that public pharmacies as well as hospital pharmacies may receive their pharmaceutical products directly from the manufacturer or wholesaler. In practice, the market is shared by manufacturers and wholesalers. Wholesalers supply pharmaceuticals to public pharmacies and to self-dispensing physicians, whereas hospitals receive their pharmaceutical products directly from the manufacturer.

Almost 70% of the total revenue made through pharmaceutical products are distributed via wholesalers, of which, 83% are distributed to public pharmacies, 12% to self-dispensing physicians and 5% to hospitals.

Medicinal products are sold to end-consumers through public pharmacies, hospital pharmacies and physicians with an in-house pharmacy. Self-service dispensing and supplying of over the counter medications through mail order or online-shopping is only permitted for pharmacies.

Once a product has been approved for sale in Austria, in most cases it will require approval for reimbursement from the national health insurance in order to be economically viable.

Under the Austrian Medicinal Products Act (*Arzneimittelgesetz*), the manufacturer must prove that the claimed benefits of a new product outweigh its anticipated side effects. To this end, the manufacturer must present analytical and preclinical data, as well as the results of clinical trials. The Federal Institute of Medicines then verifies whether or not the proof regarding the quality, safety, and efficacy of the product meet the requirements stipulated under the Medicines Austrian Medicinal Products Act. Pharmacoeconomic studies are not required for marketing authorisation.

The registration process for pharmaceuticals is complicated due to restrictions on OTC distribution. First, a determination will be made if a product is a medicinal product that requires prescription is an OTC drug, or a nutritional supplement (according to predetermined criteria). While medicinal products must be sold in pharmacies, nutritional supplements can be sold at supermarkets and online.

In Austria, there are three basic forms of registration for medicinal products:

**Mutual Recognition Procedure:** The MRP is the procedure of choice for holders of national marketing authorisations in one EU Member State, who plan on entering the market of other EU Member States as well. After national authorisation in one EU Member State, the authorisation holder applies for recognition of the national authorisation by other EU Member States of his choice.



Decentralised procedure: In a DCP, there is no existing authorisation of the medicine in any EU Member State. Seeking authorisation in several EU Member States, the respective applications are simultaneously submitted.

National Marketing Authorisation: Application for marketing authorisation of a medicinal product intending an exclusive marketing in that particular country.

### **Promotional Activities**

The Austrian Medicinal Products Act provides the legal regime for the marketing of medicinal products. It includes activities such as dispensing of samples to physicians, promotional events, sponsorship, hospitality and reimbursement of travel expenses. Different rules apply depending on whether the advertising is directed at consumers or professionals.

Generally, where advertising is allowed, it is only permitted for medicinal products that are:

- Authorised or registered in Austria.
- Approved for parallel import.
- Prepared by a pharmacy according to the instructions of a qualified physician or dentist.

Advertising for medicinal products that do not have a marketing authorisation in Austria is not permitted, except at a scientific event where the participants are mainly from outside Austria.

Further guidelines for marketing of medicinal products are contained in the Code of Conduct of the Association of the Austrian Pharmaceutical Industry (Pharmig). The Pharmig Code of Conduct is, however, only binding for members of Pharmig, which include all major pharmaceutical companies in Austria.

### **Challenges**

There are three main drivers in Austria's healthcare market: 1) the desire on the part of public healthcare payers to rein in spending without losing quality of care means that reducing spending and improving efficiency are increasingly important; 2) a high level of innovation in the sector, accompanied by increasing patient and physician awareness about options; and 3) an ageing population.

A fundamental issue in the Austrian healthcare system is the split in competencies at the federal and state level, which is outlined in the constitution. This fragmentation makes intergovernmental negotiations necessary. As a result, the system has often been referred to as both complex and fragmented.

## **Pharmaceutical Pricing and Reimbursement**

### Regulatory classification

*How are pharmaceutical products regulated?*

In Austria, there are legal provisions requiring a marketing authorisation (registration) for all pharmaceutical products on the market. Explicit and publicly available criteria exist for assessing applications for marketing authorisation of pharmaceutical products.

Authorisation of medicines on the basis of the Austrian Medicinal Products Act is one of the main duties of the Austrian Federal Office for Safety in HealthCare/Austrian Medicines and Medical Devices Agency.

The Advisory Board on Classification (*Abgrenzungsbeirat – AGBR*) is a commission set up by the *BMASGK*. Acting only by order of the *BMASGK* or the *BASG*, it prepares expert reports in connection with queries concerning the legal differentiation between medicinal products and other products.

Set up according to sec. 60 Austrian Medicinal Products Act, the so-called “*Abgrenzungskommission*” advises on distribution rights of medicines, which are only to be distributed in pharmacies, or in drugstores.

*What pharmaceutical products are eligible/ineligible for reimbursement?*

The Association is responsible for deciding whether a medicine should be reimbursed or not. Eligibility criteria for reimbursement are based on pharmacological evaluation, medical-therapeutic evaluation and health-economic evaluation. Only products listed in the so-called Reimbursement Code (which is a positive list) (*Erstattungskodex*) are reimbursed by the national health insurance system.

The Reimbursement Code has four different boxes: red; dark yellow; light yellow; and green. Reimbursement of a product listed in the red or dark yellow box is generally subject to approval by a chief consulting physician employed by the Association. For certain products, a documentation system applies, these are listed in the light yellow box.

Red box: Each product for which an application to be listed in the Reimbursement Code is filed is automatically included in the red box. The Association must decide whether the medicinal product can remain in the Reimbursement Code within 180 days, in general, in exceptions within 90 days of the application being filed. If the Association has not established an Average European Price (“AEP”), the price proposed by the applicant is the relevant reimbursement price. However, if the AEP is lower than the proposed price, the difference between the AEP and the proposed price must be refunded by the applicant.

Yellow box in general: All products with a significant additional therapeutic value – that can, however, not be included in the green box due to medical or economic reasons – are included in the yellow box. All products in the yellow box are reimbursed up to the AEP. The Association must decide whether the product is to be included and at what price, within 180 days of receipt of the complete application, taking into account the recommendation of the Medicines Evaluation Commission (*Heilmittel-Evaluierungskommission* – hereinafter referred to as “**Commission**”) as to whether the product should be reimbursed. The Commission must specifically discuss for which indication(s) and for which group of patients a significant additional therapeutic value is given, and how this can be assessed economically. Such assessment may also lead to the product only being reimbursed for a certain indication and/or group of patients.

Light yellow box products: In the light yellow box are products the Association has decided need not be approved by a chief consulting physician, but can be dealt with by way of a documentation system. Under the documentation system, the medicinal product must satisfy various economic criteria to be reimbursed.

Green box: For a product to be included in a green box, its prescription by a physician must be medically and economically justified. If products with a similar therapeutic use are already listed, the new medicinal product is only reimbursed if there is sufficient price difference when compared to products that are already included. Products with additional therapeutic value can be reimbursed at a higher price.

Furthermore, the Reimbursement Code also contains the list of substances for a pharmacist’s preparations which may only be dispensed upon prior presentation of the medical approval by a chief consultant physician. All other medicinal products not included in the Code of Reimbursement are only reimbursed in justified cases and upon presentation of the medical approval by a chief consulting physician.

Finally, the Association has to issue a list of substances that, in general, cannot be reimbursed.

This negative list, however, practically is of minor importance, because, as an exception to the rule the chief consulting physician can approve the prescription, irrespective of such list. Medicines are either fully reimbursed or not reimbursed at all (there are neither percentage reimbursement rates nor percentage co-payment rates).

### Who is/Who are the payer(s)?

Social insurance is the most important source of healthcare funding, contributing about 45% of current health expenditure. Whereas out-patient care is almost entirely financed by social health insurance funds, expenditure for in-patient care is shared between the public sector and social insurance. Long-term care services are mostly funded through taxes.

Prescribed drugs which are reimbursed are almost entirely financed by social health insurance funds. If drugs are prescribed in hospital, it will be financed from taxes. However, if medicines are reimbursed, patients have to pay a fixed prescription fee out-of-pocket amounting to EUR 6.00 (2018) per item on the prescription. Since January 2008 the spending of prescription fees has been capped statutorily, i.e. all beneficiaries spend a maximum 2% of their net annual (family) income on medicines. Vulnerable groups (e.g. low income pensioners, people suffering from communicable diseases) are completely exempt from the prescription fee.

The social insurance carriers are mainly financed by contribution systems. These systems are governed by different laws and therefore may result in varying contribution bases and rates across insurance funds. Ultimately this leads to different levels of self-funding of the insured persons, as well as different ratios between individual's contributions and funds provided by federal tax.

Social insurance is the most important source of healthcare funding, contributing around EUR 13.8 billion in 2011, which corresponds to about 45% of current health expenditure. Whereas out-patient care is almost entirely financed by social health insurance funds, expenditure for in-patient care is shared between the public sector and social insurance. Long-term care services are mostly funded through taxes.

OTC products are not subject to prescription and are therefore not included in the Reimbursement Code. They have to be financed by the patients themselves.

### What is the process for securing reimbursement for a new medicinal product?

The decision over the inclusion of drugs into the Reimbursement Code is, as stated above, reserved for the Association, which supports its decision on the recommendations of the Medicines Evaluation Commission. Application to have a product included in the Reimbursement Code must be made to the Association by the market authorisation holder. Within 14 days of receipt of the application, the Association must undertake to examine that it is complete and complies with all formalities, and a formal decision giving reasons must be given within 180 days (for pricing and reimbursement) from the date it receives the application.

The following decision criteria are applied for the assessment of the reimbursement status:

- pharmacological analysis (comparison with therapeutic alternatives and perceived degree of innovation);
- medical-therapeutic evaluation (target patient group, effectiveness, expected duration and treatment frequency); and
- economic considerations (this includes budget impact and PE evidence).

On the basis of the first two criteria (pharmacological analysis and medical-therapeutic evaluation), the Association decides with which therapeutic alternatives, if any, the medicinal

product applying for reimbursement shall be compared to economically and if the medicinal product is innovative in some way (i.e. it has an additional therapeutic value). Therapeutic alternatives are medicinal products already listed in the Reimbursement Code for use in the same indication, whereby only indications covered by the marketing authorisation may be taken into consideration.

In the case of a negative decision, the manufacturer has recourse to appeal to the Federal Administrative Court. There is a legal obligation that the Federal Administrative Court has to decide within six months.

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

The Association bases its economical assessment on the pharmacological analysis and medical-therapeutic evaluation which determines with which therapeutic alternatives, if any, the medicinal product applying for reimbursement shall be compared to economically therapeutic alternatives are medicinal products already listed in the Reimbursement Code for use in the same indication, whereby only indications covered by the marketing authorisation may be taken into consideration.

Basically, a new medicinal product, provided that products with a similar therapeutic use are already listed, is only reimbursed if there is sufficient price difference when compared to products that are already included. Products with additional therapeutic value can be reimbursed at a higher price. The economic considerations are carried out in three steps:

- the Association compares the price of the medicinal product applying for reimbursement to the price of the therapeutic alternatives;
- thereafter the cost-benefit analysis, which consists of the comparison of the new medicinal product with medicinal products already listed, plus a mark-up or deduction depending on additional therapeutic value; and
- finally, for the red and the yellow boxes the price may not exceed the AEP; in the green box the price must be below the AEP.

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

All prices and margins in the pharmaceutical distribution chain are subject to public control by authorities/social insurance. The Price Act constitutes the overall framework for pricing in Austria.

Pricing decisions on medicinal products are taken by the BMASGK which is advised by the Pricing Committee (PK). Furthermore, there is a price notification agreement in place between the Federal Chamber of Labour (*Bundesarbeiterkammer*) and the Federal Chamber of Commerce (*Wirtschaftskammer*).

In general, non reimbursable medicinal products fall under the price notification system (at the ex-factory level) and medicinal products applying for reimbursement fall under the statutory price system where BMASGK – advised by the PK – sets the EU average price.

Prices for medicinal products included in the Reimbursement Code (*Erstattungskodex*, “EKO”) are often negotiated with the HVB, in principle, granting the HVB further rebates for reimbursed medicinal products. Furthermore, regressive mark-up schemes for wholesalers as well as pharmaceutical companies are applicable for all pharmaceuticals.

Internal and external price referencing plays an important role for reimbursement:

The holder of the marketing authorisation applying for the inclusion of the medicinal product in the EKO has to provide information on whether the medicinal product is on the market in other EU Member States and if so has to submit the manufacturer price and wholesale price of the medicinal product in each of these markets (external reference pricing). The

Austrian Health Institute (*Österreichisches Bundesinstitut im Gesundheitswesen, ÖBIG*) is responsible for checking the prices submitted by the industry; the EU average price is then calculated by the PK and set by the BMASGK. A price can only be set if the product is marketed in at least half of the EU25. If this is not the case, the PK will re-evaluate pricing data every six months. If a price cannot be set at the second re-evaluation, an average EU ex-factory price is calculated based on available EU pricing data. Until a final price can be set, the ex-factory price submitted by the manufacturer is temporarily applied for reimbursement purposes. If this price is subsequently found to be above the EU average, the manufacturer has to pay back the difference to the Association.

Once the ex-factory price has been established products are placed into the red box of the reimbursement code, where the permitted maximum price is the EU average price. Once medicinal products are moved into the green box, prices must be below the EU average price. If medicinal products are placed in the yellow box, manufacturers may charge a price above the EU average price.

The price notification system is in place for all medicinal products not seeking reimbursement. The PK within the BMASGK is responsible for verifying the ex-factory price notified by the manufacturer. If the BMASGK does not oppose this price within six weeks the price automatically takes effect. If the price is deemed too high, the BMASGK has the option to assign a price, a very rare practice.

Generics generally follow the same pricing procedure. However, the first generic must be priced at least 50% below the off patent original. The second generic must be priced 15% below the first. The third must be priced 10% below the price of the second generic. Once a generic is reimbursed the off patent drug price must be cut by at least 30% within three months.

Biosimilars also follow this pricing procedure. The first biosimilar must be priced at least 38% below the original. The second biosimilar must be priced 15% below the first. The third must be priced 10% below the price of the second biosimilar. Once a biosimilar is reimbursed the price of the original must be cut by at least 30% within three months.

Ex-factory prices for hospital-only drugs are determined by the BMASGK and such prices are the maximum at which the product may be sold. In practice, hospitals negotiate prices directly with manufacturers usually at a large discount. Many regions have established purchasing committees to buy hospital drugs via tender systems or negotiations with manufacturers.

### Issues that affect pricing

Only recently (April 2017), Austria switched to an External Price Referencing (“EPR”) system. The introduction of an EPR system was driven by the desire to limit pharmaceutical expenditure.

Thus, pricing of medicinal products in Austria is strongly affected by pricing in other EU-countries as well as ongoing austerity measures that generally lead to pressure from the payers to reduce prices in order to be reimbursed or remain in reimbursement by way of reduction of the published price, but also by way of negotiated substantial kick-backs. Further, market entry of one or more generics or biosimilars leads to significant mandatory price-cuts.

On a positive note, the Association, as the payer for medicinal products in Austria, does not consider off-label uses for reimbursement (as in other EU countries) and previous attempts to regulate mandatory substitution have been abandoned, although Health Care

Professionals (HCPs) are required to prescribe the cheapest, but best medicinal product for the individual patient.

## **Policy Issues That Affect Pricing and Reimbursement**

### **Population Growth**

Statistics Austria forecasts strong population growth until 2060 and a further shift in the age structure towards higher ages. Since 1995, life expectancy for men has risen by 22% and that of women by 19%. This equates to an additional 13 years. According to the forecast, Austria is set to have a population of 9.4 million in 2030.

In 2015, persons aged over 65 made up 18% of the total population. According to the forecasts of Statistics Austria, this share is expected to rise to 19% by 2025 vs. 2015.

As a consequence of the growing share of elderly people, the percentage of those in need of long-term care has increased. This is also reflected in the number of persons receiving long-term care benefits.

### **Growth in Chronic Diseases**

Due to the growth in population and increasing life expectancy, the WHO predicts a further rise in new cancer cases. In Austria, 330,492 people were living with cancer in 2014 – 38,908 people were documented with new cancer cases. This marks a clear increase, compared to 2002 (213,620 people suffering from cancer), which can be attributed to the interaction of the following factors: demographic ageing; a general rise in life expectancy; and the improved survival chances of afflicted persons. The mortality rate has also decreased significantly: compared to 1990, cancer mortality in Austria sank by 22%. The OECD average shows a decline of 15%.

In comparison with other European countries, Austria is among the Top 5 countries with regard to five-year cancer survival rates. With regard to three common types of cancer Austria comes top in Europe, namely: lung cancer; prostate cancer; and renal cell carcinoma.

Patients are able to take part in clinical trials early on and therefore gain access to innovative active substances which increase the chances of curing the disease. About a third of all clinical trials are conducted in the field of oncology. Therefore, oncology is the field which is most intensively researched in the Austrian pharmaceutical industry.

This means that on frequent occasion cancer patients have access to medication with innovative active substances from an early stage.

### **Research and Development**

According to the “Innovation Union Scoreboard 2016” (“IUS”) which has been published by the European Commission, Austria is among the group of “Innovation Followers”, its research quota of 3.07% is higher than the EU-28 average of 2.03%. However, the strategy for research, technology and innovation of the Federal government aims at establishing Austria as an “Innovation Leader” which would require an increase in the research quota to 3.76% until 2020. Further efforts will be necessary to achieve this aim.

The greatest part of research expenditures (at an amount of EUR 10.7 billion) within the last 10 years were incurred by companies, taking up 47.1% on average; on average 36.2% of spending was provided by the public sector and 16.7% from abroad.

In addition to excellent universities, Austria has outstanding and internationally recognised research institutes in the field of Life Sciences, such as the Research Institute for Molecular Pathology (“IMP”), the Institute for Molecular Biotechnology (“IMBA”), or the Research Center for Molecular Medicine (“CEMM”). Since 2008, Europe’s first “Research Center

Pharmaceutical Engineering” (“**RCPE**”) has been located in Graz, whose aim is to optimise product and process development in the pharmaceutical industry. Austria is also the location of the European biobanks research infrastructure which is aimed at connecting existing and future biobanks in Europe in order to facilitate access to biological samples for research.

### **Cost of Healthcare**

In 2015, health expenditures in Austria amounted to some EUR 37.6 billion, which corresponds to a share in GDP of 11.1%.

The largest proportion of 38.4% was spent on in-patient care. At the same time, expenditure on out-patient care made up 25.5% and expenditure on medicinal product 12.4%. Expenditures on medical products include consumption in pharmacies and hospitals including VAT.

When broken down into public and private expenditure on healthcare, nearly three quarters of the expenses are financed by public funds. In the period between 2010 and 2015, expenditure on healthcare rose on average by 3% each year.

Austria accounts for around 3% of the European medical technology market, similar in size to the Netherlands, Sweden and Belgium, with annual spending at just under \$3 billion. Recent growth has been less than the usual 5% longtime average due to austerity measures following the financial crisis in Europe, but there is expectation to return to a normal trajectory in the coming years.

Pharmaceuticals account for around 12% of Austria’s total healthcare spending, around \$6 billion/year or \$550 *per capita*. That is toward the high end of EU *per capita* spending.

### **Emerging Trends**

Innovative therapies that are currently introduced to the market are of a different order than many new medicinal products that were introduced over the past few decades. Increasingly often, new medicines are complex but successful, or for a small number of critically ill people.

However, the disadvantage is that these medicinal products are often expensive. Thus, many of the EU countries, including Austria, believe that the emergence of these medicinal products threaten the affordability of care, and will detract from the care for other patients. In addition, also, timely access of patients to medicines is often hampered due to the current pharmaceutical system, in which the position of national governments is under pressure. This is partly caused by the variety in national policies on pricing, reimbursement and on the use of medicinal products. At the same time, increasing pressure is put on the capabilities of individual authorities.

Thus, the Austrian authorities believe that in order to change these developments, cooperation is essential. BeNeLuxA is a first collaborative step. The BeNeLuxA Initiative aims for sustainable access to, and appropriate use of, medicinal products in the participating countries. In order to achieve this BeNeLuxA is:

- anticipating national health challenges by having early insight in new pharmaceutical products and in new indications of existing products coming to the market (i.e. Horizon Scanning);
- increasing the efficiency of the assessment, pricing and reimbursement of medicines by exchanging expertise and by mutual recognition of Health Technology Assessments;
- sharing policy expertise and best practices;
- improving the payers’ position in the market;

- improving knowledge on products, usage and markets;
- executing joint (price) negotiations for specific products; and
- improving transparency on pricing between the collaborating countries.

### **Successful Market Access**

Successful Market Access in Austria is highly dependent on a positive outcome of reimbursement proceedings. Thus, a sound medical, price and legal strategy for reimbursement proceedings is essential, also taking into account that further price negotiations on kick-backs will be necessary.

The above is, however, not the case, where the medicinal product is so innovative that a strategic decision is made not to initiate reimbursement proceedings, but rather rely on case-by-case prescriptions and pricing on the basis of official pricing in other EU Member States. In this case, Successful Market Access will be driven by convincing key opinion leaders of the innovative nature and the patient benefits of the medicinal product.



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# Belgium

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## Abstract

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

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

In Belgium, approximately 75% of all healthcare expenses are covered by the compulsory health insurance. However, health expenditures are increasing fast (with an expected annual growth rate of 2.7%) and are forecasted to reach EUR 49.19 billion in 2021, causing pressure on the health budget. The Belgian government is also pressured by the European Commission to make budget savings in order to meet its fiscal deficit target.<sup>1</sup> Cost-containment measures are therefore essential to keep the 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, comprised of 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 of the health insurance (the sickness funds, the representatives of persons active in the healthcare sector (for example, the 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.<sup>2</sup>

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.<sup>3</sup>

In addition to the compulsory health insurance, individuals can 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 the compulsory health insurance.<sup>4</sup>

## **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.<sup>5</sup> 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.<sup>6</sup>

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.<sup>7</sup> 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.<sup>8</sup> Just like generics, biosimilars are granted marketing authorisation via an abbreviated procedure to avoid repeating costly and unnecessary trials.<sup>9</sup>

However, given the complexity of biologicals, more studies are needed to obtain marketing authorisation for biosimilars than for generics to ensure that minor differences do not affect safety or efficacy.<sup>10</sup>

### ***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. 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.<sup>11</sup>

### ***Reimbursable vs. non-reimbursable medicinal products***

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

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 the non-prescription medicinal products (or OTC medicinal products).

### **Who is/Who 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 has been capped by law.<sup>13</sup> It should be noted that the patient contribution for pharmaceutical specialties delivered to a pharmacy (a public *officina*) and to a hospital differ; the amount of the patient contribution is higher if the products are delivered to a public *officina*.

By way of example, if the medicinal product is included in reimbursement category A, which covers the 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**”);
- the Royal Decree of 21 December 2001 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 of 2001**”); 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**”).

On 15 March 2018, the new RD Reimbursement has been published in the Belgian State Gazette. The RD Reimbursement repeals the RD Reimbursement of 2001 and applies to all reimbursement applications submitted as from 1 April 2018.<sup>14</sup> For applications submitted prior to 1 April 2018, the procedures and timelines included in the text of the RD Reimbursement 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.

The Belgian legislator has opted to work with a positive reimbursement list in accordance with Article 6 of the Transparency Directive.<sup>15</sup> This entails that the health insurance shall only reimburse the 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 Commission for Reimbursement of Medicinal Products (the “**CRM**”) (*Commissie Tegemoetkoming van Geneesmiddelen (CTG)/Commission de remboursement des médicaments (CRM)*) within the NIHDI.<sup>16</sup> The final reimbursement decision will be taken by the Minister of Social Affairs and Public Health on the advice of the CRM.<sup>17</sup> The reimbursement application must be submitted simultaneously with the separate pricing application.<sup>18</sup> 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).<sup>19</sup>

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.<sup>20</sup>

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):<sup>21</sup>

- 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.<sup>22</sup> 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.<sup>23</sup> As for medicinal products ranked in sub-classes 2C, 3B or 3C, the procedure may not take more than 90 calendar days.<sup>24</sup> For all other medicinal products, the standard period of 180 calendar days will apply.<sup>25</sup> It is to be noted that the RD Reimbursement includes specific procedures with respect to parallel imported medicinal products, orphan medicinal products and biosimilars.<sup>26</sup>

Moreover, depending on the (sub-)class in which the medicinal product is ranked, the CRM will use 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.<sup>27</sup>

The CRM's reimbursement proposal does not only set 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)<sup>28</sup> and the reimbursement basis (see below under section "How is the reimbursement amount set? What methodology is used?", "Pharmaceutical Pricing and Reimbursement").<sup>29</sup>

The Minister makes the final reimbursement decision on the basis of the reimbursement proposal made by the CRM and after having obtained the approval of the Minister of Budget. The Minister is allowed to deviate from the CRM's proposal, but only for social and/or budgetary reasons.<sup>30</sup> 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.<sup>31</sup> 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.<sup>32</sup>

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.<sup>33</sup>

#### 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).<sup>34</sup> The reimbursement categories indicate to which extent the medicinal product will be reimbursed by the health insurance and which 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/who are the payors", "Pharmaceutical Pricing and Reimbursement", the patient contribution is determined and limited by law.

Category A and Fa include the 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 for up to 15% of public expenditure on medicinal products. Category B and Fb cover the 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 up to 75%–85% of the reimbursement base. Medicinal products intended for symptomatic treatment are ranked in category C, which corresponds with a general reimbursement rate of 50%. Category Cs covers, for example, the influenza vaccine providing a general reimbursement rate of 40%. Category Cx includes the 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”.<sup>35</sup>

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”).<sup>36</sup> 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 maximum public price of the original product. Following the opening of a reference cluster, the reimbursement basis of the original product will automatically be reduced with a certain percentage. In principle, a reduction of 43.64% will occur. For medicinal products ranked in reimbursement category A, a reduction of 51.52% will occur. It should be noted that there are exceptions to the aforementioned percentages, for example, for injectable medicinal products a reduction rate of 23.37% and 27.82% (if the medicinal product is ranked under reimbursement category A) will apply. This reduction rate shall be applied on the ex-factory price. A lower reimbursement basis entails a lower contribution by the health insurance which means that the original medicinal product shall 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 maximum public price of the original medicinal product to the level of the new reimbursement basis increased with a safety margin of 25% of the new reimbursement basis; the safety margin may, however, never exceed EUR 5.00; or
- (ii) decrease the maximum public price of the original medicinal product to a level, higher than the new reimbursement basis, but lower than the maximum public price calculated under (i); or
- (iii) decrease the maximum public price to the level of the new reimbursement basis; or
- (iv) remove the medicinal product from the list.

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

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.<sup>38</sup> Price determination and price increases are a competence of the Minister of Economic Affairs, who determines the maximum ex-factory price on the advice of the Price Department.<sup>39</sup> 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).<sup>40</sup> 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.<sup>41</sup> 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.<sup>42</sup> The applicant can 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 would decide 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.<sup>43</sup> A specific procedure applies for increasing the ex-factory price; this procedure is similar to the procedure for obtaining the initial ex-factory price.<sup>44</sup>

The ex-factory price forms part of the maximum price charged to the patients, which is referred to as the “maximum public price”. The maximum public price shall, on the request



of the applicant, be calculated by the Price Department and communicated to the applicant.<sup>45</sup> 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%).<sup>46</sup> The aforementioned pre-defined profit margins for wholesalers and pharmacists will always be maximum margins,<sup>47</sup> 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.<sup>48</sup> 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 pressured by the European Commission to make budget savings in order to meet its fiscal deficit target. However, the expenditures on medicinal products are increasing fast, resulting in a high pressure on the health budget. In order to keep the expenditures within a reasonable boundary, several cost-containment measures have been or are being taken.<sup>49</sup>

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 the expenditures 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 needs of budget control.<sup>50</sup>

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”<sup>51</sup> 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.<sup>52</sup> 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. This new regime allows the health insurance to save EUR 38 million annually and to invest this amount in the reimbursement of innovative medicinal products.<sup>53</sup>

### Emerging Trends

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

First of all, there is an increased use of managed entry agreements. These agreements are often concluded for medicinal products whose therapeutic added value, impact on the healthcare expenditures and cost-effectiveness is still uncertain but for which patient access is preferred. Through these agreements, the payor tries to manage and monitor said uncertainties and the risks in relation thereto. In this respect, the product obtains a temporary reimbursement status for a period of minimum one and maximum three years, with the possibility of renewal.<sup>54</sup> 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.<sup>55</sup> 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 have come under fire when the Federal Knowledge Center (the “KCE”) published a report in which these agreements were evaluated.<sup>56</sup> The KCE states that these agreements are often used to negotiate price discounts and that the additional evidence gathered – which is often a condition under the agreement – is rather poor. However, once the product is reimbursed through a managed entry agreement, it will be difficult for the Minister to come back on his/her decision; this does not encourage pharmaceutical companies to meet the condition of gathering additional evidence. Further issues include the lack of transparency given that the specific terms and details of these agreements are not publicly available. In its report, the KCE stresses that the conclusion of these agreements should stay exceptional and be limited to situations where they are clearly beneficial for the patients.

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

Another 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, that 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.

### 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 is 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-on 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-on interactions with the stakeholders, is the ultimate key to increase the likelihood of success.

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### Endnotes

1. Belgium Pharmaceuticals & Healthcare Report Q4 2017.
2. <https://socialsecurity.belgium.be/nl/netwerk/rijksinstituut-voor-ziekte-en-invaliditeitsverzekering-riziv>.
3. KCE Report 138 – “The Belgian health system in 2010” ([https://kce.fgov.be/sites/default/files/atoms/files/KCE\\_138C\\_The\\_belgian\\_health\\_system\\_second\\_print.pdf](https://kce.fgov.be/sites/default/files/atoms/files/KCE_138C_The_belgian_health_system_second_print.pdf)).
4. <http://www.coopami.org/fr/coopami/realisation/2017/pdf/2017051103.pdf>.
5. EMA – procedural advice for users of the centralised procedure for generic/hybrid applications ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004018.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004018.pdf)).
6. Article 6bis 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](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf)).
8. EMA – Biosimilars in the EU: Information guide for healthcare professionals ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Leaflet/2017/05/WC500226648.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf)).
9. Article 6bis of the Medicines Act.

10. EMA – Biosimilars in the EU: Information guide for healthcare professionals ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Leaflet/2017/05/WC500226648.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf)).
11. Article 6, §1*bis* of the Medicines Act.
12. <https://economie.fgov.be/nl/themas/verkoop/prijsbeleid/gereguleerde-prijzen/geneesmiddelen-voor-menselijk>.
13. Article 2 of the Royal Decree of 7 May 1991 on the establishment of the patient contribution.
14. Note that Article 9, 2<sup>nd</sup> paragraph of the RD Reimbursement shall enter into force as from 1 January 2019.
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, 3<sup>rd</sup> paragraph of the RD Reimbursement.
20. Article 35*bis*, §2 of the NIHDI Act; Article 4 of the RD Reimbursement.
21. Article 35*bis*, §2 of the NIHDI Act; Article 5 of the RD Reimbursement.
22. Procedure class 1 medicinal products: see Articles 16–22 of the RD Reimbursement; Procedure class 2B medicinal products: see Articles 23–29 of the RD Reimbursement; Procedure class 2C medicinal products: see Articles 30–36 of the RD Reimbursement; Procedure class 3B and 3C medicinal products: see Articles 37–42 of the RD Reimbursement; Procedure class 2A and 3A medicinal products: see Articles 50–54 of the RD Reimbursement.
23. Article 15, §1, 1<sup>st</sup> paragraph of the RD Reimbursement.
24. Article 15, §1, 2<sup>nd</sup> paragraph of the RD Reimbursement.
25. Article 15, §1, 3<sup>rd</sup> paragraph of the RD Reimbursement.
26. Procedure parallel imported medicinal products: see Articles 43–49 of the RD Reimbursement; procedure orphan medicinal products: see Article 55 of the RD Reimbursement; procedure biosimilars: see Articles 56–58 of the RD Reimbursement.
27. Article 6 of the RD Reimbursement.
28. Note that medicinal products with similar reimbursement conditions are included in the same reimbursement group. For example, cardiovascular medicinal products are included in reimbursement group I. Some medicinal products reimbursement shall only be reimbursed upon certain conditions. These conditions can, for example, relate to the need for diagnostic examination, the maximum dosage, the age of the patients, etc.
29. Articles 20, 27, 34 and 40 of the RD Reimbursement.
30. Articles 20, 27, 34 and 40 of the RD Reimbursement.
31. Articles 3, §1 of the RD Reimbursement; see <http://www.riziv.fgov.be>.
32. Articles 22, 29, 36, 42 and 54 of the RD Reimbursement.
33. Articles 59–89 of the RD Reimbursement.
34. Article 2, §1 of the Royal Decree of 7 May 1991 on the establishment of the patient contribution.

35. Article 2, §1 of the Royal Decree of 7 May 1991 on the establishment of the patient contribution; Belgium Pharmaceuticals & Healthcare Report Q4 2017.
36. Article 35*bis*, §2*bis* of the NIHDI Act.
37. Article 35*ter* of the NIHDI Act.
38. Article 3, §1 of the RD Pricing.
39. Article V.10, §1 of the Code of Economic Law.
40. Article 3, §2 of the RD Pricing.
41. As specified in the RD Pricing.
42. Article 3, §6 of the RD Pricing.
43. Article 3, §9 and §10 of the RD Pricing.
44. Article 4 of the RD Pricing.
45. Article 3, §7 of the RD Pricing.
46. Article 35*octies* of the NIHDI Act.
47. As specified in the MD Pricing.
48. [http://ec.europa.eu/competition/sectors/pharmaceuticals/antitrust\\_en.html](http://ec.europa.eu/competition/sectors/pharmaceuticals/antitrust_en.html).
49. Belgium Pharmaceuticals & Healthcare Report Q4 2017.
50. Articles 73 and 146*bis* of the NIHDI Act.
51. For the qualification of “least costly” see Article 73, §2 of the NIHDI Act.
52. Article 35*quater*/1 of the NIHDI Act.
53. <http://www.deblock.belgium.be/nl/de-tijd-duur-medicijn-niet-altijd-meer-terugbetaald>.
54. Article 116 of the RD Reimbursement.
55. KCE Report 288 – “How to improve the Belgian process for managed entry agreements? an analysis of the Belgian and international experience” ([https://kce.fgov.be/sites/default/files/atoms/files/KCE\\_288\\_Improve\\_Belgian\\_process\\_managed\\_entry\\_agreements\\_Report.pdf](https://kce.fgov.be/sites/default/files/atoms/files/KCE_288_Improve_Belgian_process_managed_entry_agreements_Report.pdf)).
56. KCE Report 288 – “How to improve the Belgian process for managed entry agreements? an analysis of the Belgian and international experience” ([https://kce.fgov.be/sites/default/files/atoms/files/KCE\\_288\\_Improve\\_Belgian\\_process\\_managed\\_entry\\_agreements\\_Report.pdf](https://kce.fgov.be/sites/default/files/atoms/files/KCE_288_Improve_Belgian_process_managed_entry_agreements_Report.pdf)).

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

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

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Julie De Keukeleire is a corporate lawyer with a main focus on the life sciences sector. Julie has a background in M&A transactions and intellectual property law and provides transactional and regulatory support to clients active in the pharmaceutical and medical devices sector. Her main areas of expertise comprise transactional and regulatory assistance throughout the entire product lifecycle, from negotiating and drafting contracts, coordination of international R&D collaborations (H2020, IMI2), through clinical phases, marketing authorisations, advertising and promotion, pricing and reimbursement and interactions with healthcare professionals and healthcare organisations.

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# Brazil

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## General Considerations

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

Regarding 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 the 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 with drugs that are at least 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:<sup>1</sup>

*“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.”<sup>2</sup>*

The marketing approval, issued by ANVISA, is the effective authorisation for the 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*<sup>3</sup> is defined as the “innovative product registered with the federal authority responsible for the health surveillance and marketed in the Country, whose efficacy, safety and quality were scientifically proven before the pertinent federal authority, by the time of the registration”.

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

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

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”.<sup>5</sup> The similarity between the generic drug and reference drug is proven by pharmaceutical equivalence study results and relative bioavailability/bioequivalence study results.

*Pharmaceutical equivalents*<sup>6</sup> 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 it is 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 contain, or 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*<sup>7</sup> are those that prove to have equivalent bioavailability under the same experimental conditions.”<sup>8</sup>

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”).<sup>9</sup>

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.<sup>10</sup>

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.<sup>11</sup> Instead, the applicant must prove that its branded or non-branded generic drug is bioequivalent to the reference drug. If the applicant can prove bioequivalency, ANVISA will assume that the branded and/or non-branded generic drug is safe and effective by relying on the clinical data that was evaluated during the registration of the new drug.

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

#### Biological Products

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

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

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.<sup>13</sup>

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 the manufacture of the active ingredient(s), the bulk biological product, the biological product in its primary package, and the finished biological product; (3) the quality control tests conducted on the active ingredient, the bulk biological product, and the finished biological product batches; (4) the site where the respective quality control tests will be conducted; and (5) the product specifications.

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

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

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

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

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

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

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

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

#### Simplified Procedure for Marketing Approval

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

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

Under Article 15 of RDC 31/2014, the granting 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.<sup>14</sup> 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 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.<sup>15</sup> 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 it is 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).<sup>16</sup> 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 issue, 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.

## Pricing

According to Law No. 10,742/2003 and Article 1 of the Drug Market Regulation Chamber (CMED) Resolution 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 new products 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 a period of five years.

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

- Category III comprises new pharmaceutical presentation of a drug already marketed by the company itself in the same pharmaceutical form.
- Category IV comprises a new drug presentation that fits one of the following situations:
  - i) 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; and
  - 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; and
  - 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 drug in Brazil and the other brand names for the same drug, used in the countries mentioned in item VII of this paragraph and in the manufacturer's origin country;
- ii) drug approval number and EAN code, both comprised of 13 digits;
- iii) substances from which the drug is formulated;
- iv) copy of package leaflet;
- v) presentation form in which the drug will be marketed;
- vi) the price at which the company intends to market each presentation, with the discrimination of taxes and marketing margins;

- vii) manufacturer's price, accompanied by the due source proof, traded in Australia, Canada, France, Greece, Italy, New Zealand, Portugal, Spain and the United States of America and the manufacturer's price in the product's country of origin, excluding taxes;
- viii) manufacturer's name and the manufacturing site of the active ingredient and the finished drug;
- ix) potential number of patients to be treated with the drug, with the indication of the corresponding period;
- x) cost-efficacy comparative analysis between the drug and the existing therapeutic alternatives;
- xi) presentation of the following information on the product's patent: a) number of the first international patent application, date of application, and the country where it was 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 trial, in phase of approval, or approved in other countries, if any.

The Factory Price – FP proposed by the company shall not be higher than the lowest FP applied for the same product in the countries listed in item (vii), taxes being added, as appropriate. In order to check the FP authorised, the product must have been previously marketed in at least three of those countries. If such condition is not met, the Technical-Executive Committee of 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) brand name of drug in Brazil and the other brand names for the same drug, used in the countries mentioned in item VII of this paragraph and in the manufacturer's origin country;
- ii) drug approval number and EAN code, both comprised of 13 digits;
- iii) substances from which the drug is formulated;
- iv) copy of package leaflet;
- v) presentation form in which the drug will be marketed;

- vi) the price at which the company intends to market each presentation, with the discrimination of taxes and marketing margins;
- vii) manufacturer's price, accompanied by the due source proof, traded in Australia, Canada, France, Greece, Italy, New Zealand, Portugal, Spain and the United States of America and the manufacturer's price in the product's country of origin, excluding taxes;
- viii) manufacturer's name and the manufacturing site of the active ingredient and the finished drug;
- ix) phase III clinical trials conducted, which are relevant for 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 a reference for the price definition. If the gains are a result of the 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 III, IV and VI, the Informative Document to be submitted to the CMED shall contain the following information:

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

- ii) drug approval number and EAN code, both comprised of 13 digits;
- iii) substances from which the drug is formulated;
- iv) copy of package leaflet;
- v) presentation form in which the drug will be marketed; and
- vi) the price at which the company intends to market each presentation, with 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 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 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 19.27% off the FP, as per CMED Ordinance No. 06, of March 30, 2017, and it must be applied to products listed on Annex I of CMED Ordinance No. 15, of August 31, 2017.

### **Access to Drugs**

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

According to Article 196 of Federal Constitution, health is a right of all and a duty of the State. Therefore, in order to organise treatments and the supply of drugs through the Universal Healthcare System (“SUS”), it was published 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 evidences regarding efficacy, and safety of drugs, and (ii) economic evaluation of the drugs to be incorporated from the perspective of the public healthcare system.

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

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

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

For drugs not included in CONITEC’s CPRG 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.

Recently, on April 25, 2018, the Superior Court of Justice defined the requirements for the supply of drugs that are not part of the lists of SUS and stated that the drugs should be supplied to the patients as long as they present evidence regarding the following:

- i) existence of a well-founded medical report issued by the respective physician confirming the absolute necessity of the medication as well as the inefficacy of the drugs provided by SUS for the treatment of the disease;
- ii) financial incapacity of the patient to bear the costs of the prescribed drug; and
- iii) existence of registration of the drug before ANVISA.

Finally, reimbursement procedures, pay-for-performance/risk models are not applicable in Brazil.

\* \* \*

## 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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He is well familiarised with the challenges of the Life Sciences and Intellectual Property fields, always coming around with creative solutions and strategies, being the co-creator of Project Constellation®. He is the co-author of “Chapter 18 – Pharmaceutical Regulation and Litigation in Foreign Countries” in *ANDA Litigation: Strategies and Tactics for Pharmaceutical Patent Litigators*.

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# Canada

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## **Abstract**

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

## **Market Introduction/Overview**

Canada has a population of approximately 36 million and it was forecast by the Canadian Institute for Health Information that prescription drug spending in 2017 would be approximately \$34 billion. Approximately 40% of prescription drug spending is funded by public plans. Generic drugs account for approximately 80% of claims.

Healthcare in Canada is primarily, but not exclusively, publicly funded. Prescription drugs, in particular, are reimbursed both publicly and privately. As discussed further below, whether or not a drug is publicly reimbursed depends on (i) the patient, (ii) the drug, and (iii) the setting. Further, given the division of powers between the federal and provincial governments, eligibility for public reimbursement also varies from province to province.

## **Pharmaceutical Pricing and Reimbursement**

### Regulatory classification

#### *Market Authorisation*

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

Generic drugs are often approved by way of an Abbreviated New Drug Submission (ANDS) in which safety and efficacy of the generic drug is established by reference to an already-approved innovative product. Generic drugs also receive an NOC and DIN. When approved by way of an ANDS, the NOC also includes a declaration of equivalence to the reference product. Biosimilars are not eligible to be approved by way of ANDS in Canada and must be approved by NDS. Accordingly, biosimilars do not receive a declaration of equivalence.

#### *Prescription vs. non-prescription*

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

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

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

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

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

### *Interchangeability*

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

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

### *Eligibility for reimbursement*

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

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

### Who are the payers?

In Canada, drugs can be reimbursed publicly or privately. Public payers include the 13 provincial/territorial health plans and various federal programmes (covering Canada’s Indigenous population, military, and prison populations).

The largest public health plans are the provincial health plans. These plans are created by provincial statute and establish a formulary of drugs that are reimbursed for eligible residents. Generally, the provincial/territorial plans provide coverage to older individuals and those with limited incomes, although some provinces provide broader coverage. For example, Ontario recently began providing coverage to individuals under 25 years of age.

Private payers include private insurance plans and cash-paying patients. Private insurance

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

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

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

##### *Innovative products*

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

For each submission, CADTH constitutes a review team based on qualifications, expertise, and compliance with conflict of interest guidelines. The review involves an examination of the clinical, economic, and patient evidence. The outcome of the CADTH review is a listing recommendation to public drug plans: 'reimburse', 'reimburse with clinical criteria and/or conditions', or 'do not reimburse'. Drugs are recommended for reimbursement if they demonstrate comparable or added clinical benefit and acceptable cost/cost-effectiveness when compared with other drugs. Drugs are recommended for reimbursement with conditions if they demonstrate (i) comparable or added clinical benefit and acceptable cost/cost-effectiveness only in a subgroup or only when compared with a drug that is also reimbursed with conditions, (ii) comparable or added clinical benefit but unacceptable cost/cost-effectiveness, or (iii) clinical benefit with uncertainty in a therapeutic area with unmet clinical need. Drugs receive a recommendation of 'do not reimburse' when they do not demonstrate comparable clinical benefit or demonstrate inferior clinical outcomes or significant clinical harm.

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

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

Unless the drug is considered unsuitable for national negotiations, the next step is for the manufacturer to negotiate with the pan-Canadian Pharmaceutical Alliance (pCPA) to agree on conditions for listing on public formularies. The pCPA was formed by provincial drug plans with various goals, including improving the consistency of drug-listing decisions and capitalising on combined buying power. Under the pCPA, a lead jurisdiction will undertake negotiations with manufacturers on behalf of most or all of the Canadian public payers, resulting in a Letter of Intent (LOI). Generally, the LOI will include the list price and any clinical criteria for reimbursement, and may also include a confidential payment to public payers.

Finally, after entering into an LOI, each individual public payer will enter into a listing agreement with the manufacturer. The listing agreement will largely reflect the contents of

the LOI and result in the inclusion of the product on the payer's formulary. The formulary will include the agreed formulary list price and clinical conditions for reimbursement, if any.

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

### *Generic products and biosimilars*

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

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

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

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

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

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

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

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

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

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

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

### Issues that affect pricing

As discussed above, when making reimbursement decisions CADTH considers whether a new drug represents a therapeutic advantage and, based on the price submitted by the manufacturer, if it is cost-effective. In doing so, it considers the clinical evidence provided the manufacturer undertakes an independent literature review, and considers pharmacoeconomic data. Input is also sought from stakeholders including patient groups and clinicians.

Once generic products are available on public formularies, the public payer will only reimburse the lowest-cost alternative, except in limited situations. Although not technically

mandatory, in practice, this results in automatic substitution to the generic product. Some provinces have legislation in place that allows pharmacists to interchange to the low cost alternative without informing the patient prior to making the change.

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

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

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

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

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

In practice, the PMPRB often negotiates with patentees to achieve voluntary compliance with the requirements of the *Patent Act*. In particular, many patentees choose to enter into voluntary compliance undertakings (VCUs) to deal with excess revenues, rather than taking the matter to a hearing before the PMPRB. These VCUs may include similar terms to an Order of the PMPRB regarding offsetting price reductions or payments to the Crown, and are made public on the PMPRB's website.

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

### **Policy Issues That Affect Pricing and Reimbursement**

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

### **Emerging Trends**

There have been recent discussions surrounding the development of a national pharmacare plan. Recently, the federal Standing Committee on Health released a report entitled *Pharmacare Now: Prescription Medicine Coverage for all Canadians*. In this report, several recommendations are made regarding the establishment of a national pharmacare system. Additionally, in the most recent budget, the federal government included an announcement of an Advisory Council on the Implementation of National Pharmacare with a goal of starting a national dialogue on pricing and reimbursement of prescription medications.

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

### **Successful Market Access**

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

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



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Sara Zborovski practises regulatory, commercial and intellectual property law. She assists companies regulated by Health Canada in obtaining market access and in all areas of compliance. Ms. Zborovski has experience in a wide range of matters involving the innovative pharmaceutical and biotechnology, natural health product, medical device and food and beverage industries.

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Mr. Guerreiro has particular experience with complex pharmaceutical, biologic, and medical-device patent infringement and impeachment actions, as well as prohibition and damages proceedings under the Patented Medicines (Notice of Compliance) Regulations. In addition, Mr. Guerreiro regularly advises on issues concerning the Patented Medicine Prices Review Board and other intellectual property-related regulatory structures affecting the life sciences industries.

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Prior to law school, Dr. Trimble gained valuable experience working as a pharmacist in Ontario and British Columbia in both hospital and retail settings. He holds a Bachelor of Science in Pharmacy and a Doctor of Pharmacy.

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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 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 simplification of pharmaceutical registration, market authorisation holder regime, two-invoice regime, pricing regime, reform of public hospitals in connection with pricing of medical services, telemedicine, reform of the online sale of pharmaceuticals, reform of public health with elder caring systems, 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 MOHRSS 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 in April 2018 by the Health and Family Planning Commission of the PRC, the PRC had 31,000 hospitals at the end of February 2018 including 12,000 public hospitals and 19,000 private hospitals. All the medical institutions throughout the country received 0.61 billion visits in February 2018. The average outpatient expenses per time are RMB 314.50 for first-class public hospitals and RMB 200.90 for second-class public hospitals and the average inpatient expenses per time are RMB 13,079.0 for first-class public hospitals and RMB 5,904.30 for second-class public hospitals according to the statistics of January and February 2018.

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

According to the *Planning Report of the Chronic Diseases (2017–2025)* issued by the State Council in January 2017, chronic diseases become the most important 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.

Establishment of pharmaceutical manufacturing companies in China is classified in the encouraged or permitted categories of the *Catalogue for the Guidance of Foreign Investment Industries (2017)*. The manufacturing of new chemical drugs, or APIs, new drugs for cancers, cardiovascular drugs, and nerve system drugs, biochemicals, etc. as well as the new preparation of pharmaceuticals (such as sustained-release, controlled release, targeted and transdermal preparations) are classified in the encouraged category of the above Catalogue for foreign investment.

Although the *Catalogue for the Guidance of Foreign Investment Industries (2017)* 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 CFDA.

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 CFDA.

In 2016, PRC implemented the market authorisation holder regime for the majority of drugs except narcotic drugs, psychotropic drug, 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, which may probably become the official regime after the pilot period. This new regime gives more flexibility with regard to the application and transfer of drug market authorisation in China in an effort to encourage the development of new drugs.

## 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 CFDA which can be purchased or used by consumers upon their own judgment without prescriptions by licensed doctors or licensed assistant doctors.

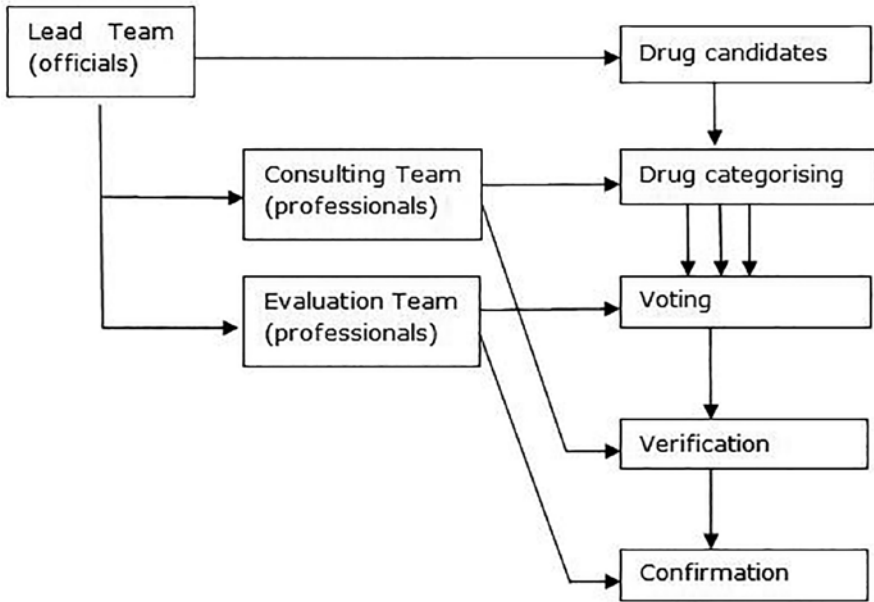
- What pharmaceutical products are eligible/ineligible for reimbursement?

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

- (1) The National Catalogue of Drugs issued by the Ministry of Human Resources and Social Security (“MOHRSS”); and
- (2) The Provincial Catalogue of Drugs issued by the provincial bureau of human resources and social security.

The MOHRSS selects the drugs to be added to the National Catalogue with the assistance of its provincial counterparts. The MOHRSS must also consult with the NDRC, Ministry

of Finance, MOH, SFDA 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 MOHRSS 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 MOHRSS 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 MOHRSS to be included in the National Catalogue or by the provincial level HRSS 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 and Family Planning 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.

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

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

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

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

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

| Drug category  | Rate of sales expenses | Profit margin |
|--|------------------------|---------------|
| Class I new drug: New drug never marketed in domestic or overseas market   | 30%                    | 45%           |
| Class II new drug: New drug never marketed in domestic market but marketed overseas which includes a new administration path (oral, injection, etc.) never marketed in neither domestic and overseas markets | 20%                    | 25%           |
| Class III new drug: New combination of chemical substances   | 18%                    | 18%           |
| Class IV new drug: Domestically marketed drug with a new administration path or a new dosage form  | 15%                    | 15%           |
| Class V new drug: Drug marketed in domestic market with new applications   | 12%                    | 12%           |
| Generics   | 10%                    | 10%           |

Relationship between pricing and reimbursement:

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

Issues that affect pricing

Except for narcotic drugs and Class I psychotropic drugs, the drugs prices are set mainly through market competition after the cancellation of government pricing on drugs.

According to the pharmaceutical pricing reform in 2015, the pricing of different categories of drugs 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 on their own according to their production and operation costs and the market supply and demand.

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

### **Policy Issues That Affect Pricing and Reimbursement**

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

- *Two-Invoice System for Drug Procurement among Public Medical Institutions* taking effect as of 26 December 2016 on a trial basis. The two-invoice system is a system under which invoices are issued by drug manufacturers to drug distributors on a once-off basis while invoices are issued by drug distributors to medical institutions on a once-off basis. This policy is aiming to improve transparency in drug prices and eliminate excessive profit margins associated with multi-tier distribution models.
- *Healthy China 2030 and 13<sup>th</sup> Five Year Plan for Deepening the Reform of the Pharmaceutical and Healthcare System*. According to the aforesaid policies, the *Circular on Fully Carrying out the Work of Promoting the Comprehensive Reform of Public Hospitals* taking effect as of 19 April 2017 was promulgated. According to this new law, the decades-long policy of drug mark-ups amounting to 15% in public hospitals must be completely cancelled in order to fully promote the comprehensive reform of the public hospitals.

### **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.

### **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 known worldwide as a solidarity-based system that is very comprehensive and protective for its users. One result, however, is relatively high expenditures that are becoming harder for the government to sustain.

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

## Market Introduction/Overview

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

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

In France, there are five types of healthcare workers:

- Professional service providers, which include:
  - Health establishments: public hospitals and private clinics.
  - Mobile professionals and auxiliaries: doctors; pharmacists; midwives; nurses; and physiotherapists.
  - Emergency medicine.
  - Social welfare services and associations.
  - Ambulatory surgery.
  - Telemedicine.
  - Home hospitalisation and treatments.
  - Nursing home services.
  - Specialised establishments for accommodating patients with specific needs, such as neurovascular units or centres for obese patients.
- Producers of goods and services (pharmaceutical industry).
- Public health institutions: the French healthcare system is overseen by the Minister of Health and the Minister of Social Affairs.

- At the national level, the central government is in charge of implementing public health and safety policies. It oversees all health institutions, setting prices for products and treatments while maintaining funding for health institutions. For example, the National Institute of Health Monitoring and Public Health Council belongs to the public health institutions.
- At the regional level, regional health agencies adapt national policies to a community's needs and constraints. They ensure the coordination between prevention, care and support as well as consistent resource management in order to ensure equal access to healthcare.
- At the local level are the institutions and professionals who are in closest contact with patients and other people in the system. They are supervised by the regional health agencies.
- Providers of compulsory or supplementary health insurance plans.
- Recipients of healthcare (patients).

### Access to Care

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

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

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

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

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

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

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

### Incidence and Prevalence of Disease

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

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

## Pharmaceutical Pricing and Reimbursement

### Regulatory classification

#### *Different types of pharmaceutical products*

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

There are three types of pharmaceutical products:

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

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

- Bulk compounding: drugs prepared for a particular patient due to the lack of available pharmaceutical products.
- Hospital preparation: the drugs prepared according to pharmacopoeia instructions and in compliance with proper practices mentioned in the Article L. 5121-5 of the Public Health Code due to the lack of available or adapted pharmaceutical products.
- Compounded medication: the drugs prepared in a pharmacy that are registered to the pharmacopoeia or on a national form and aimed to be directly dispensed to patients by the pharmacy.
- Generic drug: prepared with the same molecule of the reference medicinal products and have the same composition of active substances, the same pharmaceutical form and efficacy than the model of reference.
- Biologic drugs of which the active substance is produced from a biological source and of which the quality requires a combination of physical, biological and chemical tests.
- Biological similar drugs are 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 the difference linked to the raw material or production process.

#### *Refundable pharmaceutical products*

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

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

#### Who is/Who are the payers?

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

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

### **Health Insurance**

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

#### **How is Social Security Funded?**

Resources which fund the social protection are:

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

### **Complementary Health Coverage**

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

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

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

### **Marketing Authorisation**

The marketing authorisation is issued by either:

- The European Commission, after receiving an opinion from the European Medicines Agency (EMA). The pharmaceutical laboratory chooses the rapporteur State or the referent State within the EU for submitting its product to the EMA, which has authority across the European Union. These procedures are used when the product is intended for several Member States of the European Union.
- The Director general of National Agency for Security of Medicinal product who scrutinises the product according to scientific criteria of quality, safety and efficiency.

The new product must have a risk-benefit balance at least equal to products already on the market. It can submit a favourable or unfavourable opinion or a request for some additional information.

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

This authorisation can be changed or removed.

Another option is to file for a temporary authorisation of use.

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

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

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

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

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

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

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

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

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

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

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

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

*Drugs that are no longer reimbursable*

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

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

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

The French national union of medical insurance (*Union nationale des caisses d'assurance maladie*) is composed of representatives of the general system, the agricultural system and social security for self-employed persons. It sets the support rate of healthcare as well as the reimbursement rate of drugs.

The medical service provided (MSP) takes into account the severity of the concerned disease, the efficiency of undesirable effects, the therapeutic strategy and the preventive, curative or symptomatic character of the drugs treatment.

There are several levels medical service provided (major, moderate or low) that affect the reimbursement rate of the drugs. There 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 MSP and Bulk Compounding | 65%                |
| Drugs with moderate MSP                                    | 30%                |
| Drugs with low MSP   | 15%                |

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

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

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

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

*The price fixing*

Two types of drugs can be distinguished:

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

*The criteria for fixing the price*

As previously mentioned, the Committee takes into account to set the price improvement of the drug, results of economical and medical evaluations, the price of the drugs with same therapeutic effect, volume sales and foreseeable and actual conditions of use of the drugs.

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

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

*The detailed price of drugs*

The public price of the drugs is composed of the pre-tax manufacturer price, margins (wholesalers margin, officinal margin and dispensation fees) and the value-added tax.

It comprises the payment of the wholesalers notably through margin and discounts. The ministerial order dated of December 26, 2011 created a unique payment of the wholesalers equal to 6.68% of the pre-tax manufacturer price.

This coefficient only concerns the part of the price ranging from €0 to €450. Beyond this amount, the coefficient is equal to 0.

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

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

*Evolution of the sales of reimbursable drugs, in the pharmacies<sup>1</sup>*

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

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

- The price effect, corresponding to changes in unit prices of drugs on the market.
- The box effect, or the difference between the number of units sold in 2015 and those in 2016, for example.

- The structure effect, reflecting the evolution of market share. For example, if it is negative for a certain drug, that may indicate sales migrating towards more expensive alternatives.

*The average price of drugs, in pharmacies:*

|  | 2012  | 2013  | 2014  | 2015 | 2016 |
|--|-------|-------|-------|------|------|
| Average pre-tax manufacturer price of one box (€)  | 7.46  | 7.25  | 7.15  | 7.15 | 7.15 |
| Average public price, including tax of one box (€) | 10.39 | 10.15 | 10.00 | 9.96 | 9.90 |
| Average margin <sup>2</sup> (€)                    | 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.

*Price and distribution margin of drugs in 2016:*

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

### *Discounts*

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

#### **Conventional Discounts**

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

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

#### **The Unconventional Discounts**

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

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



### Issues that affect pricing

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

#### **The Presence of Generic and Biosimilar Drugs on the Market**

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

- The partial substitution of the original drug for the generic, as the price of the original decreases automatically under French regulations. Minimal price decreases are implemented at the time of the generic product launching (20%) and 18 months later (12.5%).
- The price of the original is often cut by laboratories as well in order to keep their product competitive.

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

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

These decreases apply to the pre-tax manufacturer price.

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

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

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

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

#### *Supply chain*

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

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

#### *Drug counterfeiting*

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

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

The WHO uses the following definitions:

- Substandard: also called “out of specification”, which are authorised medical products that fail to meet either their quality standards or specifications, or both.

- Unregistered/unlicensed medical products that have not undergone evaluation and/or approval by the National or Regional Regulatory Authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.
- Falsified medical products that deliberately/fraudulently misrepresent their identity, composition or source.

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

Counterfeit medicines can take different forms. It can affect the exterior packaging, the primary packaging of the drug and 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 the entry into the legal supply chain of falsified medicinal products;
- Commission Delegated Regulation 2016/161 on how medicine authenticity should be verified; and
- Regulation 699/2014 on the design of the common logo to identify persons offering medicinal products for sale at distance to the public.

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

### **The Link Between the Price of Drugs and Research and Development**

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

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

### **Competition**

Competition authorities look very carefully at the medicines market and pricing. For instance, on December 19, 2013, the Competition Authority (*Autorité de la concurrence*) issued the opinion n°13-A-24 about the competition in the sector of drugs distribution downtown. The Authority held that dysfunctions in full competition can influence the development of the market, and therefore impact drug prices. Thus, the Authority observed a lack of information about drug pricing and suggested more transparency so that consumers would be able to compare prices between different pharmacies, hindering competition. On April 26, 2016, the Competition Authority issued an opinion on electronic commerce of medicine. Furthermore, since November 21, 2017, the Competition Authority is investigating the 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.<sup>6</sup>

### **Policy Issues That Affect Pricing and Reimbursement**

The French government can influence the price and reimbursement in several ways. The

French Court of Audit (*la Cour des comptes*) identifies several policies in its report “Social Security 2017” dated September 2017.

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

Please see section, “How is the reimbursement amount set? What methodology is used?” in “Pharmaceutical Pricing and Reimbursement”.

*The framework agreement*

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

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

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

The European price is granted for five years and may be renewed without exceeding one year. This guarantee slows down the price decline for a drug.

*The ministerial guidelines*

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

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

*The savings targets*

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

## **Emerging Trends**

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

## **Successful Market Access**

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

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## Endnotes

1. Issued from the activity report 2016 of the Economic Committee for Medicinal Products.
2. The distribution margin corresponds to margin of the wholesaler, margin of the pharmacist and fees of the dispensation.
3. Issued from the article “the patent and the brand, two invaluable sesames” on the official website of pharmaceutical industry (*Les entreprises du médicament*).
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 kicking in one year after product launch under the AMNOG process. This process was implemented in 2011 and is the key price regulation mechanism for innovative pharmaceuticals.

The AMNOG process comprises two phases, starting with a HTA assessment conducted by the G-BA, followed by the reimbursement price negotiations between the GKV-SV and the respective pharmaceutical company. The negotiated reimbursement price applies as of the 13<sup>th</sup> 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 13<sup>th</sup> month after product launch.

The AMNOG process has fundamentally changed the market access regime in Germany and therefore been labelled as a learning system. While 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 at the early stage of product launch, (iii) undue pressure on prices by choosing generic comparators as a reference point for ‘bottom-up’ price negotiations, and (iv) imbalanced governance structure by giving 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 statutory funded system, currently operating around 110 statutory health insurance funds (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 dependents of SHI members, e.g. children, are covered free of charge. Premiums of unemployed people are borne by social security. The SHI's premiums are centrally pooled and reallocated to individual SHIs using a risk-adjusted capitation formula, taking into account age, sex, and morbidity from 80 chronic and/or serious illnesses. The SHI system is based on the principle of solidarity, meaning that all members jointly carry the individual risk of the costs of treatments in case of illness. Every member of the SHI, regardless of their income level, has an equal right to medical treatment and continued payment of wages in case of illness.

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

#### *Health expenditure*

Total health expenditure in Germany in 2017 reached EUR 374 billion (approx. 11% of GDP), 33% of which was spent on in-patient treatment, 17% on out-patient treatment, 17% on pharmaceuticals, and the remaining 33% on additional services and/or administration. SHIs spent around EUR 210 billion in 2017, generating a surplus of EUR 25 billion.

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

In 2017, 31 pharmaceuticals (excluding biosimilar) with new active substances were launched in Germany. Eleven of them are licensed for the treatment of cancer, four for infectious diseases and 10 for chronic diseases. As to the incidence and prevalence of diseases, cardiovascular diseases are amongst the most frequent causes of death in Germany (approx. 40%), followed by cancer (25%).

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

### Key market players

There are various players in the market that participate in self-governing decision-making processes, while the legislator sets out the overall conditions and criteria for healthcare services.

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

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

#### *Federal Joint Committee*

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

#### *Institute for Quality and Efficiency in Healthcare*

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

#### *Federal Association of SHIs*

The Federal Association of SHIs ('GKV-SV') is the federal level association of all SHIs. Members of the GKV-SV are represented in the G-BA and can thereby influence its decision-making process. As regards pharmaceuticals with new 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') also representing medium-sized pharmaceutical companies, the federal association of pharmaceutical manufacturers ('BAH') representing RX and OTC companies, and Pro Generika representing 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 by 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-prescriptive pharmaceuticals are generally excluded from reimbursement. Thus,



this limits patients' right to treatment with pharmaceuticals. Patients requiring these non-prescriptive pharmaceuticals will need to 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 development disorders on the one hand, and specific OTC pharmaceuticals which are recognised as standard treatment for severe diseases on the other. 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 can 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 will need to purchase the product at its own expense.

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

#### Price regulation mechanisms for pharmaceuticals

In the absence of a fourth hurdle, pharmaceutical companies may, in general, freely determine market prices when launching their products. However, there are various mechanisms which directly or indirectly regulate prices or contribute to cost-savings in the healthcare system. These price regulation mechanisms range from price-freezing to compulsory rebates, reference prices limiting the reimbursement amount causing 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 which have been launched before 1<sup>st</sup> August 2009.

### *Reference price system*

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

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

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

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

## **AMNOG Process for Innovative Pharmaceuticals**

### *Background*

While the reference price system has proven to be quite effective in regulating pricing and reimbursement for established products, the situation is different for new and innovative products. As a matter of fact, reference groups can only be built if a minimum number of comparable pharmaceuticals are already available on the market. If, however, a new product with a new pharmacological mode of action enters the market, it is often difficult to include such product in an existing reference price group or to build a new reference price group. Against this background, in 2011, the German legislator decided to introduce a new price regulation scheme, the so-called ‘AMNOG process’. The AMNOG process 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.

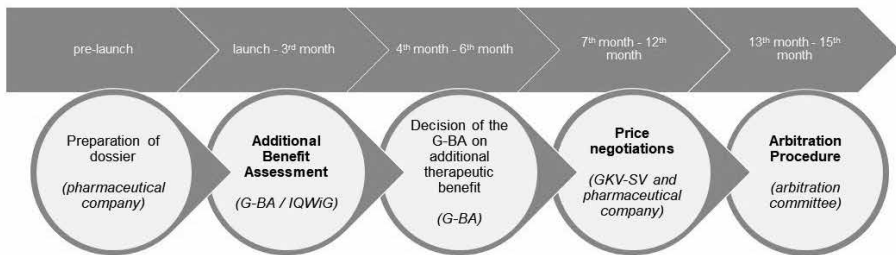
## HTA process

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 assessment 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 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 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 13<sup>th</sup> 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.

#### *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 the 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 to the 13<sup>th</sup> month after initial product launch unless suspensive effect is exceptionally granted on 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 a neutral process, 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 might need to be adjusted and modified as it evolves in its daily practice. When assessing the experience gained through the AMNOG process since its entry into force in 2011, a number of observations can be made:

#### *High number of negative assessments*

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

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

#### *Determination of low cost comparators*

Further critical comments refer to the insufficient distinction between the G-BA assessment process on the one hand and the reimbursement price negotiation process on the other. As the price negotiations are based, in practice, on the price of the respective comparator (bottom-up approach), the determination of the suitable comparator in the G-BA assessment process is of utmost importance. It is argued by the pharmaceutical industry that the selection of suitable comparators by the G-BA has been biased on 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 are conducted by himself.

*Transparency of reimbursement prices*

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

*Opt-out*

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

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

*Free pricing in first year after product launch*

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

*Limited impact on prescriptions by physicians*

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

## Emerging Trends

### Pharma Dialogue

Under the leadership of the German Ministry of Health, a campaign called ‘Pharma Dialogue’ designed to include all stakeholders (e.g. the pharmaceutical industry and the SHI), was initiated in 2014, aiming to address problems and issues which need to be resolved in order to ensure better conditions for access to innovative pharmaceuticals. With respect to the AMNOG process as a ‘learning system’, this resulted in two main proposals: first, the free pricing of pharmaceuticals in the first 12 months after product launch should be eliminated if the volume of sales exceeds a certain threshold. Second, the reimbursement price should not be publicly available in order to mitigate the negative price effects for other markets making reference to the German system. Therefore, the reimbursement price should only be shared with those institutions, and stakeholders of the SHI, which are directly involved in the reimbursement process.

### AMNOG reform act

#### *Free pricing and transparency of reimbursement price*

However, neither of these proposals have actually been implemented by the subsequent AMNOG-reform act (‘AMVSG’), which came into effect in May 2017. The petition of confidentiality of reimbursement prices has been turned down on the grounds of an alleged lack of practicability and the importance of transparency of reimbursement prices for physicians. Moreover, as no consensus as to a potential sales threshold could be reached, the principle of free pricing for the first 12 months after product launch has been upheld.

#### *New information system for physicians*

By way of the AMVSG, a new information system shall be established, aiming to provide physicians with quick and direct access to all assessments made by the G-BA. While the concrete implementation of the system is still subject to further discussion, there is a serious concern within the pharmaceutical industry that this system could be misused by restricting the freedom of therapy of physicians for the purpose of cost-saving by ‘steering’ prescriptions on the basis of economic considerations.

#### *Broader scope of AMNOG*

Moreover, the field of application of the AMNOG process was expanded to the effect that pharmaceuticals with established APIs for which a new marketing authorisation enjoying protection of clinical data has been granted are also covered. The underlying rationale was to cover situations such as with the established API Alemtuzumab, for which a new indication covering multiple sclerosis was granted. Moreover, the applicability of the agreed reimbursement price was expanded to include pharmaceuticals which are administered by hospitals for in-patient treatments. Until then, the law did not provide for an explicit regulation as to whether the reimbursement price shall apply when distributing pharmaceuticals to hospitals. Finally, the SHI is pressing for a stricter regulation of Orphan Drugs within the AMNOG process. Because it is difficult to identify an appropriate comparator for Orphan Drugs, the current system provides that an additional therapeutic benefit shall be presumed with no additional dossier to be submitted by the pharmaceutical company as long as a sales threshold of EUR 50 million is not exceeded. It is argued by the SHI that the current system would induce wrong incentives in the pharmaceutical industry for providing insufficient clinical data for Orphan Drugs.

### EU harmonisation on HTA

The recent proposal for a European regulation on harmonised rules regarding health technology assessments by the European Commission has been intensively debated in

Germany. While the national associations of the pharmaceutical industry have taken the positive view that such harmonisation could facilitate and streamline the until-now 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.

#### Initiatives by the new German government

Finally, the judgment of the ECJ issued in October 2016, ruling that foreign mail order pharmacies are not bound by the German pricing regime, has triggered a debate as to whether the hitherto liberal German pharmacy mail order regulation can still be upheld. National pharmacists are lobbying for a ban of distribution of prescriptive pharmaceuticals (**‘RX products’**) by mail order pharmacies. It is argued that a significant number of national pharmacies would not be able to survive if foreign mail order pharmacies were allowed to compete with them in the area of RX products without being bound by the German pricing regime. There are some indications in the coalition agreement that the new German government would be open to pursuing this proposal.

### **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 the marketing authorisation has been granted. Instead, market access and regulatory experts should 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 should also anticipate 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 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

India is widely acknowledged as being the ‘pharmacy of the world’ and is renowned as a haven for high-quality drugs at competitive prices. India is one of the top exporters of medicines to the world, exporting to North America, the European Union, Africa, the Middle East, ASEAN, etc. However, with no uniform policy for drug reimbursement and pricing, multiple large-scale health norms, ever-increasing demand for affordable and accessible drugs and the exponential growth rate of the pharmaceutical industry, the sector presents several opportunities as well as challenges to new entrants, existing entities, the Government and to the consumers alike.

The present chapter aims to provide to the readers a bird’s eye view of the Indian pharmaceutical sector and the broad regulations which govern it.

## Market Introduction/Overview

The Indian pharmaceutical industry is the third largest in terms of volume and the 13<sup>th</sup> largest in terms of value<sup>1</sup>. The annual turnover of the industry in 2015–16 was INR 2,04,627.15 Crores<sup>2</sup>. The size of India’s medical devices industry, which is dominated by MNCs is USD 4.9 billion<sup>3</sup>.

The industry is largely driven by private sector undertakings, with negligible involvement of the public sector. Despite the same, exports from the pharma sector are the third-largest source of foreign exchange in India, contributing a turnover of INR 11,05,342.20 Crores in 2015–2016<sup>4</sup>.

India also has the largest number of U.S Food and Drug Administration (USFDA) approved manufacturing facilities outside the U.S (262) and 2,633 FDA-approved drug products and over 546 USFDA-approved company sites, the highest number outside the U.S<sup>5</sup>. 253 plants are European Directorate for the Quality of Medicines (EDQM) approved and 1300 World Health Organization (WHO) Good Manufacturing Practices (GMP) compliant plants<sup>6</sup>.

The cost of manufacturing in India is also significantly lower than in the U.S (by 33%) and in other western countries (by a staggering 50–55%). Further, the *per capita* sales of pharmaceuticals in India have expanded at a compound annual growth rate (CAGR) of 17.6% in 2016<sup>7</sup>. With a plethora of opportunities for market entry and growth, the sector is set to touch USD 45 billion by 2020 and USD 100 billion by 2025<sup>8</sup>, showcasing the potential for exponential growth in the coming decade.

Since the pharmaceutical sector is highly unregulated, there is an ease of entry into the market for new players. This is supplemented by the policy of allowing a minimum 74% foreign direct investment in brownfield projects (acquisition of existing facility) and up to 100% Foreign Direct Investment (FDI) in greenfield projects (building of a new facility)<sup>9</sup>. New entry is further eased due to the well-developed distribution channels and existing supply chains.

Having said this, owing to its multicultural society and a vast traditional knowledge base, only about half the population consumes allopathic medication. The remaining treatments are based on Ayurveda, Unani and Homeopathy. While communicable diseases like tuberculosis and malaria are most prevalent in the country, recent years have seen a manifold increase in lifestyle diseases like diabetes, cardiovascular diseases, etc.

## **Pharmaceutical Pricing and Reimbursement**

### Regulatory classification

Pharmaceuticals in India are regulated by the Drug Controller General of India (DCGI) operating within the Central Drugs Standard Control Organization (CDSCO), Ministry of Health and Family Welfare, Government of India. The DCGI regulates drug approvals and licenses for manufacturing and/or marketing of pharmaceuticals within the country. The governing statutes are the Drugs & Cosmetics Act, 1940 and the Rules framed thereunder, as also the Essential Commodities Act, 1955.

In India, there exists no linkage between the patent regime and the regulation of drugs for the purposes of manufacturing and/or marketing. These two function independently and in a parallel fashion. At the same time there are also no laws for Data Protection in India which essentially means that clinical trial data of innovator companies can be used by other companies.

Most of the drugs can only be sold under prescription. However, recent initiatives have been taken to introduce the concept of over-the-counter drugs whereby only specific categories of drugs would be permitted to be sold over the counter.

In India, drugs are considered ‘essential commodities’ under the Essential Commodities Act, 1955. By including drugs within the ambit of the Act, the Government can ensure that steps are taken, in a timely manner, to monitor/regulate their supply to the consuming public. Having said that, the Government does not control the prices of all drugs. Only such medicines which satisfy the priority healthcare needs of the majority of the population are termed as Essential Medicines. Therefore the medicines in the National List of Essential Medicines (NLEM) are made available at affordable costs and assured quality. The list is a dynamic one and is periodically discussed and revised by the Ministry of Health and Family Welfare to include drugs which are to be governed by price-fixation.

The price control order which is currently in force is the Drugs (Price Control) Order (DPCO), 2013. The underlying policy document, which was implemented by DPCO, 2013 was the National Pharmaceutical Pricing Policy (NPPP) 2012. The key principles for regulation of prices as per the NPPP are:

- (1) Essentiality of Drugs.
- (2) Control of Formulations prices only.
- (3) Market Based Pricing.

Drugs which fulfil the aforesaid criteria were brought under price control by DPCO, 2013. Prior to the DPCO, 2013, the following price control orders were put in effect:

- (1) the Drugs (Display of Prices) Order, 1962;
- (2) the Drugs (Control of Prices) Order, 1963;
- (3) the Drugs (Prices Control) Order, 1966;
- (4) the Drugs (Prices Control) Order, 1970;
- (5) the Drugs (Prices Control) Order, 1979;
- (6) the Drugs (Prices Control) Order, 1987; and
- (7) the Drugs (Prices Control) Order, 1995.

DPCOs notified since DPCO, 1966 onwards were issued in exercise of the powers conferred by Section 3 of the Essential Commodities Act, 1955. Prior to 1966, they were promulgated under the Defence of India Act.

In order to further the objectives of the DPCO and to implement the same, the National Pharmaceutical Pricing Authority (NPPA) was set up in the year 1997, under the aegis of the Department of Pharmaceuticals (DOP), Ministry of Chemicals & Fertilizers, Government of India.

In Schedule I of the DPCO, 2013, 652 formulations were included, which were brought under price control by the Government. This Schedule was amended in the year 2015 (brought into effect on March 10, 2016) and a total of 640 formulations are now under price control. All the manufacturers of the scheduled formulations are mandated by law to follow the ceiling price fixed and notified by the NPPA and failure to do so would attract penal provisions.

So far as formulations which do not form part of Schedule I, i.e. the non-scheduled formulations, the companies are at liberty to increase the Maximum Retail Price (MRP) of such drugs by not more than 10% of the MRP prevalent in the preceding 12 months.

For the purposes of price regulation, drugs may be classified as:

- patented drugs or non-patented drugs;
- innovative drugs – certain drugs are exempt from a price ceiling for a period of five years if they qualify the requisite criteria of innovation, particularly if they result from indigenous innovation;
- bulk drugs or formulations – only finished formulations, with specified dosages and strengths, are subject to price ceiling under the DPCO, 2013; and
- scheduled and non-scheduled formulations – Schedule I to the DPCO, 2013 contains a list of finished formulations which are subject to price ceiling as per the provisions of the DPCO, 2013. The schedule may be updated from time-to-time to include or remove certain drugs. Drugs not named in the schedule are categorised as non-scheduled formulations and while the same are freely priced by the manufacturer, are still monitored by the NPPA.

Apart from drugs, the NPPA of late has commenced price control of medical devices as well. Most notably, the prices of coronary stents and knee caps have been capped.

Despite periodic orders for price fixation and multiple pharmaceutical policies over the years, there exists no policy in India till date regarding reimbursement of the cost of drugs. The majority of the expenses on medicines are made out-of-pocket by the consumers.

Reimbursement of medicines, if any, is based on whether the same is claimable under insurance policies held by the consumer or whether the concerned drug has been purchased from a Central Government Health Scheme (CGHS) dispensary and is included in the consumer's medical allowance/reimbursement quota of his/her salary. More information about this can be found in the succeeding section.

### Reimbursement of drugs

There are two types of healthcare payment systems:

- Private sector reimbursement – Consumers may claim reimbursement of drugs through private sector companies. This is done through insurance policies. For these, the premium for the insurance is paid by the consumer/policy holder. Upon usage of medical treatment, the patient/consumer claims the expenses under the insurance policy and the reimbursement of medical expenses is obtained. However, not all insurance companies provide reimbursement for medicines, and only reimburse other medical expenditure like hospitalisation costs, etc. Further, more often than not, obtaining insurance amounts

can be a tedious task and most patients who are able to afford private healthcare prefer not claiming medicine expense, and would rather claim the exorbitant hospitalisation and/or surgical procedure costs. Therefore, the costs are reimbursed by the insurance companies based on the premium paid by the insured consumer.

- Public sector reimbursement – Reimbursement from the Government is a benefit afforded to those employed by the Government or in public sector undertakings in India. Furthermore, the reimbursement is of two types.
  - i. Through medical allowance or reimbursement – For persons employed by the Government or in a public sector undertaking, a part of their salary could be devoted for medical allowance. Any expenditure on medical treatments, including medicines, is then paid by the person through this allowance. A medical reimbursement could also be fixed. As per this system, a certain amount is fixed by the employer for the medical expenditure of the employee and also his dependent family members. Upon incurring any expenditure on healthcare, the employee can thereafter claim such reimbursement from his employer, up to this maximum amount already set by the employer.
  - ii. The Central Government Health Scheme (CGHS) – A Government employee may be entitled to buy medicines and avail healthcare services through the CGHS. The CGHS network comprises both dispensaries and healthcare centres. Certain private hospitals are also included within the CGHS panel periodically. An employee can obtain subsidised or even free healthcare services from these centres and hospitals. In terms of the medicines, the CGHS has a list of medicines that are available free of cost or at subsidised rates from the CGHS dispensaries. A Government employee, whose employer offers such an arrangement, may also claim a reimbursement of medicines purchased from a CGHS dispensary. The cost of medicines is then either borne by the employer undertaking or the Government.
  - iii. This discussion would be incomplete without a mention of the Tamil Nadu model of public health, which is prominent for its success in providing quality health services at an affordable cost. The state has dedicated itself completely to the cause and, with little or no financial aid from the Central Government, has on its own ensured affordable and easy access to healthcare to its people. Illustratively, the Chief Minister's Comprehensive Health Insurance Scheme which was launched in the State in 2011–12, aims to provide Universal Healthcare to all by providing free medical surgical treatment in the Government and private hospitals to any family whose annual income is less than INR 72,000 by meeting all expenses relating to the hospitalisation of the beneficiary. The scheme provides a coverage up to INR 1,000,000 per family per year on a floater basis for ailments and procedures. For certain specified ailments and procedures and critical nature, the overall limit is increased to INR 1,500,000. As of 2013–14, the scheme was implemented through 829 hospitals (Government 142 + private 687). The total number of health cards issued in the State was 1.29 Crore and a total number of 6.47 lakh persons benefitted<sup>10</sup>.

Despite the above, no guidelines or policies govern formal reimbursement of cost of drugs for either private sector or public sector healthcare systems.

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

- Drug prices are set using the various provisions and formulae provided under the various Drug Price Control Orders, which are in force from time to time by the National Pharmaceutical Pricing Authority (NPPA). The current DPCO in force is of 2013.
- As per the Pharmaceutical Policy of 2012, and the resulting DPCO, 2013, there is no

regulation of pricing for bulk drugs or active pharmaceutical ingredients (APIs). The prices of only finished formulations (commercial products) are regulated.

- The maximum price or ceiling price of scheduled drugs, i.e. those mentioned in Schedule I of the DPCO, 2013 (or in the schedules updated and published subsequently), is the average of the price of all the brands under which the drug is available. However, only prices of brands that occupy more than 1% market share in that medicine's market are considered for obtaining the average price. Trade margins and dealer margins are taken into consideration while fixing the ceiling price.
- The prices of the drugs that are not mentioned in the schedule are free to be priced according to the manufacturer. Further, the prices of these non-scheduled drugs can be increased annually by not more than 10% of the MRP existing in the preceding 12 months.
- There also does not exist any concept of discounts to the consumers, except when manufacturers desire to encourage sales of their product in the market or when they seek to popularise a new drug in a market which has an existing well-established brand. Normally, the discounts offered by a manufacturer in the trade channels are 20% of the Maximum Retail Price (MRP) with respect to the retailer and 10% of the MRP with respect to the wholesaler.

#### Issues that affect pricing

- As mentioned above, pricing of drugs in India is essentially market-based.
- It is pertinent to mention that while the maximum price of medicines is fixed under the DPCO, there is no bar on the minimum price that can be charged by the manufacturer. This results in severe competition, more so when the cost of production of medicines in India is extremely low, providing a sufficient margin for the manufacturers to commercialise their product at low and competitive prices.
- Several factors affect drug pricing, a few of which are enlisted below:
  - competition in the market – manufacturers are likely to refrain from increasing prices due to high competition;
  - average market price of the drug – this parameter is considered in fixing the ceiling price of the drug as per the DPCO, 2013;
  - average market prices of the drug in turn may be determined by the alternative medicines available and pricing thereof; and
  - cost of manufacturing the drug – this includes the cost of operating a manufacturing unit, cost of machinery, cost of workers and manpower.
- As mentioned above, certain types of innovations can qualify drugs for exemption from price control for a period of five years. Three types of drugs are considered for the exemption:
  - i. drugs resulting from indigenous research and development and patentable under the Patents Act, 1970;
  - ii. development of a new drug by a new process developed through indigenous R&D and patented under the Patents Act, 1970; and
  - iii. development of a new drug involving a new delivery system developed through indigenous R&D.
- Capping the price of patented drugs presents another challenge. Innovators invest immense funds and energy into research and development in order to innovate. On one hand, these innovators enjoy monopoly in the market as a result of the patent regime. On the other hand, these companies may also restrict entry or even research on their patented drugs by instituting *quia timet* civil proceedings seeking injunctions from infringement of their technology. Such monopoly also entitles them to set the average price in the market as theirs is the only brand available. Several innovators have in the

past exploited this monopoly and freedom to fix the price and set the market average by charging exorbitant amounts for their medicines. For example, one innovator company's cancer treatment would cost the patient around INR 3,000,000, with each dosage costing the patient about INR 250,000!

- The factors that may underline the pricing of new patented drugs depend upon:
  - i. prices the patentee would wish to charge;
  - ii. steps that can be taken to regulate prices set by the patentee through price control or negotiation; and
  - iii. the increasing competition from pharmaceutical companies manufacturing similar biologics or biosimilar versions of the patented drug.
- Other factors that affect pricing of drugs are:
  - cost of the research and development involved;
  - cost of the innovation, if any;
  - cost of raw materials for the manufacturing of the drug – while the DPCO controls the maximum price for the finished formulations, the API used in the finished product is not controlled. Apart from the API, several other raw materials may be required for the production and are not subject to price control. The price of the drugs set by the manufacturer, may therefore, take into account the cost of the raw materials involved;
  - affordable access to care: the mission of the Government, various policies and statutes has always been to ensure affordable access to the majority of the Indian population. Several schemes to keep the prices of medicines at bay, encouragement of generic versions of drugs, and the recent support to development of similar biologics (or biosimilars) are all aimed at the same objective; and
  - requirement of exporting to other countries: India has strived to maintain its position as the 'pharmacy of the world' by regulating export costs of medicines, encouraging establishment of manufacturing facilities for pharmaceutical giants to enable easy export of drugs and even providing for voluntary and compulsory licensing within the patent regime. Although, not all of its initiatives have garnered support from innovator companies, India continues to remain one of the largest exporters of pharmaceuticals to the world.

### **Policy Issues That Affect Pricing and Reimbursement**

India, being the robust economy that it is, implements several schemes and policies each year that affect pharmaceuticals and their pricing. Some of the major policy issues that govern price fixing are:

- The "Make in India" policy – As is evident from the name, this policy is aimed at incentivising and encouraging indigenous manufacturing and supporting start-ups and small- and medium-sized enterprises (SMEs). Under the influence of this policy, indigenous innovation in the pharmaceutical sector has been incentivised by permitting 100% FDI in greenfield projects. India has also made the working of patents in India mandatory to ensure that monopolies are not granted to merely exclude others but to actually guarantee that the patent is applied on an industrial scale and that the public benefits therefrom. This is further exemplified by the exemption from price fixation enjoyed by drugs developed through indigenous research and development.
- Several steps have been taken to increase the availability of drugs to the common general public. In India, not all medicines may be accessible to all strata of society. Initiatives

like the CGHS and the Jan Aushadhi scheme are aimed at increased accessibility and availability of medicines to all.

- There has been an increased need to support the growth of the generics sector in India. This is also in line with the “Make in India” mission and steps such as encouraging prescription of drugs through their International Non-proprietary Names (INNs) are targeted at this policy.
- The Patents Act, 1970, provides for compulsory licensing for patented drugs that are not meeting the reasonable requirements of the public. Under this provision, if the patents are not being worked in the territory of India; or, the reasonable requirements of the public are not being satisfied; or, even if the patented invention is not being made available to the public at a reasonably affordable price, such patent may be compulsorily licensed to any person.
- More often than not, this increased pressure on patentees to sufficiently work their patents adds as another policy factor to ensure that the medicines covered under a patent are either manufactured within India by the patentee by setting up a manufacturing unit or else license the same to Indian manufacturers and allow them to import the medicines into India and market the same.
- It is also important that the ever-expanding pharmaceutical sector remains an open market for both innovators and generics alike.
- Over the last five years, the Government has progressively focused on public healthcare. All initiatives in the healthcare sector intended to provide subsidised healthcare services and insurance to general public.

## Emerging Trends

As the pharmaceutical sector is one of the leading contributor’s to India’s GDP, there is an increased interest in regulating the entire healthcare sector. The aim of any new legislation or policy is to increase the manufacturing of drugs in India in order to strengthen the “Make in India” initiative. This is further supplemented with the need to increase the accessibility of drugs at affordable prices for all, particularly the poor and disadvantaged and to reduce the out-of-pocket expenses.

The Government of India has recently taken several initiatives in view of the above:

- i. National Health Policy, 2017 – focus on the production of APIs and incentivising indigenous products/devices/technology;
- ii. National Health Protection Scheme for health coverage for lakhs of families;
- iii. Ayushman Bharat programme – establishment of 1.5 lakh health and wellness centres;
- iv. E-Health – bringing together the ePharmacy, eDiagnostics and eHospital initiatives;
- v. Jan Aushadhi – Centres to provide generic drugs, which are available at lesser prices but are equivalent in quality and efficacy as expensive branded drugs;
- vi. promotion of generics and promotion of prescription of INNs instead of brands; and
- vii. the Essential Commodities (Control of Unethical Practices in Marketing of Drugs) Order, 2017 (Order) – to eradicate bribing of doctors and health professionals by way of, *inter alia*, gifts and payments for travel and food.

## Successful Market Access

Given the dynamics of the pharmaceutical industry in India and the limited barriers to entry, there exist plenty of opportunities for new entrants. Policy initiatives by the Government have increasingly promoted establishment and entry of new players in the pharmaceutical markets. However, the competition in the market is also ever increasing.



Any new entrant in the sector must be mindful of the following parameters that can affect both entry and sustenance of an entity in the Indian pharmaceutical market:

- i. A rigorous price regulation regime operates in the country. The DPCO orders are periodically revised and new drugs are added to the list of essential medicines and a list of scheduled drugs for price fixation. At present, the prices of nearly 640 formulations are regulated by the DPCO, 2013. However, as and when the National List of Essential Medicines is updated, it shall bring into purview more formulations. Apart from drugs, medical devices are gradually being included within the price regulation regime.
- ii. Since there exists a robust and widespread distribution and marketing system for the existing players, any new entrant shall have to strategise accordingly in order to find its way into the system and establish competitive trade channels to gain significant foothold in the market.
- iii. Another factor that would have to be considered is that once the draft National Pharmaceutical Policy of 2017 comes into force, the concept of loan licensing would cease to operate. As per this system, any new entrant in the industry who does not possess enough funds or expertise to set up its own manufacturing unit was permitted to approach the licensing authorities along with an existing entity to obtain a licence to use the latter's manufacturing unit for production of its drugs. Once loan licensing is barred, a new entrant does not only need to establish its trade channels but also to establish its own manufacturing unit.
- iv. A new entrant should also be mindful of the fact that apart from being a developing country, India is an extremely price competitive market considering that it is dominated by generics. High costs of innovation and research & development shall not entitle the patentee/innovator to commercialise its product at prices akin to those charged in other more developed countries.
- v. The new entrant shall have to create a niche for itself in the market without advertising its products. Advertisement of drugs is barred under the Drugs & Cosmetics Rules, 1945 which are framed under the Drugs & Cosmetics Act, 1940.
- vi. Further hurdles may be faced at the stage of introducing the drug to healthcare professionals. The proposed Essential Commodities (Control of Unethical Practices in Marketing of Drugs) Order, 2017 places several restrictions on the practices of companies of incentivising prescription of drugs by healthcare professionals.
- vii. Intense pre-launch planning shall need to be adopted in order to ensure that all regulatory requirements imposed by the Drugs & Cosmetics Act, 1940 and the Rules thereunder are met sufficiently in advance of the commercialisation date. This includes obtaining the requisite approvals for research and testing, concluding all requisite trials envisaged under the Rules, permissions to manufacture and market, etc.
- viii. As there exists no concept of patent linkage in India, the entrant shall have to pursue its application for a patent and that for regulatory approvals in an independent and parallel manner to obtain both in time. However, applicants are allowed to rely on clinical studies conducted in other countries like the USA in order to skip certain phases of trials in India. The innovator company will also have to bear in mind that there are no laws for Data Protection in India which essentially means that clinical trial data of innovator companies can be used by other companies.

Other considerations that may be relevant are:

- i. The pharmaceutical industry in India illustrates the peaceful co-existence and encouragement to innovative drugs, as well as to generics and biosimilars. Several policies and guidelines have been framed and implemented to ensure the simultaneous survival of all types of drugs. In fact, biosimilar versions of drugs are allowed to rely

on regulatory data filed by the innovator for the main drug and may skip either or both phase I (human pharmacology studies) and phase II (therapeutic exploratory) trials under the drug regulatory scheme.

- ii. As discussed in the preceding sections, the new entrant must show the manufacturing of its drug in India if the same is a subject matter of a patent. This is to satisfy the requirement of ‘working’ of the patent. Failure to sufficiently work the patent or to meet the reasonable requirement of the public or to provide access to the drug at affordable prices may attract the consequences of revocation of the patent or compulsory licensing thereof under Sections 64 and 84 of the Patents Act, 1970, respectively. Several pharmaceutical companies have therefore followed the Gilead licensing model whereby Gilead entered into generic licensing agreements with Indian manufacturers for its blockbuster drug, Sofosbuvir.
- iii. The requirement provided under Section 3(d) of the Patents Act, 1970 for pharmaceutical substances to show enhanced therapeutic efficacy if they are new forms of known substances has been a subject matter of intense debates globally. However, this threshold can be crossed easily if the patentee is not indulging in ever greening, as was illustrated in the authoritative *Novartis AG v Union of India*<sup>11</sup> decision by the Supreme Court of India.

Overall, a new entrant shall be required to have an in-depth grasp of the existing market scenario, prevalent regulatory and policy requirements, and knowledge of existing and future products in order to strategise entry into the great India pharma market.

\* \* \*

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# Ireland

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## Abstract

In Ireland, State expenditure on medicines is approximately €2 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 is no distinct approval pathway for rare disease medicines or high-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 cost-effectiveness of their products. Despite this, suppliers face significant challenges in securing reimbursement of new medicinal products in Ireland, especially high-tech medicines and those for rare ‘orphan’ diseases.

## Market Introduction/Overview

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

In Ireland, healthcare policy and expenditure is 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 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 high-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 new framework agreement with industry in 2016 for the supply and pricing of medicines to help contain pharmaceutical costs.

Despite the savings provided by these measures, there has been little growth in the HSE budget for medicinal products. Consequently, suppliers face significant challenges in securing reimbursement of new medicinal products, in particular high-tech medicines and those for rare orphan diseases. This is compounded by the fact that there 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 cost effective are facing reimbursement delays due to the lack of overall affordability for the Irish healthcare system.

The high cost of new innovative drugs and delays in reimbursement are among the key challenges for market access in Ireland.

## **Pharmaceutical Pricing and Reimbursement**

### Regulatory Classification

There are two main supply categories of medicinal products in Ireland: (i) prescription-only; and (ii) non-prescription products.

Prescription-only medicines are those which require medical supervision and are available only with a doctor's or dentist's prescription, and dispensed through pharmacies. Prescription-only medicines tend to be dispensed to patients by community pharmacists and are reimbursed by the State.

Non-prescription medicines consist of two classes: (i) pharmacy-only products that are available under the supervision of a pharmacist; and (ii) general sale products that can, with reasonable safety, be sold without the supervision of a pharmacist. In general, non-prescription medicines are not reimbursed by the State, but certain non-prescription items are reimbursable where a doctor prescribes them.

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

### Who is/Who 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 €2.50 per item prescription charge (up to a maximum charge of €25.00 per family per month) and the pharmacist receives a dispensing fee, but no mark-up. The GMS scheme applies to those who do not have sufficient means to pay for their medicine.
- Drug Payment Scheme (DPS): a patient pays a maximum of €144 per month for medicines supplied to them and their family, and the pharmacist receives both a mark-up and a dispensing fee.
- Long Term Illness Scheme (LTI): provides medicines to patients with specific long-

term medical conditions, such as diabetes and epilepsy, free of charge. The LTI scheme is not means tested and therefore does not depend on a patient's income or other circumstances. Similar to the DPS, the pharmacist receives a mark-up and a dispensing fee.

- **Hi-Tech Scheme:** a patient receives expensive medicines required for long-term care and either pays the first €144 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 in the month when an item is dispensed and €30.26 in the months where no item is dispensed.

Payments to pharmacists are regulated by HSE Community Pharmacy Contractor Agreements and the Health Professionals (Reduction of Payments to Community Pharmacy Contractors) Regulations 2013 (SI 279/2013), as amended.

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

The HSE is the relevant decision-making body for state reimbursement of medicines in Ireland. For this purpose, the Health (Pricing and Supply of medical Goods) Act 2013 (2013 Act) requires the HSE to maintain a positive list of reimbursable medicines (Reimbursement List).

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

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

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

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

- the health needs of the public;
- the cost-effectiveness of meeting health needs by supplying the item concerned rather than providing other health services;
- the availability and suitability of items for supply or reimbursement;
- the proposed costs, benefits and risks of the item or listed item relative to therapeutically similar items or listed items provided in other health service settings and the level of certainty in relation to the evidence of those costs, benefits and risks;
- the potential or actual budget impact of the item or listed item;
- the clinical need for the item or listed item;
- the appropriate level of clinical supervision required in relation to the item to ensure patient safety;
- the efficacy (performance in trial), effectiveness (performance in real situations) and added therapeutic benefit against existing standards of treatment (how much better it treats a condition than existing therapies); and

- the resources available to the HSE.

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

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

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

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

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

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

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

For products falling outside this criterion, the HSE requests a recommendation from the HSE Drugs Group, which performs an in-depth assessment of the product. As part of the Drugs Group review, the HSE’s Corporate Pharmacy Unit (CPU) may interact and lead any commercial negotiations with the applicant.

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

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

The 2013 Act requires the HSE to provide the applicant with a formal notice of its proposed

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

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

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

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

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

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

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

The 2016 Agreement sets the ex-factory price at the currency-adjusted average ex-factory price (price to wholesaler) in 14 EU Member States, namely, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Luxembourg, Portugal, the Netherlands, Spain, Sweden and the UK. Medicinal products are subject to an annual price realignment to the average ex-factory price of the 14 Member States and only downwards price realignments are permitted. Suppliers must pay the HSE a rebate of 5.25% (1 June 2016–31 July 2018) and 5.5% (1 August 2018–31 July 2020) of the ex-factory price.

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

The wholesale mark-up for community reimbursement schemes is set out in statutory instruments. The current statutory wholesale mark-up is 8% for room temperature medicines and 12% for medicines which require refrigeration. A wholesale mark-up of approximately 10% is currently paid for hi-tech medicines.

The 2013 Act also introduced a system of reference pricing for generic and brand-named medicines that are deemed interchangeable. The Act permits pharmacists to substitute



lower cost or generic medicines when a more expensive product is prescribed, provided all the medicinal products fall within the same group of interchangeable products. The Irish Health Products Regulatory Agency (HPRA) decides (on a case-by-case basis) which products are interchangeable and publishes the national list of interchangeable product groups. The 2013 Act specifically excludes biological medicines from being considered interchangeable.

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

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

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

The final criterion above requires the HSE to take into account the terms of the 2016 Agreement and agreements between the HSE and the Irish Generic Medicines Association (IGMA). It is important to also note the penultimate criterion which specifically states that the “resources available to the HSE” must be taken into account. Lack of resources has been a factor which has been cited in decisions to not reimburse a number of drugs in recent times. In summer 2017, nine drug treatments which the HSE had approved were not reimbursed due to lack of resources.

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

A supplier does not need to agree a price for a medicinal product before it is placed on the Irish market if reimbursement will not be sought. Where the product is to be included in the Reimbursement List, the price of the new medicine is subject to the criteria in the 2013 Act and the 2016 Agreement. That is, the product must be priced at the currency-adjusted average ex-factory price in the 14 reference EU Member States. If the product is not available in all 14 Member States on the date the supplier submits its initial reimbursement application to the HSE, the price of the product is calculated as the currency-adjusted average ex-factory price in those reference Member States in which the medicine is available. Where the medicinal product is not available in any of the reference Member States, the supplier must propose a price. In addition, if the product is subject to a HTA and the supplier submits a lower price in the HTA application, the lower price will apply.

Where the proposed price of a medicine means that the product has an ICER exceeding €45,000 per QALY, and thereby is deemed not 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 billion *per annum*. This is approximately 14% of the total health budget and represents over 7% of GDP. The long-term expenditure on medicinal products is expected to increase due to factors such as demographic trends and the development of hi-tech drug treatments.

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

In the context of such an ageing population, demand for medicines, especially for chronic diseases, will increase. As a result, there is likely to be additional pressure on future State funding and supply of medicinal products. This funding challenge is exacerbated by the fact that new innovative medicines are in the main high-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. 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, 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.

The State needs to adopt a pricing and reimbursement policy that strikes a balance between affordable access to medicines and fostering innovation. The introduction of additional severe price control measures in the reimbursement of innovative medicines to constrain public expenditure risks significantly impacting the future development and manufacture of innovative medicines, a key industry for the Irish economy.

## Emerging Trends

The pricing and reimbursement of medicinal products in Ireland has undergone significant changes in recent years. The 2013 Act and the 2016 Agreement introduced a number of measures to reduce healthcare expenditure, however, the pricing of drugs and market access remains controversial.

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. Generally delays occur when price negotiations are required between the HSE and pharmaceutical companies, but increasingly delays are occurring after a new medicinal product has received a positive HSE decision that it will be added to the Reimbursement List. This is due to a lack of affordability of the HSE to fund these medicines within its current budget. Consequently, there are considerable delays in market access for innovative medicinal products in Ireland compared to the 14 reference Member States. This is leading to increasing frustration and lobbying from the Irish innovative industry and from patient groups.

Recently, the reimbursement process has come under scrutiny in relation to orphan products. In 2017, the marketing authorisation holder for the orphan product Translarna® (INN: Atularen) launched the first legal proceedings in the Irish Courts appealing a HSE reimbursement decision. Also, in February 2018, the Oireachtas Joint Committee on Health issued a report on the evaluation of orphan drugs that highlighted the inadequacy of the current reimbursement system and the use of the QALY assessment criterion for orphan products. The Committee recommended considerable change to the evaluation process of orphan drugs and for the Department of Health to commence a review of the 2013 Act to identify potential legislative barriers to the reimbursement of orphan drugs and corresponding legislative amendments.

With an ageing population in Ireland and the increase in new innovative high-tech drugs, the cost pressures for reimbursement means the HSE is increasingly focused on real world evidence and patient outcomes to demonstrate clinical and cost-effectiveness. Suppliers are also entering into novel contractual arrangements, in particular nurse led support services and medication adherence programmes for chronic diseases to add value, and risk-sharing or performance-based agreements to manage uncertainty as to clinical value and cost-effectiveness of products.

The Irish Government also is seeking greater co-ordination on access to medicines and has joined two cross-border initiatives, the BeNeLuxa Initiative and the Valleta Declaration, that seek to collaborate on HTAs and price negotiations of new medicines across various EU Member States.

## Successful Market Access

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

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# Japan

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## **Abstract**

Japan has adopted a universal public healthcare system, and on this assumption all prices of prescription drugs are determined by the government in a unified way. As a general rule, the price of a new drug is determined by an efficacy comparison method with the most similar drug existing, however, in the absence of a similar drug, it is determined by the cost allocation method based on cost. Although drug prices are currently revised once every two years in principle, the drug pricing system will be drastically reformed. The manufacture and sales, etc. of pharmaceutical products is regulated by various laws and regulations. Although we have to say that the barriers to entering the pharmaceuticals market in Japan are high due to various regulations, there appears to be plenty of opportunities for entry to the market through innovative pharmaceutical products such as biopharmaceuticals, and by the use of M&As and alliances.

## **Market Introduction/Overview**

Japan's population is steadily decreasing with a situation of a progressively declining birth rate and ageing population.<sup>1</sup> Conversely, the market size of the Japanese pharmaceutical industry is largely expanding, and as explained in section "Policy Issues That Affect Pricing and Reimbursement" below, national medical expenses are also increasing due to the increase in the ageing population, etc.

Japan's medical system has the characteristics of (1) a universal public health insurance, (2) free access, and (3) medical fee points (official price) system centering on a fee-for-service basis. Japan's medical insurance system is highly evaluated, Japan has one of the longest life expectancies in the world, and it has leading health indicators, such as the infant mortality rate. However, as stated in section "Emerging Trends" below, institutional reforms are underway to curb medical expenses, etc. Further, the price of prescription drugs and the end users, etc. are described in section "Pharmaceutical Pricing and Reimbursement" below.

## **Pharmaceutical Pricing and Reimbursement**

### Premise

With respect to the development, manufacture, import and sales, etc. of pharmaceutical products, it is difficult to comprehensively and briefly describe all of the various regulations because they are subject to various laws and ordinances, including the Pharmaceutical and Medical Devices act (the "PMD Act"). Therefore, here we shall briefly describe the important points.

## Classification of Pharmaceutical Products

Pharmaceutical products are classified depending on the usage and the supply route as follows.

- (1) Pharmacy-only pharmaceuticals: Refers to pharmaceutical products other than drugs requiring guidance and non-prescription drugs. Among these are prescription drugs (pharmaceutical products used by physicians or dentists or supplied for the purpose of being used by prescription of these persons).
- (2) Drugs requiring guidance: The efficacy effect on the human body is not significant, they are used by the end user's choice based on information from the pharmacist, etc., and face-to-face sales by the pharmacist is mandatory for their proper use. Deleterious and switch over-the-counter ("OTC") drugs fall under this classification.
- (3) Non prescription drugs: The efficacy and effect on the human body is not significant, and they are used by the end user's choice based on information from the pharmacist, etc. Depending on the degree of risk, they are classified as Class 1 OTC drug (especially high risk), Class 2 OTC drug (relatively high risk) and Class 3 OTC drug (risks are relatively low).

In addition, there are pharmaceutical products with strong toxicity, severe side effects and products that have a tendency to addictiveness and dependency, etc. among these products, and they are classified and regulated from a safety aspect, etc. in accordance with related laws such as the PMD Act and the Stimulants Control Act. There are other classifications and regulations regarding products of biological origin and regenerative medicine products, etc.

## Main Regulations, etc.

To conduct manufacturing and sales of pharmaceutical products, etc. as a business, it is necessary to obtain a licence for the corresponding type of manufacturing and sales business from the prefectural governor. In the pharmaceutical products manufacturing and sales business, it is a licensing requirement to assign a pharmacist as a marketing supervisor general of the pharmaceuticals, etc., and to comply with the standards for quality control and the standards for post-manufacturing and sales safety management. A manufacturing and sales licence is valid for five (5) years.

In addition, in order to manufacture pharmaceutical products, etc. as a business, it is necessary to comply with the Regulations for Buildings and Facilities for Pharmacies which are the standards of structural equipment corresponding to the classification specified by the Ordinance of the Ministry of Health, Labour and Welfare (the "MHLW") for each manufacturing facility, and a manufacturing licence must be obtained for each classification. Persons that intend to manufacture pharmaceutical products, etc. exported to Japan from foreign countries (foreign manufacturers) must obtain certification from the MHLW.<sup>2</sup> The criteria for certification and the classifications are the same as the standards for manufacturing licences for domestic manufacturers. The manufacturing certification is valid for five (5) years. The application for renewal of certification must be submitted five (5) months prior to the expiry date of the certification.

Furthermore, in order to manufacture and sell pharmaceutical products, the manufacturing and marketing approval for each product must be obtained in advance from the Minister of Health, Labour and Welfare or prefectural governor after conducting a mandatory review of the quality, efficacy and safety of the pharmaceutical products. In order to obtain manufacturing and marketing approval for each product, a manufacturing facility that has a manufacturing licence must comply with ministerial ordinances on GMP, which are the

standards of manufacturing control and quality control for each item of structural equipment and the products to be manufactured, etc.

In addition, a licence must be granted from a prefectural governor, etc. to conduct the business of sales and provision of pharmaceutical products. The sales business licence of pharmaceutical products is categorised into: (1) retailers at stores (businesses that sell or provide drugs requiring guidance or non prescription drugs at stores); (2) household distributors (business to sell or provide non prescription drugs by distribution); and (3) wholesalers (business to sell or provide pharmaceutical products to a pharmacy proprietor, manufacturer and seller, manufacturer, and distributor of pharmaceutical products, hospitals, clinics and other persons specified by an Ordinance of the Ministry of Health, Labour and Welfare). A business sales licence of pharmaceutical products is valid for six (6) years. For (1) retailers at stores and (2) household distributors above, a pharmacy proprietor or a registered seller can sell pharmaceutical products of Class 2 and Class 3 OTC non prescription drugs. Products sold online must be sold from a physical store that has obtained a sales licence. For (3) wholesalers above, a pharmacy proprietor must be present in each sales office and must manage such sales office.

Further, it is necessary to pay attention to the Japanese Pharmacopoeia (“JP”). The JP is the standard of medical products to regulate the properties and quality of drugs published by the Minister of Health, Labour and Welfare after hearing the opinion of the Pharmaceutical Affairs and Food Sanitation Council (“PAFSC”). A full revision is conducted every five (5) years, and partial revisions are done in between that time.<sup>3</sup> In addition, there are also various regulations on indications, attachments, advertisements, information provision, etc. in regards to pharmaceutical products.

### Drug Pricing System

The price of a prescription drug in Japan, regardless of whether it is a new drug to the market or an existing one, or whether it is a drug still under patent or a generic drug, is determined by the government in a unified way. That is, it is stipulated that, in the case of insurance medical treatment, “When an insurance medical institution or insurance pharmacy makes an insurance claim, the price of the drug is calculated based on the price prescribed by the drug pricing standard”. The drug price is the official price for insurance medical treatment and is a unified price nationwide. In Japan, the determination of this drug price is referred to as the listing to the drug pricing standard. The drug pricing standard has the meaning of a drug price list, and it also has the characteristic of a product list that prescribes drugs that can be used for medical insurance treatment.

After obtaining manufacturing approval of a prescription drug, the price for prescribing the drug to a patient of a medical institution is determined in two to three months, in principle, and it is put on the market. In principle, 70% of the price will be covered by medical insurance and the remaining 30% will be borne by the patient. Therefore, the medical institution receives 30% of the drug price prescribed to the patient from the patient, and the remaining portion covered by insurance is claimed from the payer (such as a health insurance society), and is then reimbursed from the payer to the medical institution.

In principle, the products listed in the National Health Insurance (“NHI”) drug pricing standard are manufactured and approved as prescription drugs under the PMD Act. Pharmaceutical products that fall under non-prescription drugs or drugs requiring guidance, etc. are not listed in the NHI price list, and the pricing is determined by the seller. Hereinafter, “drugs” and “new drugs” shall mean “prescription drugs”.

The price of new drugs shall be determined, in principle, by the similar efficacy comparison method. The similar efficacy comparison method is a method that selects the most similar

drug from the same type of existing drugs, in terms of efficacy effect, composition, etc., and makes slight modifications based on that as the price of the new drug. At that time, a particularly low price is set for those drugs that are certified as having a lack of novelty. Conversely, the cost accounting method is used when launching a new drug without a similar drug efficacy. The cost accounting method is a method of calculating the price by multiplying the total cost of the drug by a certain profit margin and adding a distribution expense and the consumption tax. It is prescribed that an additional amount should be added for the innovation, usefulness, marketability (small market size), etc. to the price calculated by the above method.

After the drug goes on the market, market mechanisms are used without distinction between an original drug or a generic drug, and the price is revised once every two (2) years in principle. Although redemption is made in the official price, the wholesale price, i.e., the price charged by the wholesaler to the medical institution can be determined by the seller (free pricing), and it will decrease through market competition. In the price revisions conducted once every two (2) years, the wholesale price is investigated by the government, and the new redemption price is determined by adding an adjustment range of 2% to the weighted average value.

An exception to the above is the premium to promote the development of new drugs and eliminate off-label use. After the new drug goes on the market, the redemption prices should basically be decreased based on the wholesale prices with medical price revision every two (2) years; however, under this rule, the price level is maintained for the purpose of promoting the creation of innovative new drugs. Another exception is the expansion re-pricing rule. This rule is for drugs whose sales increased more than originally expected, and at the time of drug price revision, the price is further decreased from the price calculated based on the wholesale price. There are several other re-calculation methods.

### Criticism and Issues of the Drug Pricing System

As described in “Drug Pricing System” above, the listing in the NHI drug pricing standard has a very important meaning since a drug cannot be used for insurance treatment unless it is listed in this standard. However, it can be pointed out that the review process related to the listing in the NHI drug pricing standard lacks transparency on grounds that no information is disclosed during the process except for certain materials.

While the drug price is determined as stated in “Drug Pricing System” above, there is criticism that the government is attempting to keep the drug price as low as possible in order to reduce medical costs. Furthermore, it can be pointed out that innovation is being obstructed by such price restraint.

In addition, as price revisions should be conducted once every two (2) years for prescription drugs, there was supposed to be a price review for Opdivo for a revision of the NHI drug pricing standard in December 2017 (effective April 2018), however, since there was an urgent price decrease made in February 2017, it was pointed out that this incident exposed the high level of uncertainty in Japan as a drug discovery environment (meanwhile, some voices pointed out the advantage that Japan’s social security expenses were suppression by JPY 19.6 billion based on the budget of fiscal year 2017).

### **Policy Issues That Affect Pricing and Reimbursement**

National medical care expenditure for the fiscal year 2015 was JPY 42.36 trillion which is a 3.8% increase from the previous fiscal year. National medical care expenditure per person was JPY 333.3 thousand which is a 3.8% increase from the previous fiscal year. Also, the



ratio of national medical care expenditure to gross domestic product (GDP) was 7.96% (the previous fiscal year was 7.88%), which is increasing every year.

One of the factors of increasing national medical care expenditure is the rising number of the elderly population. The national medical care expenditure by age categories are: JPY 2.53 trillion for ages 0–14 (6% of total of all age categories); JPY 5.32 trillion for ages 15–44 (12.6% of the same); JPY 9.38 trillion for ages 45–64 (22.1% of the same); and JPY 25.13 trillion for ages 65 and above (59.3% of the same). The population of ages 65 and above uses more than half of the expenses while it constitutes 26.7% of the aggregate population. Since the proportion of the elderly population is expected to increase for another 25 years or so,<sup>4</sup> in terms of securing financial sustainability of medical insurance, cutting medical expenditure is one of the primary issues of Japan.

### Situation of Research and Development of New Drugs

Japan aims to make the pharmaceutical products and medical device industry the Japan's leading industry to achieve its economic growth as well as to provide the world's-best-standards pharmaceutical products and medical devices to citizens. However, the success rate of innovative new drug development is only one out of 20 thousand to 30 thousand, which is very low. The risk is high as it requires long-term investment from 10 billion dollars up to 100 billion dollars per item making the process challenging.

Furthermore, in recent years, self-developed products are decreasing and, in turn, the ratio of in-licensed products from other companies are increasing, attributable to soaring research and development costs for development, etc. of biopharmaceuticals fulfilling the unmet medical needs, accelerating demand for higher safety level and decreasing operating profit resulting from competition with generic drugs.

## **Emerging Trends**

### *Radical Reform of Drug Pricing System*

A drastic review of the drug pricing system will be implemented to pursue both “sustainability of universal national healthcare” and “promotion of innovation”, and to realise “reduction of citizen's burden” and “enhancement of quality of medical care” from the fiscal year 2018. Major points to be reviewed are as follows:

- Correspondence to growing market after NHI price listing. Review drug prices by making maximum use of the opportunity of new drug listings (four times a year) in order to correspond promptly to market growth of a certain size following addition of efficacy, etc.
- Drug price survey and revision for the in-between years. In addition to the drug price survey currently conducted once every two years, conduct a drug price survey for all items for the in-between years and revise drug prices of those with a large price gap in accordance with the result of such surveys.
- Assessment of innovation (Review of the premium to promote the development of new drugs and eliminate off-label use and adopt cost efficiency assessment).
- Zero-based drastic review of the premium to promote the development of new drugs and eliminate off-label use system to promote the development of innovative new drugs.

In addition, to fully adopt a cost efficiency assessment including raising drug price for cost-efficient drugs (considering implementation methods such as an organisation system).

### Criticism Against Radical Reform Policy of Drug Pricing System

Among the radical reform, the pharmaceutical industry criticises the reviewing policy of the premium to promote the development of new drugs and eliminate off-label uses on the

grounds that the new policy will reduce the number of items covered by this system by 40%. It is said to: increase the risk of not being able to collect the research and development investment; cause pharmaceutical companies to significantly lose motivation to develop new drugs; hinder development of innovative new drugs; and distance research investment from overseas to Japan.<sup>5</sup>

## **Successful Market Access**

### Creation of Innovative Medical Products

As stated in section “Emerging Trends” above, although the range of products covered by this year’s drastic reforms has been narrowed, the development of innovative pharmaceutical products is of key importance because innovative pharmaceutical products are still protected by the premium to promote the development of new drugs and eliminate off-label use, and drug prices can be maintained. In particular, with regard to biopharmaceuticals, domestic pharmaceutical companies have focused on the development of low molecular drugs in the past, so they have been lagging behind in the development of new drugs and there is plenty of opportunity to access this market.

Also, like in other countries, the cost-benefit performance assessment (“HTA”) has also been introduced experimentally in Japan, and it is expected that the trend of determining the price of pharmaceutical products by assessing the value of pharmaceutical products from multiple point of views will spread. In the future, in addition to the development of innovative new drugs, it is necessary to negotiate with the government based on the comprehensive data on the improvement of quality of life, the reduction of medical expenses and the improvement of social productivity, etc.

### M&As and Alliances

It is important to utilise M&As and alliances to enter the pharmaceutical market in Japan. As stated in section “Policy Issues That Affect Pricing and Reimbursement” above, domestic pharmaceutical companies have no choice but to pursue alliances, M&As, open innovation with pharmaceutical companies overseas, and bio ventures, and not only their own development. Recently, Japan’s largest pharmaceutical company announced an offer to buy Ireland’s leading pharmaceutical company for the purpose of strengthening the R&D framework focusing on the creation of pipelines and groundbreaking innovation. Other Japanese pharmaceutical companies have also shown a willingness for large-scale M&As, and it is expected that cross-border M&A activity will be activated with the purpose of obtaining synergies such as sales growth due to obtaining the rights of developed drugs.

\* \* \*

## **Endnotes**

1. Please refer to the following link: <http://www.stat.go.jp/english/index.html>.
2. Please refer to the following link: <http://www.pmda.go.jp/english/review-services/reviews/foreign-mfr/0001.html>.
3. Please refer to the following link: <http://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0009.html>.
4. Please refer to the following link: [www.mhlw.go.jp/english/wp/wp-hw9/dl/01e.pdf](http://www.mhlw.go.jp/english/wp/wp-hw9/dl/01e.pdf).
5. Please refer to the following link: [http://www.phrma-jp.org/wordpress/wp-content/uploads/2017/12/phrma\\_efpia\\_pressrelease20171220\\_e.pdf](http://www.phrma-jp.org/wordpress/wp-content/uploads/2017/12/phrma_efpia_pressrelease20171220_e.pdf).

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# Mozambique

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## **Abstract**

Mozambique has a very preliminary Pricing and Reimbursement system. Recent legislative developments show a growing and encouraging concern with access to medicinal products. However, further regulation, as well as improvement of the country's general economic outlook, is required before the system can become more sophisticated and effective.

## **Market Introduction/Overview**

Mozambique is a large country in East Africa, with an area of 801,590 km<sup>2</sup> and an estimated population of 28,861,863 inhabitants.

The health and pharmaceutical sector in Mozambique is still small and lacking in diversification. However, it is rapidly expanding.

Healthcare services are provided by: (i) the public sector, under the National Health Service ("NHS"), which is the most geographically extensive and technically advanced; (ii) the private sector that is divided into profitable, with almost exclusive presence in the urban areas, and non-profitable, comprising national and international NGOs with strong links to the public sector; and (iii) traditional medicine practitioners, widely accepted by local communities, offering non-allopathic medicines and complementary to conventional medicine.

The performance of these sectors is still below their potential for growth, due to the various limitations that affect the market, such as undeveloped medical facilities, shortage of medicines, and lack of qualified human resources. Studies carried out in 2010 indicated that the country had only 3.05 physicians and 25 nurses per 100,000 inhabitants, a proportion that is among the lowest in the world.

Even though the NHS benefited from major progress in the last few years, healthcare units still only cover about half of the population and some of them lack adequate conditions to provide healthcare services, including medicine distribution. In addition, the NHS is underfunded, and heavily dependent on external financing to purchase medicines. In September 2013, the Ministry of Health approved a Strategic Plan for the Health Sector 2014–2019 that defined several strategies and reforms aimed at solving the main problems in the health and pharmaceutical sectors.

Recent improvements in Mozambique's standard of living and public commitment with the creation of an enhanced Health System offer promising signs of improvement.

## **Pharmaceutical Pricing and Reimbursement**

### Regulatory classification

Regulation of pharmaceutical products is governed by Law no. 12/2017 of 8<sup>th</sup> September

(“Law 12/2917”), which establishes the rules applicable to the production, distribution, use and marketing of medicines, vaccines, biologic products and health products. Medicines are generally subject to medical prescription. Medicines that are not subject to medical prescription are those included in a list that is periodically approved by the Ministry of Health. Medicines can only be purchased by and used within the NHS if they are included in the National Medicine Form or in the List of Essential Medicines. Both the National Medicine Form and the List of Essential Medicines are periodically revised and published by the Ministry of Health, which is also responsible for ensuring that the medicines included in these documents are, in fact, used. Only private sector providers of healthcare services can prescribe medicines and other health products that are not included in these documents, provided that these products are included in the list of medicines that are registered and authorised in Mozambique.

Reimbursement of medicines is not specifically regulated by Mozambican laws. The applicable legislation does, however, establish situations in which medicines can be provided free of charge. Law no. 2/77 of 27<sup>th</sup> September (“Law 2/77”) establishes that medicines for hospitalised patients should be provided free of charge. Law 2/77 also establishes that “basic medicines” could be provided free of charge for outpatient treatment, and that such medicines would be indicated in a List to be defined by the Ministry of Health and the Ministry of Finances. Said list was later approved by Ministerial Order no. 24/85 of 3<sup>rd</sup> of July (“Ministerial Order 24/85”). Ministerial Order 24/85 further established that all medicines distributed by Community Health Workers (a network of healthcare providers in remote areas) would be free of charge, and that medicines dispensed by the primary care network in rural areas would have a single price of 20 MT per prescription (and should be paid by the State in the price exceeding that amount). Medicines provided free of charge pursuant to Law 2/77 and Ministerial Order 24/85 can only be distributed in medicine distribution points and pharmacies of the Government which are attached to the healthcare units where such medicines are prescribed. Medicines which are part of the National Medicines List and which are not included in the list of medicines provided for free pursuant to Ministerial Order 24/85 are purchased at their approved sales price.

Additionally, Decree no. 16/88 of 27<sup>th</sup> December created a Social Fund for pediatric medicines and food supplements, whereby population groups in need of economic support because they suffer from chronic conditions or because they belong to economically deprived groups (physically handicapped, elderly, unemployed, etc.) have access, in NHS pharmacies, to medicines subsidised by the State (state contribution to the price of medicines varies between 100%, 80% and 50% of their public sales price).

#### Who is/Who are the payer(s)?

The funding of the pharmaceutical and health sector of Mozambique comes from multiple sources and is greatly dependent on external resources, including donations. According to a report from the Medicines and Medical Supplies Department of the Ministry of Health, in 2012, the implementation rate of funding allocated for medicines was 99.9%. The main source of funding is public – the State Budget allocated by the Ministry of Finance, which includes direct contributions from the donor countries to Mozambique’s State Budget, funds from Mozambique’s Common Fund of Support for the Health Sector (designated in Portuguese as “PROSAÚDE”) and funds from vertical programmes. There are other less documented funding sources such as private contributions and contributions from families through payments in private clinics and hospitals and co-payments in State hospitals, among others. Apart from the State budget and PROSAÚDE, funds are controlled by the Ministry of Health, including earmarked revenue.

One of the strategies envisaged by the Strategic Plan for the Health Sector 2014–2019 approved by the Ministry of Health in September 2013 is to identify and document the gaps in the funding of medicine and liaise within the Ministry of Health and partner countries in order to obtain more funds. This Strategic Plan further designs a specific Funding Strategy for the health sector, which includes the exploration of more funding mechanisms.

Medicines can also be donated by other countries and foreign organisations to NHS institutions, as well as to other public or private institutions which are not part of the NHS, as provided for in Order of February 3<sup>rd</sup> 2010. In principle, the Government can only accept donations of medicines included in the National Medicines List.

Public institutions purchase medicines pursuant to public procurement procedures.

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

Since the Mozambican legislation does not currently establish a specific regime for reimbursement of medicines, there is no reimbursement procedure to be followed by pharmaceutical companies. When medicines are provided free of charge pursuant to Law 2/77 and Ministerial Order 24/85, the selection and payment of medicines are entirely handled by the Ministry of Health and the Ministry of Finances. The law does not specifically allow companies or suppliers to request that their medicines be included in the List. As for medicines that are funded through the Social Fund for pediatric medicines and food supplements, approved by Decree 16/88, the person belonging to a disadvantaged group is required to submit a request in his/her local pharmacy (or the place where they will retrieve the medicines) to gain access to the applicable co-payment.

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

As we have seen, there is not a specific reimbursement framework or methodology. The criteria for providing medicines free of charge to outpatients pursuant to Law 2/77 is the inclusion in a list of “basic medicines” approved by the Ministry of Health. In the case of funding of medicines pursuant to Decree 16/88, the percentage of funding attributed depends on the condition or status of the person receiving the medicines.

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

Law 12/2017 created a National Regulatory Authority of Medicines (designated in Portuguese as “ANARME”), replacing the Medicines Council created by the previous regime.

A new price regime was also approved by Ministerial Order 21/2017 of 13<sup>th</sup> March (“Ministerial Order 21/2017”). The former regime established different criteria for price calculation. The methodology differed in accordance with the category of the medicine. A reference prices system was also in force, based on a price comparison with the average price of reference countries, and the price of medicines whose active substance already existed in the market (and generics) depended on the price of medicines that were currently on the market.

The regime enacted by Ministerial Order 21/2017 does not, however, consider these aspects, and is rather focused on simplifying price setting, and adapting it to the particular costs associated to importing medicines to Mozambique.

Pursuant to Law 12/2017, ANARME is the authority responsible for proposing the pricing of medicines, vaccines and biologic products, while the Council of Ministers is responsible for regulating the public sales price of medicines, profit margins and the price revision mechanisms.

The pricing of medicines, as noted above, is regulated by Ministerial Order 21/2017. The Public Sales Price of medicines is set by the Pharmaceutical Department of the Ministry

of Health for all national territory, based on a proposal by the Importer-Wholesaler. This proposal should contain the following elements:

- (i) Indication of the Free on Board (“FOB”) price;
- (ii) Indication of the Cost, Insurance and Freight (“CIF”) price;
- (iii) Indication of the Wholesale Price;
- (iv) Indication of the Retailer Sales Price;
- (v) Indication of the Public Sales Price; and
- (vi) Indication of the Sales Price to FARMAC Pharmacies (FARMAC – Empresa Estatal de Farmácias; E.E. is the State Pharmacies Company that holds several public street pharmacies).

Ministerial Order 21/2017 further defines the criteria to calculate the Wholesale Price, the Retail Sales Price, Public Sales Price and the Sales price to FARMAC pharmacies. The Wholesale Price is calculated based on the CIF price, with the addition of bank, customs clearance, and harbour expenses, as well as other direct import fees charged until the distributor warehouse, until a maximum of up to 9% of the CIF price.

The Retailer Sales Price is calculated based on the Wholesale Price, to which accrues the Importer-wholesaler trade margin, which is set on 23.5% of the CIF price, and the trade margin of the distributor (to cover the transportation costs to the entire country), which is set on 5% of the CIF price.

The Public Sales Price is calculated based on the Retailer Sales Price, to which accrues the retailer trade margin that is set on 66.3% of the CIF price. The Public Sales Price of medicines dispensed in Farmac Pharmacies is deducted by 7%. Ministerial Order 21/2017 expressly forbids the sale of medicines at a different price than the prices set therein, except if medicines are dispensed in pharmacies attached to NHS health units. Notwithstanding, importers-wholesalers are entitled to submit a request (to practice higher prices) before the Pharmaceutical Department of the Ministry of Health if they consider the prices to be unbearably low.

#### Issues that affect pricing

Several issues affect the pricing of medicines in Mozambique. Lack of control and monitoring of the price throughout the supply chain, as well as the lack of a more developed legislation affects the price of medicines, since it increases the risk of medicines being sold at a higher price than they should, for instance, by the application of random mark-ups or by the adjustment of mark-ups according to the demand of specific medicines.

In addition, disparities in costs can lead to differences in prices based on geographical location, with a tendency for higher prices in urban areas. Surges in prices prevent the population from purchasing medicines at affordable prices, which in turn fosters the black market and counterfeiting of medicines. Furthermore, the lack of a Pharmaceutical Policy, the insufficient revision of the National List of Medicines, and the virtual absence of quality control due to limited capacity gives rise to quality issues. Indeed, only medicines that raise suspicion are monitored. Irrational prescription and consumption also affect the market and negatively influence the prices of medicines.

### **Policy Issues That Affect Pricing And Reimbursement**

Demographics, healthcare costs and political factors may influence pricing of medicines in Mozambique. Mozambique’s current population is estimated at approximately 28,861,000 inhabitants.

Mozambique suffers from a high incidence of HIV/AIDS and associated diseases, such as tuberculosis, which plagues most Mozambican families. Apart from infectious diseases,

the country is also beset by diseases that are characteristic of tropical countries, such as malaria, as well as seasonal, warm weather diseases, such as cholera, which had a serious outbreak in the North of the Country in the beginning of 2018. These diseases affect young people in the economically active range.

5.6% of the population is comprised of the elderly population. Most of that share of the population suffers from diseases such as hypertension, diabetes, cancer, osteoporosis, among others, aggravated by nutritional problems and physical inactivity.

Access to healthcare is extremely limited, especially in rural areas where the only healthcare providers are public. In urban areas, there is already a shift in this paradigm of supply, and private healthcare providers are increasing and becoming more visible.

Pursuant to the Strategic Plan for the Health Sector 2014–2019, the total expenditure on health was estimated at 6.2% of the GDP, and is increasing. Nevertheless, the system is still underfunded since the GDP *per capita* spent on health is below regional averages and the value that is recommended by the World Health Organization and the World Bank to finance a basic level of care. Politically, the legal and political environment is prone to the prosecution of health objectives; however, there are still situations of overlap, fragmentation and lack of coordination between laws and policies that hinder the creation and development of laws and policies regarding the pharmaceutical sector, including price and reimbursement of medicines.

### Emerging Trends

The Strategic Plan for the Health Sector 2014–2019 is still the best indicator of health-related trends in Mozambique. The Plan's main goals and strategies do not concern pricing and reimbursement. Nevertheless, this Strategic Plan did anticipate the revision and approval of a legal framework of medicines regulation. This goal seems to have been achieved with the entry into force of the new Medicines Law, approved by Law 12/2017, as well as the approval of a new pricing regime of medicines by Ministerial Order 21/2017. However, the new pricing regime is strictly based on the costs of freight. There is room for additional sophistication and fine-tuning, namely in the regulation of prices in accordance with the medicine's category or therapeutic indication. There is therefore a chance that the regime will be updated and replaced by a more ambitious regime in the next few years and when these conditions are met there will be perhaps a shift to reimbursement.

The Parliament's Annual Social and Economic Plan for 2018 recommends an increase in antiretroviral therapies for pregnant women, and an increase in child vaccination coverage.

A significant market trend has also recently emerged. A large part of the Mozambican population of the upper middle class has been seeking healthcare in neighbouring South Africa. This cross-border movement is a clear sign that the population's standard of living is increasing, and that demand of quality healthcare is higher than the supply. The country is bound to advance in this area, and it is predictable that creation of private clinics, construction of hospital infrastructures in rural areas, and the importation of medicines are stimulated by this tendency.

### Successful Market Access

The primary success factors for entering into Mozambique's market are to engage with local stakeholders. Interested parties should also monitor international calls for tender, considering that Mozambique's government often invites foreign companies to bid for tenders for the supply of medicines, which may provide a relevant opportunity for companies to enter in the market.



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# Norway

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## Abstract

All prescription-only medicines are given maximum prices by the Norwegian Medicines Agency prior to the placing of the product on the market. In the last 15 years, the maximum price has been set by external reference pricing, based on the average of the three lowest prices in nine countries in Europe.

The Norwegian healthcare system is primarily funded by taxes. Norwegian authorities reimburse the cost of the use of medicinal products through different regimes based on approval. In general, reimbursement decisions are based on health technology assessments performed by the Norwegian Medicines Agency and taking into consideration three prioritising criteria: benefit of the treatment; use of resources; and severity of the condition. If the conditions for reimbursement are not considered met at the medicinal products maximum price, price negotiations to lower the maximum price are possible.

From 2013 to 2016, a major investigation was carried out by the Ministry of Health and Care Services concerning priorities in the public health services. Based on this work, the three prioritising were introduced. The prioritising criteria were applicable as of 1 January 2018. Consequently, there is still uncertainty as to how these criteria will be applied in practice.

## Market Introduction/Overview

In 2017, Norway had a population of 5.3 million inhabitants, in which 25% were less than 20 years old, 62% between 20 and 55 years old and 13% older than 66 years. Average life expectancy for men was 80 years and 84 years for women (2017). The percentage of the population above 64 years is rising slowly. It is expected to increase significantly as a result of the ageing of the post-war generations.

In 2016, the total pharmaceutical market in Norway for medicinal products used in humans was NOK 26.6 billion, which corresponds approximately to EUR 2.8 billion.

The Norwegian healthcare system has developed gradually in the context of Norway's welfare policy. It is primarily funded by taxes. All residents of Norway are insured under the National Insurance Scheme (NIS), which is run by central Government. The healthcare system is mostly publicly owned. 422 municipalities (1 January 2018) are responsible for the provision and funding of primary healthcare. All citizens have the right to healthcare services in their community. Norway's four Regional Health Authorities (RHAs) are responsible for the financing, planning and provision of specialised care. There are about 25 health enterprises under the four RHAs. The Ministry of Health and Care Services (the Ministry) provides instructions to the RHAs by a "letter of commission".

The total number of deaths in 2012 was about 42,000. Diseases of the circulatory system are the leading cause of deaths – 31% of the total. Malign tumours accounted for 26% of deaths and diseases in the respiratory system accounted for 10%.

Being a member of the European Economic Area Agreement (EEA, consisting of the EU Member States and Norway, Iceland and Liechtenstein), Norway has implemented EU pharmaceutical law and takes part in EUs regulatory co-operation in medicinal products. The Norwegian Medicines Agency (NoMA) contributes to the work of the European Medicines Agency. As a consequence, the necessary marketing authorisation for entry into the national market may be obtained by pharmaceutical companies the same way and at the same time as for the Member States of the European Union. The Norwegian system for pricing and reimbursement is different from other countries, as these systems are largely decided on a national level.

## **Pharmaceutical Pricing and Reimbursement**

### Regulatory classification

#### **How are pharmaceutical products regulated?**

In Norway, no medicinal products may be placed on the market unless a marketing authorisation (MA) has been granted, *cf.* Section 8 of the Act on Medicinal products of 4 December 1992. MAs are granted either in a national procedure, or if the application for MA concerns more than one EEA Country, in the mutual recognition procedure, the decentralised procedure, or in the centralised procedure.

For new medicinal products, a full application is required providing data on quality, safety and efficacy as provided for in Article 8(3) of Directive 2001/83/EC, *cf.* Section 3–4 of Regulation No. 1839 of 18 December 2009 regarding medicinal products (MPR). For generic medicinal products and biosimilars, the medicines product regulation provides for an abridged application for a MA referring to the safety and efficacy data of the reference medicinal product (the original), *cf.* Section 3–9 of MPR. However, if the biosimilar does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

When a MA is granted, the competent authorities shall specify the classification of the medicinal product based on whether it is subject to medical prescription (POM), or a medicinal product not subject to medical prescription (OTC), see Chapter 7 of the MPR. Medicinal products shall be subject to medical prescription if they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision, or are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or are normally prescribed by a doctor to be administered parenterally.

POMs are only to be sold in pharmacies, including small outlets belonging to the pharmacies, *cf.* Section 16 of the Medicinal Products Act. Pharmacies are regulated by the Norwegian Pharmacy Act and the associated regulations on pharmacies. Most OTCs shall also exclusively be sold in pharmacies. Some outlets not connected to a pharmacy, such as grocery stores, gasoline stations, health stores, etc. are allowed to distribute a restricted list of OTCs. Doctors are in general not allowed to dispense medicines directly, beyond what

is necessary for the start of treatment before the patient can get access to a pharmacy, *cf.* Section 17 of the Medicinal Products Act.

In general, POMs holding a marketing authorisation are eligible for reimbursement within its approved indications. A positive decision on reimbursement is, however, in essence, dependant on a positive outcome of a health technology assessment (HTA) performed by NoMA. OTC and medicinal products not holding a MA are in general ineligible for reimbursement.

While hospitals and institutions pay for the use of medicinal products used in-house, there are different systems of reimbursement for medicinal products paid by the NIS. The most important is reimbursement under the so-called blue prescription regime. This system has its legal basis in Section 5–14 of the National Insurance Act, and is further regulated in Regulation No. 814 of 28 June 2006 on grants to cover expenses for important medicinal products (the Blue Prescription Regulation), and Chapter 14 in the MPR. It consists of pre-approved reimbursement and individual reimbursement.

Pre-approved reimbursement is the main scheme with nearly 2.36 million unique users and total refund of NOK 8.1 billion, while individual reimbursement had 139,000 unique users and total refund of NOK 2.1 billion (2016).

A system is also established to ensure that all patients with serious communicable diseases are given necessary treatment, *cf.* Section 4 of the Blue Prescription Regulation. This scheme had 34,000 users in 2016 and a total refund of NOK 449 million.

#### Who is/Who are the payer(s)?

There are mainly four payers for medicinal products in Norway. These are the Regional Health Authorities (hospitals) paying for the use of medicinal products in hospitals, NIS paying for medicinal products sold through the retail market used outside hospitals, the municipalities who pay for medicinal products used in municipal institutions such as nursing homes, and individuals who pay for medicinal products which are not reimbursed by the government.

Of the total sale of NOK 26.6 billion, 49% was paid by the NIS, 26% by the hospitals, 11% being the sale of OTC paid by individuals and 10% was related to the sale of POM not reimbursed (2016).

5% of the total sale was related to patients self-pay for medicines reimbursed by NIS. According to Section 8 of the Blue Prescription Regulation, the patient shall pay 39% of the prescription amount, but not more than NOK 520 per prescription. In the course of one year, the patient shall pay a maximum of NOK 2,258, *cf.* Section 4 of Regulation 18 April 1997 No. 334. Children under the age of 16 and persons holding only a minimum pension shall not pay.

Pharmaceutical expenditure in the Regional Health Authorities (hospitals) is covered by the hospital budgets. The patients do not have to pay for the medicines used in their treatment as long as the treatment takes place in the hospital, i.e. the medicines are purchased and paid for by the hospital.

#### The process for securing reimbursement for a new pharmaceutical product

From 1 January 2018, both the MPR and the Blue Prescription Regulation were amended concerning reimbursement of medicinal products. The new regulation is based on some general principles:

- Decisions on public funding of medicines should be based on the same principles of prioritisation, regardless of where the financial responsibility lies.

- A HTA shall be performed for all new medicinal products and new indications prior to reimbursement.
- Reimbursement should be assessed on the basis of the performed HTA and three prioritising criteria: benefit of the treatment; use of resources; and severity of the condition.
- A higher use of resources may be accepted for particularly small patient groups with a very serious condition.

### **Pre-approved reimbursement**

The pre-approved reimbursement under Section 2 of the Blue Prescription Regulation is a positive list containing medicinal products that shall be reimbursed for specified diagnoses, provided other given criteria are fulfilled.

Reimbursement under this system requires that the medicinal product is used outside hospitals. Furthermore, reimbursement presupposes that the patient has a serious disease for which long-term medication is necessary (more than three months per year), *cf.* Section 1a and 1b of the Blue Prescription Regulation.

In addition, the medicinal product must have a MA for the particular use, *cf.* Section 14–6 in the MPR. Some exceptions from this requirement apply to medicinal products used in palliative treatment in the final phase of life, and for medicinal products for children under the age of 18 years in which the active substance is reimbursed for the same indication in adults. NoMA may also in exceptional cases make other exceptions from the requirement, provided that the medicinal product has obtained an MA for the relevant indication in at least one EEA country.

The process for being included in the positive list is governed by Chapter 14 of the MPR.

Prior to the granting of pre-approved reimbursement, NoMA shall carry out a health technology assessment (HTA) to assess the benefits, use of resources and severity of the disease in which the medicinal product is used. The benefit should be measured by how many good years of life the measure provides for in patients within the current patient group, compared with relevant treatment practices. The use of resources should include the average cost of the medication as well as other use of resources in the health and care services, compared to relevant treatment practices. Severity should be measured by how many good years of life patients in the patient group lose on average in the absence of the measure which is being considered, *cf.* Section 14–3 of the MPR.

The right holder must submit the necessary documents enabling NoMA to perform the abovementioned HTA, *cf.* Section 14–4 of MPR. The submission must contain information on the following:

- which part of the medicinal products indication the information relates to;
- a description of the disease and epidemiology, including description and calculation of the severity of the disease;
- existing treatment options, including a description of Norwegian treatment practice within the relevant indication and the medicinal products place in the treatment;
- the use of the medicinal product in the sought indication including relative efficacy and adverse reactions;
- pharmacoeconomic analysis of benefits and use of resources; and
- expected number of patients and budget implications.

NoMA is obliged to clarify the matter adequately and may collect additional information from the right holder, clinical experts and representatives of the users.

The decision on whether to include the medicinal product in the positive list for the sought indications shall be taken no later than 180 days after NoMA received information pursuant to section 14–4, *cf.* Section 14–10 of the MPR. If the documentation for pre-approved reimbursement is submitted prior to the granting of the MA, the 180-day period will not start until there is a positive opinion for the granting of the MA. The deadline is suspended if NoMA considers it necessary to request additional information.

NoMA has competence to decide on whether a medicinal product should be included in the positive list, *cf.* Section 14–5 of the MPR. The decision shall be based on the performed HTA. A positive decision requires that the use of resources is considered to be in a reasonable proportion to the benefits of the medicinal product taking into consideration the severity of the disease.

There is no fixed amount limit for when a medicinal product is considered to meet the above criteria. However, the severity of the disease influences on the amount accepted. For small patient groups with a very serious condition and where the expected benefit of the medicinal product is high, NoMA may deviate from the above proportionality requirement. The use of resources must nevertheless be acceptable in relation to its benefit.

If NoMA considers that the granting of reimbursement will lead to a growth in the cost of medicines exceeding NOK 100 million in at least one of the first five years after the date of the decision, NoMA has no competence to add the medicinal product to the positive list. In such situations, consent from the Parliament is necessary, *cf.* Section 14–7 of the MPR.

Decisions on pre-approved reimbursement are influenced by the right holder providing data supporting a positive decision. When performing the HTA, NoMA may request the opinion of clinical experts. Based on our experience, the clinical experts' opinions may have significant influence on NoMA's decisions.

A decision on pre-approved reimbursement by NoMA may be appealed to the Ministry in accordance with the rules of the Public Administration Act. Section 28 provides that individual decisions may be appealed by a party or another person having a legal interest in appealing the case. The time limit for lodging an appeal is three weeks from the date on which notification of the administrative decision has reached the party concerned. According to Section 34 of the Act, the Ministry may try all aspects of the case and thereunder take new circumstances into account. It shall consider the views presented by the appellant, and may also take into consideration matters not addressed by him. Based on our experience, an appeal procedure will normally take at least six months, and often longer.

Even if the Ministry has competence to assess all aspects of the case, it normally sustains the decision by NoMA. However, last year the Ministry revoked a decision by NoMA not to grant pre-approved reimbursement, and referred the matter back to NoMA for reassessment.

The validity of NoMA's decision may also be tried in the court system.

### **Individual reimbursement**

According to Section 3 of Blue Prescription Regulation, reimbursement based on an individual application from the patient's doctor is possible. This option may be used when the actual use is not pre-approved under Section 2. Applications are to be sent by the doctor to the Health Economics Administration (HELFO). Reimbursement presupposes that the product is used outside hospitals for a serious disease for which long-term medication is necessary. For medicinal products receiving a MA after 1 January 2018, individual reimbursement may no longer be provided unless a HTA is performed.

Reimbursement may be granted for medical use not reimbursed under Section 2, if it is

documented for the individual patient that the use of resources is in a reasonable proportion to the benefit, taking into account the severity of the condition. If relevant pre-approved medicinal products for the particular disease exist, weighty medical considerations must be present in order to allow for individual reimbursement.

A decision on individual reimbursement is possible also for off label use. In such situations, reimbursement may be granted if the medicinal product has a scientifically well documented and clinically relevant efficacy for the particular disease. If relevant medicinal products holding a MA for the sought indication exist, weighty medical considerations must be established in order to allow for individual reimbursement.

A decision on individual reimbursement is taken by HELFO and may be appealed to *Nasjonalt klageorgan for helsetjenesten (Helseklage)*.

### **Medicinal products for the treatment of serious communicable diseases**

Medicinal products for the treatment of serious communicable diseases are reimbursed under Section 4 of the Blue Prescription Regulation. There is no patient co-payment for these medicines and normally the patient does not have to be a member of NIS. Examples of products reimbursed are medicines used to treat HIV/AIDS, Hepatitis C, tuberculosis and vaccines against communicable diseases. Most of such medicines are automatically included in this schedule, and no further application is necessary to obtain reimbursement.

### **Medicinal products used in and paid by hospitals**

Pharmaceutical expenditure in publicly funded hospitals is covered by the hospital budgets, and patients do not have to pay for the medicines used in their treatment. “A National System for Managed Introduction of New Health Technologies within the Specialist Health Service” was launched in 2013. The system also covers the introduction of new medicinal products.

The system should, *inter alia*, ensure that patients gain equal access quickly to new methods that have proved to be effective and fulfil safety and cost-efficiency requirements, and establish a systematic and predictable process for the introduction of new methods.

The system is not described in any laws or regulations. The Ministry has stated that decisions on public funding of medicines should be based on the same principles of prioritisation, regardless of where the financial responsibility lies.

The decision to introduce a new medicinal product in hospitals is based on a HTA performed by NoMA. The documentation requested by NoMA should correspond to the documentation described in Section 14–4 of the MPR.

A decision on whether or not to introduce a new medicinal product in hospitals is made by a Decision Forum (*Beslutningsforum*) comprised of the four CEOs (one for each regional health authority). The decision is taken on the basis of the HTA performed by NoMA and on the three prioritising criteria: benefit; use of resources; and severity of the disease.

No exact time limit for the procedure is provided for in law or regulations.

If the price is considered too high to allow for a positive decision from *Beslutningsforum*, price negotiations may take place.

As NoMA performs the HTA, *Beslutningsforum*’s decisions will be influenced by NoMA and experts’ involved during NoMA’s assessment. The decision is also influenced by the right holder providing data supporting the application for pre-approved reimbursement. Some decisions of *Beslutningsforum* get considerable media attention, which might influence the decision taken.

One example is the decision from October 2017, in which *Beslutningsforum* decided not to introduce Spinraza in Norwegian hospitals. After negotiating with Biogen, in February 2018 the *Beslutningsforum* allowed for a limited introduction of Spinraza in Norwegian hospitals. As the results of the price negotiations are not in the public domain, we are not aware of the cost of the medicinal product.

It has been a long debate on whether decisions of the *Beslutningsforum* may be appealed. As the system is not described in laws or regulations, no specific rules on appeal are provided for. At present, the Ministry of Health and Care Services has taken the position that a decision of *Beslutningsforum* may not be appealed. Hence, in practice appeals are not possible. However, and as described above for Spinraza, *Beslutningsforum* does reconsider its previous decision based on new information.

#### How is the reimbursement amount set? – Value-based reimbursement

For pre-approved reimbursement, a positive decision requires that the use of resources is considered to be in a reasonable proportion to the benefits of the medicinal product, taking into consideration the severity of the disease. Hence, if this condition is not considered met by NoMA, the product will not receive reimbursement.

According to Section 14–9 in the MPR, at the same time as the decision on pre-approval of reimbursement is made, NoMA shall set a reimbursement price. This price may be the maximum price of the product, or a price determined by price negotiation with the right holder. If the maximum price is not considered to meet the conditions of Section 14–5, the right holder will have to reduce its price to obtain a decision on pre-approved reimbursement. This new price will also be the new maximum price for the medicinal product. If *Beslutningsforum* hands down a negative decision, price negotiations may take place.

#### How are drug prices set?

All POMs are given maximum prices by NoMA prior to the placing of the product on the market, *cf.* Section 12–1 of the MPR. NoMA sets maximum prices for all POM at the pharmacy purchasing price level (AIP). The pharmacy retail price (AUP) is regulated upwards of a maximum pharmacy mark-up set by NoMA.

The maximum price is set by external reference pricing, *cf.* Section 12–2 of the MPR. According to administrative practice, the Norwegian maximum prices for original medicinal products are in general based on the average of the three lowest prices in Austria, Belgium, Denmark, Finland, Germany, Ireland, the Netherlands, Sweden and the United Kingdom. The same rules are applicable to generic medicinal products. According to administrative practice, the MA holder is entitled to receive the same maximum price as for the original medicinal product, but the holder may also apply for a lower price. There is no automatic price cut for the original's maximum price after generic entry.

NoMA reevaluates most of the maximum prices on a yearly basis, *cf.* Section 12–5 of the MPR.

OTC has free price setting.

#### Issues that affect pricing – What is the relationship between pricing and reimbursement?

For original medicinal products without competition, the products are normally sold at the maximum price determined by NoMA, or by the negotiated reimbursement price. Medicinal products used in hospitals are also purchased through tenders, which may affect pricing of the products.

The introduction of a generic medicinal product may reduce the maximum price reimbursed.



This is done in the so-called step price model, *cf.* Sections 12–13 to 12–18 of the MPR. The model is applicable when NoMA has decided that the original and the generic medicinal product are interchangeable, as well as stable generic competition is established.

From the start of generic competition, the price reimbursed is reduced with 35% on the basis of the existing maximum price. Six months later, the price is reduced with 59% on the basis of the said maximum price. For medicinal products with a turnover above NOK 100 million, after six months, the reimbursed price is reduced with 81%. Further reductions are possible.

Pharmacies must secure the ability to supply at least one pharmaceutical product at a retail price equal to the stepped price. In practice this is often a generic and not the original. If the patient requests to be dispensed the original at a higher price, the pharmacy may request the patient to pay the difference. In practice, if the medicinal products are made part of the step price model, the generic medical product may quickly achieve a significant market share.

The step price model is not applicable to biosimilar medicinal products and may not be used as an instrument to reduce prices when biosimilar competition is established. However, a significant price reduction has been achieved for biosimilar medicinal products used in hospitals through tenders.

### Policy Issues That Affect Pricing and Reimbursement

By the end of the 1990s, Norway had relatively higher prices on medicinal products compared to other European countries. In the early 2000s, Norway introduced the external reference pricing described above, which is still in force. As the maximum price is based on the average of the three lowest prices in nine other European countries, prices of pharmaceuticals in the original market are not particularly high. So far, no legal proposal is put forward to amend this practice.

The possibility of using pharma-economic analysis in the application for pre-approved reimbursement in Norway has been an option since 1998, and mandatory as of 2002. For medicinal products used in hospitals, the National System for Managed Introduction of New Health Technologies within the Specialist Health Service was launched in 2013.

From 2013 to 2016, a major investigation was carried out by the Ministry of Health and Care Services concerning priorities in the public health services. This investigation focused on challenges as a consequence of the gap between available resources and the possibilities of modern medicine, that health services must serve a larger and older population, the development in health and illness – new groups and new needs and on the development in medical technology. Based on this work, the new prioritising criteria were introduced: benefit of the treatment; use of resources; and severity of the condition.

Prior to 2018, reimbursement required, *inter alia*, that the cost of using the medicinal product was reasonable in relation to the therapeutic value and costs associated with alternative therapies. Based on the short period of time since the new prioritising criteria entered into force on 1 January 2018, it still remains to be seen whether this change has consequences in future reimbursement decisions. However, in a public consultation in 2017, the Ministry of Health and Care Services stated that some health technologies aimed at minor or moderately severe conditions may be priced lower than previously to be reimbursed. However, the Ministry also assumed that the assessment of methods targeted at very serious conditions would largely correspond to current practice in the Norwegian Medicines Agency and the Decision Forum.

## Emerging Trends

The legal framework for reimbursement was amended in 2017 entering into force as of 1 January 2018. For the next years to come, we expect the authorities to focus on implementation of the changes and to consider their effect.

In December 2017, the Government submitted a legal proposal to the Parliament suggesting to limit the Ministry of Health and Care Services competence when handling appeals on negative decisions for pre-approved reimbursement. While the Ministry today may try all aspects of the matter, the proposal limits the competence to assess the legality of the decision. As a consequence, NoMA's professional discretion can no longer be overruled by the Ministry. The Parliament adopted the amendment to the law on 5 April 2018.

## Successful Market Access

For new innovative medicinal products, pre-approved reimbursement or a positive decision of Beslutningsforum is essential for successful market access. This is dependent on a positive outcome of the health technology assessment performed by NoMA.

It is advisable to contact NoMA at an early stage to discuss the development of the documentation to be submitted at a later stage. This may ensure that the documentation submitted corresponds to NoMA's expectations, while at the same time reducing the risk of delays following a request for additional information. As uncertainty concerning the documentation and budget implications shall be emphasised in the decision, it is important that the information submitted is of good quality.

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# Poland

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## Abstract

The following report outlines basic information on the Polish healthcare system, in particular the pricing and reimbursement procedure initiated on the basis of companies' applications.

## Market Introduction/Overview

In 2017, the total value of the pharmaceutical market, calculated in retail prices, amounted to PLN 38.3 billion, which means an increase by 4.9%.

In 2017, Poland's population was approximately 38.1 million. Despite Poland, compared to other EU countries, being a relatively young country, demographic statistics show that Poland has an ageing population.

The Polish healthcare system is multi-layered and its respective segments are subjected to hasty change. The healthcare system is generally dominated by public financing schemes. Generally, all insured Polish citizens have guaranteed free access to healthcare services. However, the private sector of healthcare services in Poland is predominant and still growing. Uninsured patients are obliged to cover the full costs of medical services. In general, access to healthcare services is rather difficult.

## Pharmaceutical Pricing and Reimbursement

Reimbursement issues are generally regulated in the Act of 12 May 2011 on Reimbursement of Medicinal Products, Food for Special Nutritional Purposes and Medical Devices, and several regulations laying down more precise requirements and technical rules for the reimbursement process. There are three groups of products that can be covered by reimbursement: (1) medicinal products; (2) medical devices; and (3) food for special nutritional purposes.

Products may be subject to reimbursement if they fulfil the following requirements:

- are authorised for the market or remain marketed;
- are available on the Polish market; and
- 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.

Reimbursement does 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; or
- products 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 or if they are otherwise included in the list of guaranteed healthcare services.

The reimbursement approval process is executed by the Minister of Health (the "MoH"). The MoH decides in administrative proceedings which products will be reimbursed and on what terms. Companies are obliged to file reimbursement applications to the MoH. From 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; and HTA analysis – clinical, economic, substantiating, and of effects on the budget. The MoH can also determine in the decision (basing 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 to health risks;
7. cost to health effects ratio of the previously reimbursed medicines, compared to that 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 the 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; or
- used in chemotherapy (in the full scope of registered indications and intended uses, or in an indication determined by a specific clinical condition).

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, 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**

Politics in Poland has a significant impact on pricing and reimbursement policy. The factors limiting the development of the reimbursed medicinal product market were the transfer of some drugs used in oncological treatment to the hospital market. The other factors are drops 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 Ministry of Health 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, the RSS are highly required by the MoH. Additionally, political trends in Poland indicate that generic products are more likely to be refunded.

### **Emerging Trends**

Currently, there are two proposed amendments to the reimbursement act, which are in the legislative phase of the Council of Ministers. Proposed amendments are likely to significantly change the pricing and reimbursement system for among others medicinal products. Proposed changes include: relaxing the strict reimbursement criteria for ultra-orphan drugs; introduction of compassionate use; simplified reimbursement procedure for

well-established off-label indications; prolonged duration of reimbursement decisions; and reimbursement lists.

### **Successful Market Access**

The negotiation process with the MoH setting official prices and pressure of minimal reimbursement price policy are the critical success factors for market access. In general, preparing for various scenarios regarding price negotiations of reimbursed medicinal products is highly recommended.

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Agata has been advising pharmaceutical entities since 2004 as an expert in issues concerning the pricing of medicinal products and medical devices, as well as their reimbursement. She has prepared and provided opinions on clients' internal procedures and has cooperated during their implementation within compliance review processes. She has participated in legislative processes concerning legal acts important within the pharmaceutical industry, representing applicable organisations which incorporate pharmaceutical companies and their representatives. Currently, she also provides legal assistance for companies from the food and cosmetics sector especially in terms of proper labelling and advertisement of products. She represents clients in administrative proceedings concerning the appropriate qualification of products, etc. Since 2009, she has been recommended by *Chambers Europe* as an expert in Life Sciences in Poland.

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Marta deals with issues related to a wide area of pharmaceutical law, medical devices law and food law. Her scope of practice concentrates on issues related to the reimbursement of medicinal products, marketing of medicinal products, medical devices, food supplements and cosmetics, and labelling and advertising of these products. Her additional areas of interest include issues related to the protection of intellectual property, acts of unfair competition and white-collar crime. She also provides legal assistance related to ongoing proceedings before administrative authorities and courts in a variety of regulatory matters and before civil courts. Marta graduated from the Faculty of Law and the Faculty of Marketing and Management at Kozminski University and completed Postgraduate Studies at the Faculty of Law and Administration at the University of Warsaw.

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# Portugal

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## Abstract

Following a recent reform in 2015, the Portuguese pricing and reimbursement system is sophisticated and comprehensive. Nevertheless, substantial discretion is allowed to the competent national authority, and this is the source of most challenges for innovators.

## Market Introduction/Overview

Portugal is a relatively small country, with about 10.3 million inhabitants. The main indicators of public health have registered a positive and steady evolution over the last decade. According to the most recent data (2016), average life expectancy at birth is 80 years old, and is increasing, just like life expectancy at 65 years old, and the infant mortality rate is per 2.9 live births in 1000.

Adjustments in the health system have yielded life year gains in respiratory, digestive, and infectious diseases.

Some indicators, however, raise concerns.

Portugal suffers from the ailments that are associated with an ageing and decreasing population.

Healthy life years are steadily decreasing. Chronic diseases are growing factors of mortality. Heart diseases, cancer, respiratory, nutritional, endocrine and metabolic diseases are the greatest causes of premature mortality, and still play a significant role in later deaths. Risk factors, such as inadequate eating habits, hypertension, smoking, and high body mass greatly contribute to this outcome.

The Portuguese Health System is thus a mature, complex, and rather successful structure that – as with many other developed countries – is now faced with the consequences of its success.

Higher life expectancy is associated with an ageing demographic, and an increase in health-related costs. The better the system becomes, the harder it is to ensure its sustainability.

Policies are headed towards preventing diseases rather than curing them. While innovation is commendable, the State is not focused on rewarding innovative therapies, but rather in taking steps to guarantee that they are not necessary.

Pricing and reimbursement of medicines is therefore perceived as a double-edged sword: while it satisfies basic needs of citizens, and fulfils fundamental duties from the State, it should be achieved without excessive sacrifice of a declining Public Budget. Public regulators very much agree that this paradox should not be settled at the taxpayer's expense. Pressure on innovators is therefore at its highest.

In what the legal regulatory framework is concerned, the Portuguese legal framework follows the EU legislation closely. Decree-Law 176/2006, of 30<sup>th</sup> August, consolidated in one single piece of legislation the regime applicable to, among others, the marketing authorisation, manufacture, import, export, marketing, classification, labelling, promotion and pharmacovigilance of medicines, transposing into Portuguese Law several directives, including Directive 2001/83/EC, as amended (the Directive).

Pricing and reimbursement, in contrast, are exclusively dealt with at the national level, being beyond the scope of EU legislation, with the exception of transparency measures and procedural requirements provided for in Council Directive 89/105/EEC, of 21<sup>st</sup> December 1988, relating to the transparency of measures regulating the pricing of medicinal products for human use (“Transparency Directive”).

The general regime applicable to pricing and reimbursement is provided for in Decree-Law 97/2015, of 1<sup>st</sup> June, as amended. This diploma approved SiNATS, the National System of Evaluation of Health Technologies, congregating in one single piece of legislation topics related with pricing and reimbursement of pharmaceuticals. This general framework is complemented by several Ministerial Orders and densified by the Portuguese Agency’s – *Infarmed – Autoridade Nacional do Medicamento e Produtos de Saúde*, I.P. (“Infarmed”) – Practice and Informative Notes.

In addition to technical health regulation, Infarmed’s powers cover pricing and reimbursement. Price approval of prescription products, including products for hospital use, is also attributed to this Agency. Infarmed plays a significant role in the reimbursement of medicines, being the entity responsible for conducting the relevant procedures and proposing decisions to the Ministry of Health.

## **Pharmaceutical Pricing and Reimbursement**

### Regulatory classification

The classification of medicines is identical to that arising from EU legislation.

Two major classifications exist: prescription; and non-prescription products.

Medicines are subject to medical prescription where they (a) are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision, (b) are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, (c) contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or (d) are to be administered parenterally.

Prescription medicines are then divided into sub-categories, including, for renewable delivery, special medical prescription and restricted medical prescription for use in certain specialised areas. Concerning this last subcategory, products will be classified as subject to restricted prescription when, in general terms, the respective use is reserved for a hospital setting or require special supervision throughout the treatment.

Prescription products can only be sold in pharmacies or, in the case of a restricted medical prescription, dispensed and/or exclusively at a hospital setting (including hospital pharmacies).

In turn, all medicines which do not meet the criteria to be classified as subject to medical prescription are classified as non-prescription products.

Under this broad classification of medicines – subject to medical prescription or not – medicines can be of several types, depending essentially on the marketing authorisation (hereinafter “MA”) procedure followed and composition of the product.

The following types may be identified:

### **Branded medicines**

Branded medicines are divided into six sub-categories: (a) full application; (b) well-established use applications; (c) fixed combination applications; (d) informed consent applications; (e) hybrid applications; and (f) biosimilar applications.

Full application products are commonly known as “reference medicines”, i.e. medicines which have been granted an MA by a Member State or by the European Medicines Agency (“EMA”) based on a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data. These medicines may be biological or not, depending on their composition.

Products arising from well-established use applications are those regarding the results of preclinical and clinical trials which are replaced by detailed references to published scientific literature if it is demonstrated that the active substances of the product have been in well-established medicinal use within the community for at least 10 years, with recognised efficacy and an acceptable level of safety.

Fixed combination applications are those related to medicines containing active substances used in the composition of authorised medicines but not hitherto used in combination for therapeutic purposes. In these cases, the results of new pre-clinical tests or new clinical trials relating to that combination must be provided, it not being, however, necessary to provide scientific references relating to each individual active substance.

There are also the so-called informed consent applications, in which following the granting of an MA, the authorisation holder allows use to be made of the pharmaceutical, non-clinical and clinical documentation contained in the dossier of its medicinal product with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

Hybrid applications, which rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data, differ from generic applications in that the results of appropriate pre-clinical tests and clinical trials need to be submitted. This occurs in the following circumstances: where (i) the strict definition of a generic is not met; (ii) bioavailability studies cannot be used to demonstrate bioequivalence; and (iii) there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic compared to the reference medicine.

Finally, there are the biosimilars, i.e. biological medicines, similar to a reference biological product but which do not meet the conditions of the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in the manufacturing processes of the similar biological medicine and the reference biological medicine, and, therefore, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

All the above categories are considered as “branded products” for the purposes of pricing and reimbursement rules, with the exception of biosimilars in respect of which a specific regime exists.

### **Generics**

Generics are products which have the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicines, which are or have been authorised for no less than eight years in a Member State or in the community. The applicant is not required to provide the results of pre-clinical tests and clinical trials,

provided bio-equivalence with the reference medicinal product is demonstrated by appropriate bio-availability studies.

In terms of pricing and reimbursement, the following categories are relevant, the rules differing depending on which category the product falls under: (a) branded products (which include: full applications; well-established use applications; fixed combination applications; informed consent applications; and hybrid applications); (b) generics; and (c) biosimilars.

Generics are subject to specific pricing and reimbursement rules.

The critical distinction for the purposes of reimbursement is whether the product is subject to medical prescription or not.

Whereas non-prescription medicines are not subject to price control and, as a rule, are not eligible for reimbursement, save in exceptional circumstances, prescription medicines are subject to a price control regime and are eligible for reimbursement. This principle applies to all types of products identified above (i.e. branded, generics, biologic and biosimilar).

#### Who is/Who are the payer(s)?

The payer varies depending on the product's classification.

Non-prescription products and medicines subject to common medical prescription, renewable and special medical prescription can be purchased directly by individuals – should they be sold in street pharmacies – and by private hospitals and national health service hospitals (“NHS Hospitals”) for internal use. Restricted medical prescription products are only purchased by hospitals, be it private or NHS Hospitals, with patients having access to these products *via* the hospital pharmacies.

Should the product be reimbursed, part or the whole of its sales price is borne by the Health Ministry's share of the State Budget.

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

A distinction should be drawn between products which are to be sold and dispensed at street pharmacies and those which are to be sold to NHS Hospitals.

The first follow a reimbursement procedure. The second follow a very similar procedure with a view to being sold in NHS Hospitals – the so-called prior evaluation procedure.

The *ratio* underlying both procedures is, in essence, the same: evaluating whether, in light of the therapeutic alternatives, it is justifiable from an economic and therapeutic perspective for the State to purchase the product – be it via reimbursement or through the budget of NHS Hospitals.

The reimbursement procedure is initiated by the MA holder, or its representative, before Infarmed. The MA holder is encumbered with demonstrating that the product fulfils the criteria for reimbursement: i.e. that the medicine is innovative, or therapeutically equivalent to current alternatives and presents an economic advantage. This being the general principle, the law further lists the situations which can give rise to reimbursement and specifies the criteria which should be met – particularly to demonstrate the economic advantage.

The reimbursement request should be accompanied by a comprehensive set of documents, comprising both technical and scientific information about the product that demonstrates its efficacy, safety, and effectiveness for the claimed therapeutic indications and an economic evaluation study. Such a study is not required for generics, which follow a simplified procedure.

In fact, reimbursement of generics is subject to specific rules strictly linked to the respective price – be it by comparison with the reference medicine or other reimbursed generics, depending on how many generics are already present in the market.

The same logic applies to the reimbursement of biosimilars: a price is also set for reimbursement purposes. The first biosimilar will be reimbursed should its price not exceed 80% of the price of the reference biologic product. Said percentage decreases to 70% should there be more biosimilars in the market representing at least 5% of the market share of the respective active substance.

The reimbursement procedure is conducted before Infarmed. The Ministry of Health, however, is responsible for the reimbursement decision, although said power may be delegated to the Infarmed.

Reimbursement may be subject to the execution of a contract between the MA holder and Infarmed which sets forth the terms and conditions subject to which a reimbursement depends upon. These conditions may include:

- (a) a maximum amount of public expenditure with the product, considering the number of patients and applicable therapeutics;
- (b) consequences of exceeding this maximum amount, such as the MA holder being required to (i) pay back the amounts in excess, and (ii) lower the price of the product concerned or of other products;
- (c) existence of a limited period of time, elapsing which the amount of reimbursement is reduced with a consequent reduction of the price of the product or the product is delisted; and
- (d) risk sharing arrangements.

Even though the execution of a reimbursement contract is not mandatory, in the case of innovative products, Infarmed typically chooses to execute a contract with the MA holder. If Infarmed proposes to enter into a reimbursement contract, negotiations should be concluded in 30 days. In practice, however, contract negotiations take significantly longer.

Although contracts are bilateral, reimbursement is a unilateral decision, which almost entirely depends on Infarmed's discretion. Accordingly, Infarmed has an exceptional edge in contract negotiations.

While MA Holders may try to influence the reimbursement decision or contract – especially, the maximum amount of public expenditure with the product – through negotiation, the decision ultimately depends on Infarmed and on its assessment, taking into account available public funds or budgetary concerns, of the market and the product's expected performance. The MA Holder should be able to demonstrate that the medicinal product complies with the reimbursement criteria at all times.

Informed can exclude medicines from reimbursement, or change their reimbursement conditions upon re-evaluation of market conditions – especially if new medicines that are either therapeutically innovative or economically advantageous in relation to the reimbursed medicine.

The situations that may trigger exclusion from reimbursement or the change in reimbursement conditions are provided for in the law. Amongst these we find, for instance: the medicine becoming less effective in relation to other reimbursed medicines with the same therapeutic purpose; consumption data demonstrating that the medicine has been used off-label, in indications that are not covered by the reimbursement; the price of the product becoming 20% higher than non-generic reimbursed alternatives; and the medicine no longer being subject to medical prescription or changing its classification to restricted medical prescription. Illegal promotional practices may also determine exclusion from reimbursement.

As noted above, prescription medicines must undergo a prior evaluation procedure with a view to being bought by NHS Hospitals – unless otherwise decided by the Ministry of Health or Infarmed, should the Ministry delegate the competence to take this decision. Non-prescription products may also be subject to such a procedure if their sales volume to NHS Hospitals is very significant.

The purpose of the prior evaluation procedure is very similar to that of the reimbursement procedure: the applicant must demonstrate that the medicine is innovative, or therapeutically equivalent to current alternatives and presents an economic advantage. Also, and similarly to what happens with reimbursement, the law specifies the criteria which should be met for a favourable decision to be awarded – particularly so as to demonstrate the economic advantage.

If favourable, the prior evaluation decision sets a maximum price of acquisition for NHS Hospitals and entails the execution of a contract between the MA holder and Infarmed. These contracts, further to being entered into for a fixed term, can provide for conditions similar to those we have seen above for reimbursement. The most common ones are the establishment of obligatory discounts over the maximum sales prices and the setting of a maximum amount of public expenditure with the purchase of the product which, if exceeded, should be paid back by the MA holder.

Medicines subject to prior evaluation cannot be purchased by NHS Hospitals until a favourable decision is issued and a valid contract executed. In exceptional circumstances, for example, in the absence of a therapeutic alternative and should the patients' life be at risk, and on a case-by-case basis, Infarmed may authorise the purchase of these products.

Rules of procedure specify clear deadlines for issuing a reimbursement and a prior evaluation decision: (a) 30 business days, for generics and biosimilars; (b) 75 business days, for new therapeutic indications of an active substance which is already reimbursed; and (c) 180 business days, for new active substances. These deadlines are suspended and extended if, during the process, Infarmed asks for additional elements from the applicant, or opinions from independent Committees.

Decision deadlines are merely indicative, with no consequences arising from non-compliance thereto. Should a decision not be issued within these timeframes, the applicant cannot assume that its product has been reimbursed or approved – neither can it assume that it is not. Unfortunately, reimbursement and prior evaluation procedures of innovative products, both new active substances and new therapeutic indications, take far more time than that provided for in the law.

Negative decisions in the context of reimbursement and prior evaluation procedures are subject to appeal.

MA holders are entitled to file an administrative appeal before Infarmed or the Ministry of Health – depending on whom issued the final decision. This appeal, which is not mandatory to resort to judicial action, has extremely limited chances of success. A judicial challenge before administrative courts is also admissible, even though the court's powers are limited to judicial review. A judicial claim can take as much as two years to be decided in the first instance.

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

The general rule is for reimbursement to be set as a percentage of the maximum public sales price of the product.

The reimbursement amount is set in one of four tiers, ranging between 15–90% of the

product's maximum public sales price (15%, 37%, 69%, 90%). A Ministry of Health Order provides the pharmacotherapeutic groups that correspond to each reimbursement tier – so the reimbursement tier in which medicines are included depends on the diseases they are indicated to treat. The reimbursement tier rises in accordance with the priority the Government assigns to the treatment (or access to treatment) of a certain disease.

In addition to this general regime, medicines can be included in special or exceptional reimbursement regimes, which may follow specific rules and set specific reimbursement amounts. Specially or exceptionally reimbursed medicines are usually reimbursed in full, and concern specific diseases which raise significant health concerns. HIV and Hepatitis medicines, for instance, benefit from a special reimbursement regime and are dispensed at no cost to patients at NHS Hospital pharmacies.

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

Medicines subject to medical prescription (yet not restricted medical prescription), both generics and non-generics, must undergo a price approval procedure before being launched in the market. Price approval – contrary to reimbursement – is a condition to market the product.

In the context of the price approval procedure, a maximum sales price is approved, which, in the case of branded products, is determined by reference to the wholesale price applied in three reference countries. The reference countries are defined annually (in 2018: Spain; France; and Italy). The maximum sales price cannot exceed the average of the wholesale price applied in the reference countries (with exclusion of applicable margins and taxes). If the medicine does not exist in the reference countries, the price cannot be higher than the price of identical or essentially similar medicinal products in those markets (excluding generics). If such a product does not exist, the price should not be higher than the price of identical or essentially similar products in the national market. If similar medicines are not marketed in Portugal or the reference countries, the price cannot be higher than the price in force at the country of origin. This maximum sales price is subject to annual revision according to the same criteria.

Branded medicinal products subject to medical prescription which are not reimbursed and are sold before NHS Hospitals are also subject to a price approval and annual revision procedure. The logic, similarly to what happens with retail pharmacy products, is that in comparison with the price applied in three reference countries, it is the same as those defined for the pharmacy setting. However, in the case of these products, the maximum sales price to hospitals cannot exceed the lowest wholesale price applied in three reference countries.

The maximum sales price of generics, in turn, is set by reference to the price of the reference medicine. The price of the generic cannot exceed 50% of the maximum sales price of the reference medicine or 25% of that price, should the reference product's wholesale price be lower than €10. Generics are also subject to an annual price revision. Under said revision, the price of the generic should continue to maintain the same price difference *vis-à-vis* the reference product.

The price of the generic may, however, be affected for reimbursement purposes.

In fact, the placement of a generic in the market gives rise to the creation of a “homogeneous group”, composed of branded medicines and generics (with the same active substance, dosage, method of administration and pharmaceutical form). The creation of the “homogeneous group” triggers the approval of a reference price for the products which make part of said group. The reference price corresponds to the average of the retail sales price of the five lowest-priced products included in the group. Following approval of the reference price, the maximum amount of reimbursement for products included in the group

will be determined by applying the applicable reimbursement percentage to the reference price. With a view to being reimbursed, the maximum sales price of generics entering the market after the group's creation must be at least 5% lower than the price of the cheapest generic already in the group (up to the limit of 20% of the reference medicine's maximum sale price). This successive lowering of the price of generics and of the reference price leads to significant savings in expense with reimbursement, but also to a substantial gap between over the counter prices of generics and branded medicines.

Finally, generics which are not reimbursed and are sold to NHS Hospitals are also subject to a price approval and revision procedure. Under this regime, the price of the generic should be at least 30% lower than the price of the reference product.

While biosimilars are not subject to a specific price approval procedure, price control of these products is set within the context of the reimbursement procedure. As noted above, reimbursement of a biosimilar can only be approved if the respective price does not exceed 80% of the reference medicine's price.

Similarly to what happens with generics, a biosimilar entering the market also triggers the creation of a "homogeneous group", and of a reference price as well. Two differences occur. Reimbursement of similar biological medicines can only be approved if their price does not exceed 80% of the reference medicine's price, and, in case a "homogeneous group" with at least one biosimilar medicine already exists, the price of the following biosimilar cannot exceed 70% of the reference medicine's price.

Lastly, discounts can be granted throughout the medicine's marketing circuit (manufacturer, wholesaler and pharmacy). However, discounts can only be granted in relation to the non-reimbursed part of the sales price of the medicinal product.

#### Issues that affect pricing

As noted above, Portugal follows a referencing system in what price definition is concerned.

Limiting public expenditure is therefore done, on the one hand, through price control and, on the other, through reimbursement or prior evaluation procedures – in general terms, market access. The major factor influencing market access is cost. Rather than assessing the medicine's performance and market behaviour independently, public authorities are compelled to lower maximum amounts of public expenditure, based almost exclusively on the budget that is allocated for the expense of medicinal products.

Although the launching of a generic in the market does not directly affect the price of the reference medicines, competition of generics and therapeutic alternatives – particularly if cheaper – greatly influence the sales of the branded products.

This is achieved through several means:

- Firstly, through the renegotiation of the maximum public expenditure levels provided for in reimbursement/prior evaluation contracts.
- Secondly, as a result of substitution. In fact, the general rule, in which generics are concerned, is for mandatory substitution.

Prescription of medicines should be done by the International Non-proprietary Name ("INN") – although the brand of the product may be added. Once generics are placed in the market, the rule is that of substitution and the physician is only allowed to prevent substitution in the limited and exceptional cases provided for in the law. Similarly, pharmacists, when confronted with a prescription, are required to inform patients of the existence of products with an identical active substance, pharmaceutical form, dosage and presentation of the prescribed product, as well as whether these are reimbursed and those which have the lowest



sales price. Pharmacies should have available for sale at least three products with the same active substance, pharmaceutical form, dosage and presentation, between the five products with the lowest sales price. Unless the patient chooses otherwise, the pharmacist should dispense the medicine with the lowest price. The patient is further entitled to replace the prescribed product with one with that has the same active substance, pharmaceutical form, dosage and presentation unless the physician has prevented substitution. Even in the latter case, the patient may choose to replace the product for a cheaper product if the circumstance on the basis of which the physician prevented substitution was due to the fact that the product was destined to a long-term treatment (i.e. that which is anticipated to last over 28 days).

On the other hand, and concerning NHS Hospitals, medicines are purchased pursuant to mandatory public procurement procedures. Supply contracts awarded through these procedures are overwhelmingly awarded to the bidder with the lowest price – meaning that generics and biosimilars are expected to take over the market as soon as they begin marketing. Several instructions have also been directed to NHS Hospitals with a view to increasing the purchase of biosimilars.

Finally, the Ministry of Health has taken measures to ensure that NHS Hospitals and Services can begin purchasing generics and biosimilars as soon as they enter the market.

### **Policy Issues That Affect Pricing and Reimbursement**

Portugal's population is currently estimated at around 10.3 million people. The population has stagnated, and is not expected to grow in the next years. The elderly population is growing steady and significantly. According to the latest census (2011), the population of all age groups up to 30 years old decreased between 2001 and 2011, while the population of older age groups increased in all tiers. Significantly, the age group of 75+ increased from 701,366 to 961,925 between those years, and other senior age groups substantially increased their population (source: [www.pordata.pt](http://www.pordata.pt)).

While no aggregated data is immediately available, authorities recognise that growth in elderly population considerably contributes to growth in prevalence of chronic diseases, and that these are responsible for more than 80% of disease related mortality.

As of 2016, the cost of State-funded healthcare is estimated at 4.8% of the GDP and the cost of drugs covered by the State Budget was €1,189.8 M. (source: [www.pordata.pt](http://www.pordata.pt)). In this same year, the total NHS expense was €9,397.2 M, the cost of drugs amounting to approximately 12.66% of the Health Budget (source: [www.pordata.pt](http://www.pordata.pt)).

These demographic and financial data strongly suggest that public authorities will be confronted with great pressure to lower the prices of medicines.

Aside from pricing policies and budget-oriented evaluations, the most significant political influence over pricing and reimbursement policy is a shift of priorities, from treatment to prevention. Public authorities are focusing on disease deterrence programmes that concern lifestyle and nutrition changes, and essentially seek to prevent the appearance of chronic diseases. Health authorities are favouring this approach over counting on the approval of innovative medicines. This naturally involves a transfer of State Budget funds towards prevention. Notwithstanding this growing inclination in policy, the increase in prevalence of chronic diseases has generated a need to create disease-specific programmes, which may involve the increase of reimbursement for diseases that are becoming more frequent (such as cancer and cardiovascular and respiratory diseases).

## Emerging Trends

Considering that the pricing and reimbursement system was completely overhauled in 2015, with the approval of SiNATS (the National System of Evaluation of Health Technologies), which was later revised in 2017, no significant changes in legislation are currently anticipated.

The enactment of this new legislation did not, however, remedy challenges with which Innovative Pharma Companies are faced with. Delays in deciding prior evaluation and reimbursement procedures have not been dealt with. Even though legal deadlines exist, the delay of the procedure significantly exceeds these deadlines, in what branded medicines are concerned, with practically no consequence attached to it.

Another recent trend following the approval of SiNATS is the increased imbalance between Infarmed and MA holders in reimbursement and prior evaluation contracts. Such imbalance is particularly evident when Infarmed has the power to unilaterally change the contract and the maximum amounts of public expenditure with the medicine which, if exceeded, trigger payback of the excess.

Reimbursement contracts have of late experienced an important development. Infarmed usually sets the maximum public expenditure cap by product and indication. Recently, Infarmed proposed reimbursement contracts that provided a maximum expenditure cap for an entire therapeutic indication, covering all products indicated for the treatment of said disease. In this case, if there is an excess, companies will pay it back *pro rata*, based on their market share.

In spite of recent improvements, transparency in reimbursement and prior evaluation procedures still raises concerns. The regime is far from being compliant with the Transparency Directive which clearly provides that measures regulating the pricing of medicinal products should resort to objective and verifiable criteria.

The entry of biosimilars in the market is still surrounded by some uncertainty. While a regime – largely based on what is applicable to generics – has been approved, it is too soon to tell whether this will be effective.

## Successful Market Access

The top factor to secure successful market access is to protect the MA holder's credibility before Infarmed. During the submission of reimbursement or prior evaluation requests, the negotiation of contracts, or the re-evaluation of the medicine's compliance with the applicable criteria, the MA holder may feel tempted to overstate the product's economic advantage or therapeutic added value – which may happen, for instance, if the economic evaluation study submitted with the request heavily relies on less tangible or probable economic advantages.

This strategy will often backfire, and lead Infarmed to disregard the information submitted by the MA holder and delay the procedure focusing solely on price. Lack of consistency of the data submitted with the reimbursement request may therefore result in poorer conditions than those that could be approved if the MA Holder resorted to more agreeable estimates and projections.

Credibility is also an asset in subsequent re-evaluations and negotiations. If effective consumption is very wide off the mark of a former estimate of consumption, the Agency will feel strongly compelled to ignore the MA Holder's revised estimates and acutely lower the expenditure limits.

Flexibility can also be accounted as a success factor. Considering the frequent changes in regulation and policy orientation, MA holders should be open to several scenarios, and have sufficient strategic insight to negotiate contracts in a fast-changing environment, where several reimbursement or payback solutions are theoretically possible.

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# Romania

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## Abstract

In a society subject to rapid technological developments and globalisation, as well as economic and social evolution, human healthcare is the central, perpetual element that has to benefit from a high level of protection at all times.

In such context, in order to observe the fundamental right of individuals to healthcare, the access to medical treatment and medicinal products should be guaranteed by both European and national laws and practices.

## Market Introduction/Overview

As an EU Member State, Romania is constantly adapting the legislative enactments in the field of pricing of medicinal products so as to address the local specifics and demands of the policies and requirements existing at the European Union level.

Being generally aligned with principles set forth under the Council Directive 89/105/EEC 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 legal framework in terms of pricing and reimbursement was repeatedly amended in the last years.

In terms of pricing regulations, two enactments have been adopted in the last two years, regarding the pricing computation, while the enactment regulating the health technology assessment procedure (which is the specific procedure to be used for including, extending the indications, not including or excluding medicinal products from the list of the reimbursed medicinal products) was subject to four amendments since 2014, the last one being enacted early this year.

In an environment in which the challenges of the local pharma industry are relatively the same, most probably the continuing legislative changes are also related to the overall political context of the last years and the changes that took place at the level of the Romanian Government, which through one minister or another tried to address some of the local difficulties or gaps in terms of enactments regulating the pricing of medicinal products.

According to the “*State of Health in the EU – Country Profile 2017-Romania*”,<sup>1</sup> “*the health status of Romanians has improved, but life expectancy at birth remains among the lowest in the EU*”, while “*per capita health spending of EUR 814 in 2015 is the lowest in the EU, and under a third of the EU average*”.

In line with the Press Release of the National Statistics Institute dated 29 August 2017,<sup>2</sup> “*the resident population in January 2017 was of 19,638 thousand decreasing with 122.0 thousand individuals as compared to January 2016*”. Furthermore, the National Statistics

Institute states that the main cause of such decrease is the fact that the number of deceased individuals exceeded the number of new-borns, while the demographic ageing process gradually deepened.

Furthermore, the *State of Health in the EU – Country Profile 2017-Romania*<sup>73</sup> provides that “cardiovascular diseases and cancer account for the majority of deaths”, “musculoskeletal conditions and mental health problems are among the leading determinants of poor health”, “infectious diseases, particularly tuberculosis, present major public health risks [...] Romania having the highest rate of tuberculosis in the EU”.

The conclusion of the *State of Health in the EU – Country Profile 2017-Romania*<sup>74</sup> in terms of access to healthcare is that “this is especially poor in rural areas and is exacerbated by gaps in population coverage”.

Romania has a deficit of medical personnel, due to the fact that numerous young physicians choose to practice outside Romania, in other EU Member States, primarily due to the low public-sector salaries. Primary care is provided by family medicine physicians and the specialised ambulatory being provided through hospital outpatient departments and polyclinics, specialised medical centres, individual medical practices.

With respect to the market access, this might prove to be challenging for reasons related to pricing computation rules for medicinal products which in certain cases, by the price to be approved in Romania, generates a new minimum at the European level (thus affecting the operations of pharma companies in other jurisdictions as well).

Another potential challenge is related to the post marketing authorisation bureaucracy, especially in terms of reimbursement. This is due to the fact that, on one hand, the Health Technology Assessment is not sufficiently developed so as to be in line with other EU Member States practices, whilst the approval of a price of the medicinal product is not correlated with the reimbursement procedure, hence significant delays in practice.

## Pharmaceutical Pricing and Reimbursement

### Regulatory classification

Similarly, with the EU legal provisions, the Health Law sets forth the rule pursuant to which no medicinal product may be placed on the market in Romania in lack of a marketing authorisation to be granted by the National Medicines and Medical Devices Agency (the “NMMDA”) or in lack of an authorisation issued through centralised procedure.

The local legislation differentiates between several categories of medicinal products, *inter alia*: prescription-only medicinal products, over the counter medicinal products, proprietary medicinal products, generic medicinal products, biological medicinal products, biosimilar medicinal products.

From a pricing perspective, the local legislation provides, as a rule, that it is necessary to obtain a price approval from the Ministry of Health (the “MoH”) in case of:

- (i) Prescription-only medicinal products whose marketing authorisation was granted by the NMMDA or those authorised by the European Commission in a centralised procedure;
- (ii) medicinal products authorised for special needs; as well as
- (iii) over-the-counter medicinal products that are included in the list of reimbursed medicinal products, being borne from state budget sources.

As regards the eligibility of the medicinal products for reimbursement, in case of new molecules (i.e., newly authorised international non-proprietary names (“INN”)), the criteria considered during the health technology assessment procedure are related to:

- (i) a health technology assessment grounded on the therapeutically benefit;
- (ii) a health technology assessment grounded on the cost-effectiveness;
- (iii) the reimbursement status of the relevant INN in other EU Member States/Positive Assessment Report of NMMDA; as well as
- (iv) the cost of therapy.

Who is/Who are the payer(s)?

In Romania, public health assistance is guaranteed by the State and is financed from the State budget, local budgets and National Social Health Insurance Fund; however, co-payment from patients may also be incident in some cases.

In practice, the Social Health Insurance system is administered by the National Health Insurance House (directly or through its local branches), while the Ministry of Health, as the central authority, is competent, *amongst others*, in elaborating and coordinating the national health insurance programmes in view of achieving the objectives of the public health policy.

What is the process for securing reimbursement for a new pharmaceutical product?/How is the reimbursement amount set? What methodology is used?

In order to benefit from reimbursement, the relevant medicinal products should be included in the *List comprising the international non-proprietary names corresponding to medicinal products from which the insured persons benefit with or without personal contribution, based on medical prescription in the health insurance system, as well as the international non-proprietary names corresponding to the medicinal products that are granted under the national health insurance programs, and also on the remedy at law procedure* (the “**Reimbursement List**”).

The Reimbursement List is divided, depending on their reimbursement percentage, in several sub-lists, as follows:

- (i) the compensation percentage of the medicinal products provided in sub-list A is 90% of the reference price;
- (ii) the compensation percentage of the medicinal products provided in sub-list B is 50% of the reference price;
- (iii) the compensation percentage of the medicinal products provided in sub-list C is 100% for C1 and C3 subsections; and
- (iv) the compensation percentage of the medicinal products provided in sub-list D is 20% of the reference price.

As regards the C2 sub-list, this covers the INNs that are released in national health insurance programmes; in practice, the medicinal products which correspond to the INNs included in subsection C2 of Sub-list C and:

- (i) are released to pharmacies and are to be borne at the level of the reimbursement price; and
- (ii) are released in hospitals during the confinement period or are released through closed circuit pharmacies for ambulatory care of the patients included in the national health insurance programmes and are to be borne at a price which cannot exceed the reimbursement price.

The inclusion of a new INN in the Reimbursement List is subject to prior evaluation carried out by NMMDA during the health technology assessment procedure. Such evaluation procedure is to be done based on the criteria mentioned under “Regulatory classification”, “Pharmaceutical Pricing and Reimbursement”, (i) to (iv) above.

From a procedural perspective, the applicant submits before NMMDA a standard form application along with relevant documentation (both hard copy and electronic format), which in case of HTA for new INNs includes without limitation:

- (i) health technology assessment reports belonging to authorised agencies from France, Germany and Great Britain;
- (ii) the necessary data (which is provided in a pre-requisite format) requested for the computation of the therapy costs;
- (iii) the summary characteristics of products, as approved by NMMDA or, as the case may be, by the European Commission through centralised procedure;
- (iv) compensation status in other EU Member States;
- (v) the price approved by the Ministry of Health; and
- (vi) a deed ascertaining the intention of the relevant marketing authorisation holder to be engaged in a cost-volume or cost-volume-result mechanism in case the individually computed score corresponds to conditional inclusion on the Reimbursement List.

The decision to include the medicinal product in the Reimbursement List is taken by NMMDA, which, during its assessment, may request opinions and information from the specialised committees of the Ministry of Health, National Health Insurance House and any institutions subordinated to the Ministry of Health.

The decision passed by NMMDA with respect to the inclusion or not of a new INN on the Reimbursement List (which also provides the reimbursement percentage and the inclusion of the relevant INN on one of the available sub-lists) is communicated to the applicant within seven working days as of the date the decision was adopted.

In case the applicant disagrees with the abovementioned decision, it is entitled to challenge such in a term of seven working days to be computed as of the date the decision was communicated, by lodging a preliminary complaint before NMMDA.

The complaint is assessed by a commission which includes representatives of the Ministry of Health representatives of NMMDA and of the National Health Insurance House representatives. The marketing authorisation holder or its representative are summoned to attend the meeting when the commission assesses the complaint.

Both the decision of the commission and the minutes of the meeting are to be communicated to the complainant within a seven working days term as of the date the meeting took place, being also published on the website of the NMMDA. In case the marketing authorisation holder does not agree with the final decision of the commission, it is entitled to defer such to the competent court of law.

In practice, challenging the decisions/reports of NMMDA regarding the results of the HTA assessment does not necessarily have a positive impact due to the fact that:

- (i) the legal deadlines are not always observed; and
- (ii) the marketing authorisation holders choose, mostly due to business grounds, to challenge only before NMMDA, without further pursuing their cause before the courts of law (as this might be time consuming and might prove to be ineffective due to the fact that, in certain cases, the legislation allows the applicant to resubmit the relevant documentation for HTA assessment).

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

Due to the fact that, in some cases, Romania applies as a benchmark, with respect to the medicinal products that are borne from budgetary sources, the reference to minimum prices of the relevant medicinal products from 12 other EU Member States (which are set forth

by the applicable legislation), in practice, a major problem over the years was the fact that such computation method determined that the approved price in Romania represented the minimum price at the EU level, thus significantly affecting the operations of pharma players in other jurisdictions as well.

As a consequence, in Romania, there are currently two price catalogues: (i) the National Catalogue of medicinal products authorised to be placed on the market in Romania, so-called “*CANAMED*” (the “*CANAMED*”); and (ii) the Public National Prices Catalogue (the “*Public Catalogue*”).

CANAMED comprises the maximum prices of medicinal products of human use valid in Romania that may be used/traded by the marketing authorisation holders or their representatives, by wholesale distributors and by suppliers of medicinal products and medical services for those medicinal products that are subject to a contractual relationship with the Ministry of Health, the health insurance houses and/or the county public health departments or the Bucharest public health department.

On the other hand, the Public Catalogue comprises the maximum prices of medicinal products of human use valid in Romania that may be used/traded solely by the community pharmacies/local distribution units/closed circuit pharmacies and medicines that are not in a contractual relationship with the Ministry of Health, the health insurance houses and/or the county public health departments or the Bucharest public health department.

As regards the computation methods for determining the price of the medicinal products for human use, in principle, the following rules are incident:

- (i) The manufacturer price proposed for CANAMED has to be lower or at most equal to the lowest price of the same medicinal product from the list of countries<sup>5</sup> that are considered for the comparison.

By way of exception to the abovementioned rule, in case of immunological medicinal products and in case of medicinal products derived from human blood or plasma, the price proposed by the marketing authorisation holder or its local representative has to be equal to the arithmetic mean of the lowest three prices of the same medicinal product from the list of countries<sup>6</sup> that are considered for the comparison.

- (ii) The manufacturer price approved in the Public Catalogue is equal to the arithmetic mean of the lowest three prices of the same medicinal product from the list of countries<sup>7</sup> that are considered for the comparison; the Ministry of Health posts in a transparent way on the website of MoH only the prices which are approved in the Public Catalogue.

The secondary legislation also provides specific rules for computing: (i) the innovative/proprietary reference price; (ii) the generic reference price; and (iii) the biosimilar reference price.

However, for the prices included in the Public Catalogue, no innovative/proprietary reference prices, generic reference prices or biosimilar reference prices are approved. Also, the manufacturer’s price for innovative drugs/proprietary medicinal products has to be proposed by reference to the innovative/proprietary reference prices, generic reference prices or biosimilar reference prices only after the expiry of the relevant patent.

As a rule, prices of medicinal products (both prices included in CANAMED and those included in the Public Catalogue) are subject to:

- (i) an annual update (by applying the medium exchange rate RON/EUR of the Romanian National Bank corresponding to the first quarter of the year in which the update is done); and
- (ii) an annual correction (*i.e.*, the annual re-computation of the maximum prices approved in



CANAMED and in the Public Catalogue by reassessing the initial approval conditions according to the applicable legislation, which might lead to maintaining, diminishing or, as the case may be, increasing the approved price); by derogation to the above, the annual correction is not applicable with respect to the medicinal products authorised for special needs.

For 2018, the applicable legislation sets forth that the documentation for the approval of the price for the annual correction has to be submitted by the marketing authorisation holder/its representative starting on 30 April 2018 until 31 May 2018.

### Issues that affect pricing

- Parallel export

One of the most important issues affecting prices of medicinal products and the local pharma market in Romania is the parallel export.

In line with the abovementioned, due to the computation mechanisms provided by the applicable legislation, in many cases, Romania may have one of the lowest prices in the European Union. In practice, this allows the distributors to trade medicinal products in other Member States, thus affecting the demand/need of the local market.

However, since the jurisprudence of the European Court of Justice confirmed that medicinal products are not exempted from the rules of the common market and condemned countries that have resisted parallel exports without a just cause, in practice, there were many cases over the years when the parallel export led to the absence of medicines on the market.

In the past, in order to try to prevent the absence of medicinal products on the Romanian market, an enactment was passed with a view to prohibiting, as a temporary measure, the parallel export of several medicinal products. On grounds that the inclusion of one molecule or another in such list was done in lack of a specific transparent procedure and objective criteria, as well as for competition reasons, this enactment was abolished.

As an alternative measure aiming at preventing parallel export, as of March 2017, the secondary legislation set forth several rules regarding the “*obligation to ensure adequate and continuous stocks of medicinal products*”. Based on this enactment:

- (i) The marketing authorisation holders shall permanently guarantee the observance of the public service obligation by ensuring a minimum monthly level equal to the monthly average turnover<sup>8</sup> for every medicinal product of the Reimbursement List for which they hold a marketing authorisation.
- (ii) The wholesale distributors shall permanently ensure the observance of the public service obligation by providing assuring stocks equal to the monthly average turnover, for every distributed medicinal product of the Reimbursement List.
- (iii) A new concept of “*Temporary List of medicinal products under surveillance*” is included, representing a list of all commercial names related to a medicinal product referred to by INN, pharmaceutical form and concentration, which is temporarily forbidden for intracommunity delivery and export.
- (iv) Wholesalers have the obligation to notify the received justified order to MAH or any other wholesalers with whom they are in contractual relationships, from whom they have traded the respective medicinal product subject to the justified order.
- (v) In case wholesalers cannot deliver the received justified order, they will provide/request MAH or any other wholesalers with whom they are in contractual relationships to deliver the justified order.

In this case, MAH or, as the case might be, wholesalers with whom they are in contractual relationships with, have the obligation to deliver the received justified

order or to communicate to the relevant applicants the fact that an exceptional situation<sup>9</sup> notified to the NMDA is incidental.

- (vi) In case of Exceptional Situations the MAH, the wholesalers and the beneficiaries are no longer required to comply with the public service obligation.
- (vii) Within a maximum of three days as of the incidence of a national alert level, the Ministry of Health will include the category of medicines having same INN, pharmaceutical form and concentration under the Temporary List.
- (viii) If a medicinal product is under Exceptional Situations, the Ministry of Health will remove such from the Temporary List, respectively, and will remove the relevant category of medicines having the same INN, pharmaceutical form and concentration.
- (ix) The MAH has the obligation to notify the National Health Insurance House on the exhaustion date of the stocks of a medicinal product subject to Exceptional Situations with respect to such exhaustion of the relevant stocks.
- (x) If NMDA deems that the reason of the national alert level is not subject to the Exceptional Situations, the category of medicinal products having the same INN, pharmaceutical form and concentration will continue to be provided under the Temporary List until the reinstating and maintenance of the stock on national level exceeding the monthly average turnover for 14 consecutive days as of the providing date of such category under this Temporary List.
- (xi) Ten days before intracommunity delivery, including transactions between two or more representative offices of the same company, from different countries, MAH, wholesaler or pharmacies have the obligation to notify NMDA in this respect via the template affidavit, i.e., the observance of the public service obligation.
- (xii) “*The monthly average turnover*” represents the average of the monthly turnover of a particular medicinal product for the last three months, representing the necessary minimum for reaching the public healthcare needs.

- Counterfeit medicinal products

Counterfeit products come to the Romanian market either through unauthorised vendors or through illegal distributors in the regular distribution chain, thus triggering economic consequences.

In order to reduce such risks, in line with the EU principles, the local legislation provides the obligations for wholesalers as well as for brokers to comply with good distribution practice guidelines which impose the obligation to have, at the end of the distribution chain, only licensed pharmacies and approved retailers that are duly entitled to sell medicinal products.

Additionally, since the online trade of medicinal products is not highly regulated (thus being an alternative to the traditional wholesale distribution system to place counterfeit medicinal products on the market), *de lege ferenda*, amendments to the existing legislation should be adopted so as to address this matter.

### Policy Issues That Affect Pricing and Reimbursement

In Romania, in 2009, the so-called “*clawback tax/contribution*” was initially implemented, which was subject to significant changes in 2011 and constantly amended thereafter. The clawback contribution is one of the most non-predicable taxes imposed in the local pharma system generating numerous case files before the competent courts of law.

Pursuant to the applicable legislation, the clawback contribution is to be paid quarterly by the Romanian marketing authorisation holders or the legal representatives of the foreign

marketing authorisation holders (not to distributors or to pharmacies) for the medicinal products included in the national health programmes, for medicinal products with or without personal contribution, used in ambulatory care based on medical prescription, through open circuit pharmacies, for the medicinal products used in hospital treatment, as well as for the medicinal products and medical services granted in the dialysis centres, borne from the National Insurance Fund and from the budget of the Ministry of Health.

In other words, the marketing authorisation holders or their legal representatives have to return to the State budget a part of the profit generated from the sales of reimbursed medicinal products borne from budgetary sources.

In case the payers do not observe the obligation to pay the clawback, the medicinal products for which the contribution is due are excluded from the Reimbursement List.

Although numerous discussions took place over the years with respect to potential changes to the clawback contribution, it appears that the amendment which is constantly promoted is the necessity to implement a differentiated clawback contribution, for generic and for out-of-patent medicinal products, as compared to new products, which are more expensive and involve a greater budgetary effort.

### **Emerging Trends**

The challenge when doing business in Romania in the pharma industry is related to the constantly changing legal framework which, due to unpredictability and sometimes lack of transparency, impedes the pharma players to make long term business plans.

The local Competition Council proposed, over time, several legal amendments which might prove to be recommendable competition-wise, such as:

- (i) in order to make the use of budget funds more efficient, the consumption of generic medicinal products is encouraged, which may imply the adoption of legislative measures to facilitate the market entry of the generic products by including them on the Reimbursement List as soon as the patent of innovative medicines has expired;
- (ii) modifying the clawback tax calculation method, so that the computation method would be different for innovative drugs (the more expensive ones involving a larger budget effort), as compared to generic ones. This measure could encourage the use of cheap medicinal products and also keep them on the market; and
- (iii) imposing a price reduction on innovative medicines after patent expiration in order to have the same price with the generic medicines.

### **Successful Market Access**

Given the constantly changing legal framework, the successful entry on the market should be based on: (i) sound assessment of the legal environment in order to determine the restrictions, risks and available options; (ii) reasonable expectations related to the price approval and the inclusion of the relevant INN on the Reimbursement List tailored to the local market and doubled by identifying legal alternatives that allow the access of patients to the relevant INNs even though not included in the Reimbursement List; and (iii) relatively flexible pricing policy at the level of the pharma player and adaptability to the local specifics of the pharma market.

\* \* \*

## Endnotes

1. [https://ec.europa.eu/health/state/country\\_profiles\\_en](https://ec.europa.eu/health/state/country_profiles_en).
2. [http://www.insse.ro/cms/sites/default/files/com\\_presa/com\\_pdf/poprez\\_ian2017r.pdf](http://www.insse.ro/cms/sites/default/files/com_presa/com_pdf/poprez_ian2017r.pdf).
3. [https://ec.europa.eu/health/state/country\\_profiles\\_en](https://ec.europa.eu/health/state/country_profiles_en).
4. [https://ec.europa.eu/health/state/country\\_profiles\\_en](https://ec.europa.eu/health/state/country_profiles_en).
5. According to the applicable legal provisions the relevant countries are: Austria; Belgium; Bulgaria; Czech Republic; Germany; Greece; Hungary; Italy; Lithuania; Poland; Slovakia; and Spain. Annually, the Ministry of Health is legally entitled to modify the list of countries taken into account for comparison purposes. In practice, such amendments were not adopted by MoH so far.
6. According to the applicable legal provisions the relevant countries are: Austria; Belgium; Bulgaria; Czech Republic; Germany; Greece; Hungary; Italy; Lithuania; Poland; Slovakia; and Spain.
7. According to the applicable legal provisions the relevant countries are: Austria; Belgium; Bulgaria; Czech Republic; Germany; Greece; Hungary; Italy; Lithuania; Poland; Slovakia; and Spain.
8. Pursuant to the secondary legislation “*the monthly average turnover*” represents the average of the monthly turnover of a particular medicinal product for the last three months, representing the necessary minimum for reaching the public healthcare needs.
9. As per the incident legal provisions, “*exceptional situation*” refers to the case when MAH informs NMMDA, under the conditions set forth by the applicable legislation, with respect to quality/safety issues, the impossibility to deliver active substances, the withdrawal of conformity Certificate issued by European Pharmacopeia or of Certificate of good manufacturing practices, the temporary discontinuity of manufacturing (“**Exceptional Situations**”).

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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

According to a report<sup>1</sup> published in April 2017 by the research and consulting firm GlobalData, the pharmaceutical market in Spain is going to increase its value from \$23.7 billion in 2016 (€19,852 million) to \$25.1 billion by 2021 (€21,018 million).<sup>2</sup> In 2015, Spain's pharmaceutical production was worth €15,625 million according to EFPIA.<sup>3</sup> The future evolution of pharmaceutical expenditure is likely to experiment extraordinary increments of specific nature as a result of the appearance of innovative medicinal products, especially in the area of oncological products and orphan drugs, and it is likely that this causes the hospital expenditure to exceed the expenditure made in pharmacies, which is where cost containment measures had been concentrated in the last years.<sup>4</sup>

As in many other EU countries, the Spanish pharmaceutical market is highly dependent on public policies, given that approximately 73% of health expenditure comes from the public sector. Spanish public pharmaceutical expenditure is said to account for 0.9% of gross domestic product, and 14.5% of all public healthcare financing. According to data of FARMAINDUSTRIA (the association of the Spanish innovative pharmaceutical industry), the characteristics of the pharma market for the year 2016<sup>5</sup> were the following: the Spanish pharmaceutical industry is the most productive sector of Spain (it doubles the industry average); it is one of the leaders in exports (it exceeds €10,600 million per year); and it by comparison to other sectors in Spain concentrates more stable, qualified and diverse employment (more than 95% of its workers are permanent, 50% have university degrees and 50% are women).

As regards demographics, at the beginning of 2016, 46.4 million inhabitants lived in Spain, with a gross birth rate of 9.2 births per 1,000 inhabitants and an average maternal age of 31.9 years. Life expectancy at birth reached 83.2 years with 80.3 years for men and 86.1 years for women.<sup>6</sup> Spain has the typical 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")<sup>7</sup> shows that the percentage of population aged 65 years and over, which in 2014 stood at 18.2% of the population, would increase to 24.9% in 2029 and to

38.7% in 2064. According to the same data, if the current demographic trends continue, Spain will lose one million inhabitants in the next 15 years and 5.6 million inhabitants in the next 50 years.

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.<sup>8</sup> However, measures<sup>9</sup> 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 beneficiary of the system.<sup>10</sup> Put into practice, these measures implied that some of the population would not access the healthcare provision. The Constitutional court declared that these limitations to the healthcare provision were valid but many regions in Spain have declared that such right is universal in their territory, and the situation is still pending resolution in the Spanish courts.

During the year 2015, 1,456 presentations of medicinal products were included in the provision of the National Health Service (“NHS”).<sup>11</sup> 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 price 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 price 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 who allocate the budget for financing such therapies. This means that in the case of high-cost products, companies must expect that access to market be subject to agreements with regional authorities (or sometimes with local hospitals) regarding the conditions under which the product will be available in such region or hospital.

### **Pharmaceutical Pricing and Reimbursement**

According to Article 19 of the Spanish Law on Medicinal Products,<sup>12</sup> when the AEMPS authorises a medicinal product, it will determine its prescription conditions by deciding whether the product is subject to medical prescription or not.

The same Article establishes that certain medicinal products which meet certain conditions will be always subject to a medical prescription. This is the case of 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, such medicinal products 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, for medicines that can only be dispensed under medical

prescription, some subcategories. This would apply to products subject to special medical prescription regime; or to medicinal products which can only be dispensed by certain means (such as medicinal products of 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 to processes or conditions that do not require an accurate diagnosis or those whose toxicological, clinical or use evaluation data and route of administration does 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.

Spanish law defines generic medicinal products<sup>13</sup> as any medicinal product that has the same qualitative and quantitative composition in active ingredients and the same pharmaceutical form, and whose bioequivalence with the reference medicine has been demonstrated by adequate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active ingredient will be considered the same active ingredient, unless they have considerably different properties in terms of safety and/or efficacy. Biosimilar products, are not defined under Spanish law, although there exist provisions under which all biological products are considered as non-eligible for substitution without the prior approval of the prescribing doctor.

Under Spanish law, the distinction between over the counter medicines and non-prescription medicines does not exist, because the law only distinguishes between prescription and non-prescription medicines.

#### What pharmaceutical products are eligible/ineligible for reimbursement?

Under Article 92 of the Spanish Law on Medicinal Products, the inclusion of a medicinal product in the financing of the National Health System (“NHS”) is decided according to a selective funding system and taking into account general objective and published criteria, more precisely, the following:

- the seriousness, duration and sequels of the pathologies for which the product is approved;
- the needs of special groups of people;
- the therapeutic and social utility of the product as well as its incremental clinical benefit, taking into account its cost and effectiveness;
- the need to limit and rationalise public pharmaceutical expenditure and the impact of the medicinal product in the NHS;
- the existence of medicines already available and the existence of other alternatives for the same illnesses, which have a lower price; and
- 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:



- The impact that financing such product may have on the public budget.
- 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 marketing authorisation holder (“MAH”) may present may also be considered.
- The innovation of the product, for its indisputable therapeutic advances for altering the course of the illness or easing the course of such illness, its prognosis, results or contribution to the NHS.
- The contribution of the product to Spain’s gross domestic product. This is awkward because it could indicate that local manufacturing or development operations may have an influence on pricing and reimbursement, something which would be totally contrary to EU law principles.
- The return mechanisms which may be proposed by the MAH (discounts, price reviews). This is the result of the increasing relevance that risk sharing schemes are having in Spanish practice nowadays, so many companies, especially for high-cost products, are offering special arrangements to obtain reimbursement.

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 the 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.

#### Who is/Who are the payer(s)?

Autonomous Regions are the ones who 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 in which Spain is divided. Because of this, the regions participate in the specific committee at the MOH responsible for assessing applications for deciding whether a product is dispensed within the structure of the NHS or not. This committee is called Interterritorial Council.

This generates a complex situation where the basic content of the pharmaceutical provision is set forth at a state level (because the MOH makes the decision on price 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.<sup>14</sup>

On the other hand, products that patients obtain at retail pharmacies are subject to copayment rules under which the patient has to pay part of the price of the product. The copayment 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 MAH

does not have the right to say that it is not interested in reimbursement and that it shall launch the product right away. Under Spanish Law on Medicines and Medical Devices (Article 92), the MAH has to go through this process so that the MOH may decide whether the product shall be reimbursed and covered by the NHS or not.

The process regarding pricing and reimbursement in Spain of a medicinal product that is centrally approved begins when the AEMPS gives final clearance to the packaging materials which shall be used in Spain.

Once the AEMPS has approved the final packaging materials of the product, it shall record this decision and it shall 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 and pricing. As explained, the reimbursement process starts then *ex officio*. The General Directorate of Pharmacy and Medical Devices shall send a letter to the MAH 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 obtain the reimbursed price should be completed within 90 days, but the process may go on for 180 days. Furthermore, the authorities usually request additional information, and these requests 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 to 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 a price committee, is the body which makes the final decision about price and reimbursement. It is also very important to note that authorities of the Autonomous Regions also 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 price committee which decides whether a product is dispensed within the structure of the NHS or not.

Under the Constitution, the Autonomous Regions are the ones who have the power to manage the provision of public healthcare services to citizens. When doing so, the health authorities of each Autonomous Region must respect some basic principles laid down by Spanish legislation, but they keep the authority to organise their activities, in particular as regards healthcare services that are provided at hospitals and other specialised and primary care centers. The central Spanish legislature and government have exclusive competence to enact legislation on medicinal products. Therefore, whilst Spanish legislation lists the healthcare services which all Autonomous Regions must offer, the Autonomous Regions keep the authority to organise how they are provided in practice. This means that the Autonomous Regions are the ones who define who and under which conditions may have access to a certain treatment.

It is also important to note that other relevant stakeholders will be doctors, medical and hospital pharmacy societies and patient associations.

#### *What is the process to appeal a decision?*

Companies may file an administrative appeal against the decision taken by the MOH. The appeal must be filed within one month since the date on which the company received the resolution of the MOH.

If the administrative appeal is rejected, the company may file a Court action seeking a declaration that the MOH acted wrongly. However, in price and reimbursement cases, the chances of a Court action being successful are rather limited given that the MOH has large 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.

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

The prices of medicinal products which are reimbursed require prior approval from the MOH. The MOH, on the other hand, is also entitled to control the price of medicinal products which are not reimbursed by reasons of public interest.

Royal Decree 271/1990 states that the maximum ex-factory price of the reimbursed medicinal products should respond to the cost of the product plus a given profit margin (12–18% on capitals allocated to exploitation). As a matter of practice, however, the process entails a negotiation with the authorities. Additionally, companies are legally obliged to grant a discount on the maximum ex-factory price.

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 shall 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 30% and 50% for the price of the reference/s product/s (the price of generics are likely to be within this range).

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

As regards setting of the price of the medicinal product, 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 Total Cost, three group 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.
  - Incidence that the manufacture of the product may have in overhead costs of the company.
- (ii) Variables which are not considered since they are treated as unjustified or unnecessary costs:
- Overvaluation of active substances in comparison with market prices.
  - Excessive royalties (trademarks or technology).
  - Promotion or advertising expenses which are not adequate to the characteristics of the product.
  - Expenses which are not necessary to the normal development of the activities of the company.
- (iii) Variables which are subject to intervention and which may be limited by the Government Delegate Commission for Economic Affairs:
- Research and Development.
  - Promotion and Publicity.

Under Order of 17 November 1990, R+D expenses are not subject to any limitation. R+D expenses may therefore be incorporated into the cost of the product if they are justified, and prior deduction of all public aids granted to the company under R+D programmes. The R+D percentage, which may be incorporated to the cost of the product, is the equivalent to the percentage that the total expenses of R+D represent on the company's total sales.

As to promotion and advertising expenses, they may only be incorporated to the cost of the product within a range of 12–16% of such cost.

As regards the profit component, the rule is that the target profit of each company shall be comprised within a range of 12–18% on capitals allocated to exploitation, including own resources (share capital, update and revaluation accounts, reserves, and others) and external resources with financial cost.

As regards the relationship between price and reimbursement, they are in theory autonomous institutions which have different aims. However, there is a relation in terms of the fact that manufacturers cannot place a product on the market if they have not gone through the process of pricing and reimbursement. Furthermore, it is evident that the price level expected by the MAH does have an impact on the decision on its public financing. It is also important to note that the decision of 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.

### 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 the prices to be determined mainly by the following two subjects:

- 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 to the authorities considering 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 six criteria which we have mentioned above when discussing reimbursement approval, and also the average price of the medicinal product in EU-27. It is not always clear in Spain which country's price is to be used as the reference price. The price which may be used as a reference price might be the lowest available price in the EU. On a separate note, it is also true that in case a similar product is commercialised on 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.

The law also states that the body which is competent for approving the price of the products shall take into account the Therapeutic Position Reports of AEMPS.

A special comment as regards transparency must be made. The general information that the pharmaceutical laboratories have provided to the administration for the purposes that the administration fixes the prices of the medicinal products is confidential. However, transparency is an important matter, and in the last few years there have been initiatives in order to increase the level of transparency of any administrative rulings. One of them has been creating transparency councils, which act as "transparency courts" at regional and national level, and which control access to public information. Recent resolutions of the Transparency Council which controls the MOH have ruled that the dossier containing information provided by the MAH when applying for price and reimbursement of a medicinal product may be confidential in itself, but that the MOH must provide access to other information on the price and reimbursement file. Given that the Council has not qualified as confidential the resolutions of price and reimbursement themselves, in our opinion these are likely to end up being public domain in the near future. 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.

### **Policy Issues That Affect Pricing And Reimbursement**

The general political environment in Spain has affected pricing of the medicinal products. Over the last few years, budget constraints have been constant and authorities have been very strict and careful as regards the pricing decisions. According to the last published annual memoire of the NHS (for the year 2016), in 2015, the pharmaceutical expenditure generated by the invoicing of NHS prescriptions in pharmacy offices meant an expense of €9,962 million. The pharmaceutical invoice of 2015 grew with respect to 2014, but remained below the expenditure of the year 2012. Between 2010 and 2015, pharmaceutical expenditure decreased by 21.6%. Such containment of public pharmaceutical expenditure was influenced by the continuity of regulatory measures and the promotion of the rational use of medicines, which had a great impact. Especially Royal Decree-law 16/2012, of 20 April, on urgent measures to guarantee the sustainability of the NHS and improve the quality and safety of its benefits, established a new contribution system for the dispensing of medicines and medical devices provided by the NHS which was determined according to

the level of income and the socio-employment situation. The modification of the reference price system (which functioning has been explained above) and the homogeneous groupings of medicines, regulated by the provisions dictated in the course of 2014 and 2015, have also contributed to the containment and reduction of pharmaceutical expenditure.

It is relevant to mention that in late 2015, FARMAINDUSTRIA reached an agreement with the Spanish Government, under which pharmaceutical expenditure is not to grow more than the real GDP growth. This is expected to be 2.1% in the period 2017–2018; and 1.8% in the period 2019–2020. The agreement contemplates charge-backs 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 expensive drugs.

As regards more specific groups of medicines, we would also like to mention the special situation for rare diseases 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 where the MOH seats 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 price 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.

Real data made public by the Spanish Association of Orphan and Ultraorphan Medicines Companies (“AELMHU”) indicate that the practical effect of the recommendation has not been very successful. A survey carried out by AELMHU, as per their press release dated 7 July 2016, indicates that since 2002, the EMA has approved 94 new orphan drugs, and that only 51 of them have been placed in the market in Spain. The data for the period 2012–2015 are especially worrying because out of the 44 orphan drugs approved by the EMA, only 13 have been accepted for reimbursement in Spain.

### Emerging Trends

The rules on price fixation 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 because of the political environment in Spain at the time. The project would have made it easier for the Spanish government to decide not to finance a drug. The mere fact that the price for a product be considered to be too high for the NHS would have been sufficient to decide not to finance it with public funds, with no need to provide any other reasoning for this decision.

Recently, in March 2018, the General Secretary of Health declared that the reference price system was being updated. Likewise, the General Secretary of Health established that standardised procedures were being prepared for the application of the upper limits of expense.

The General Secretary of Health determined that the main challenges of the pharmaceutical policy include the need to update the rules relating to price and reimbursement in the Spanish Law on Medicinal Products and Medical Devices, the modification of Royal Decree

177/2014, that regulates the system of reference prices, a new Royal Decree on prices and financing of medical devices and the Royal Decree of advertising and information to professionals. He also declared that it was not possible to address all these projects simultaneously, which is why the MOH would concentrate on the most urgent matters and whose processing can be successfully addressed. In this sense, he determined that it was crucial to introduce small changes in the reference price system, which is a key tool for the sustainability of pharmaceutical provision in the NHS. He determined that the MOH had been using this tool for more than 10 years in the containment of pharmaceutical expenditure and that it was true that, being a very valuable tool, the MOH wanted to avoid that, in the future, it could become something that delayed true incremental innovations in classic medicines which can be valuable for patients.

### Successful Market Access

Reimbursement and pricing procedures in Spain entail a lot of negotiation. As in any negotiation, defining a strategy shall be very important. When doing so, companies must not forget that the budget constraints in Spain are important and must therefore 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 the 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), be open to entering into risk-sharing agreements with the MOH, and also be ready to agreeing to caps in the number of medicinal products that the MOH will finance (meaning that the pharmaceutical company may have to assume the cost of the rest of the units of the product which are dispensed).

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### Endnotes

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9. Those measures were established by means of Royal Decree 16/2012, of urgent measures to guarantee the sustainability of the Spanish National Health System and improving the quality and security of the provisions contained in it.
10. These limitations consisted basically in the establishment of some kind of requisites in order to access healthcare benefits, such as contributing to the Spanish Social Security system, having an authorised residence in Spain, holding a pensioner status of the Social Security System or being the beneficiary of any other periodic Social Security benefit, including unemployment benefits and subsidies. Those who have exhausted the benefit or the unemployment subsidy and appear registered in the corresponding office as 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 that they proved that they do not exceed the income limit determined by regulation.
11. According to data of the Ministry of Health – “*Informe Anual del Servicio Nacional de Salud*” año 2016. [https://www.msssi.gob.es/estadEstudios/estadisticas/sisInfSanSNS/tablasEstadisticas/InfAnualSNS2016/Informe\\_Anual\\_SNS\\_2016\\_completo.pdf](https://www.msssi.gob.es/estadEstudios/estadisticas/sisInfSanSNS/tablasEstadisticas/InfAnualSNS2016/Informe_Anual_SNS_2016_completo.pdf).
12. Royal Legislative Decree 1/2015, of July 24, approving the revised text of the Law on Guarantees and Rational Use of Medicines and Medical Devices.
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# Sweden

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## Abstract

This article provides an overview of the Swedish model for pricing and reimbursement of pharmaceutical products in Sweden, including brief notes on reimbursement of medical devices.

In 2002, Sweden abandoned the reference price system for pharmaceutical reimbursement used since the 1990s, which is still widely adopted in European countries, and introduced a new value-based pricing and reimbursement scheme. Thereby and since, to a large extent Sweden has led the way on value-based pricing for pharmaceutical products. The main features of the value-based model are the use of cost-effectiveness analysis for determining the reimbursement status of pharmaceuticals and mandatory substitution of the lowest-cost generic alternative. The use of cost-effectiveness analysis in reimbursement decisions aims to relate and balance the reimbursement price to the social value of the product, but does not necessarily result in (or intend to result in) the lowest possible price.

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

Costs for subsidised out-patient pharmaceutical products included in the reimbursement scheme are formally financed by the county councils but are covered by government grants. Patients only pay a limited part of the price for such pharmaceuticals and a patient's maximum costs during a year are subject to high-cost protection.

## Market Introduction/Overview

Swedish healthcare is the shared responsibility of the state, county councils and municipalities. The state is responsible for the overall health and medical care policy, while the county councils are responsible for providing healthcare. The Ministry of Health and Social Affairs (Sw. *Socialdepartementet*) is responsible for issues concerning the welfare of society by implementing the objectives set by the Swedish Parliament and the Government. Several independent agencies answer to the ministry.

According to the Health and Medical Services Act (2017:30) (Sw. *hälso- och sjukvårdslagen*) (HSL), the goal of healthcare is good health and healthcare on equal terms for the entire population. Furthermore, the care should be given with respect to the equality of all human beings and to the individual's dignity. Those who have the greatest need of 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, the 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 with a high priority from the Swedish Government and Sweden is the EU innovation leader according to the European Innovation Scoreboard. During the year 2017, the Swedish pharmaceutical market had a turnover of SEK 43.8 billion, an increase of three per cent compared to 2016. In 2017, 203 million pharmaceutical packages were sold in Sweden. Approximately 49 per cent of these packages were prescription pharmaceutical products, while approximately 44 per cent were non-prescription pharmaceutical products.

The Swedish pharmacy market was deregulated in 2009. Since then, the number of pharmacies has increased by almost 500. Currently, there are over 1,400 outpatient pharmacies in Sweden. The industry is dominated by five pharmacy chains and there are just over 30 companies with one or a few pharmacies. In addition to out-patient pharmacies, there are hospital pharmacies, dose dispensing pharmacies and distance pharmacies. The total sales for out-patient and distance pharmacies amounted to approximately SEK 40.2 billion in 2016, of which approximately three quarters consisted of prescription pharmaceutical products and other products, while the remainder of the sales mainly consisted of non-prescription pharmaceutical products and merchandise.

Since the deregulation, the pharmacies have increased their opening hours. This, as well as the emergence of e-commerce, has contributed to an improved accessibility than before the deregulation.

## Pharmaceutical Pricing and Reimbursement

### Regulatory classification

#### **Legal framework**

Being an EU Member State, Sweden's legal framework on pharmaceutical products is to a large extent based on relevant EU directives and subject to EU regulations. The national legislative basis for regulatory issues (including marketing authorisation and substitutability), supervision and enforcement of pharmaceutical products in Sweden is primarily stipulated in the Medicinal Products Act (2015:315) (*Sw. läkemedelslagen*) and the Medicinal Products Ordinance (2015:458) (*Sw. läkemedelsförfordningen*), and for medical devices in the Medical Devices Act (1993:584) (*Sw. lag om medicintekniska produkter*) and the Medical Devices Ordinance (1993:876) (*Sw. förordning om medicintekniska produkter*). The Medicinal Product Act and the Medicinal Products Ordinance are based on Directive 2001/83/EC. The Medical Devices Act and the Medical Devices Ordinance are based on Directives 90/385/EEC, 93/42 EEC and 98/79/EC. There are also regulations and guidelines issued by the Swedish Medical Products Agency (MPA).

The legal framework concerning the granting of marketing authorisation of a pharmaceutical product differs from the framework concerning pricing and reimbursement. While the former is based on EU rules as described above, the latter is substantially regulated at a national Swedish level with little influence from the EU.

The Swedish Dental and Pharmaceutical Benefits Agency (TLV), which is an expert state agency, decides to what extent a pharmaceutical product shall be reimbursed, according to the Pharmaceutical Benefits Act (2002:160) (*Sw. lag om läkemedelsförmåner m.m.*) (PBA) and the Pharmaceutical Benefits Ordinance (2002:687) (*Sw. lag om läkemedelsförmåner m.m.*) (PBO). TLV also issues regulations and general advice.

In addition, Sweden has a system for substitution of generically equivalent medicinal products. The MPA approves all medicinal products, including generics and parallel

imported products, with regard to their quality, safety and efficacy. The MPA decides which medicinal products that 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 shall be substituted. Only products that are reimbursed can 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 generated 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 the 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 institutions 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 processes performed by the Swedish county councils.

It is possible for a specific pharmaceutical product to be subject to both prescription and requisition. In such case, two different systems of regulations will apply which can lead to different prices on 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 required.

### **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 of non-prescription pharmaceutical products being eligible for reimbursement. According to the TLV regulation TLVFS 2003:2 (regarding

non-prescription pharmaceutical products in accordance with Pharmaceutical Benefits Act) (last amended by TLVFS 2012:3), non-prescription pharmaceuticals are eligible for reimbursement. In addition to pharmaceuticals, there are also other products that are eligible for reimbursement.

As stipulated in Section 18 of the PBA, only some medical devices are eligible. Medical devices eligible for reimbursement, called *consumables*, only includes products used (i) in connection with stoma, (ii) to induce a pharmaceutical product into the human body, and (iii) for self-monitoring of medication. Stoma-consumables are covered by the same rules regarding reimbursement as pharmaceutical products in general, while consumables used to induce pharmaceuticals and for self-monitoring of medication are entirely reimbursed and are free of charge for the patient.

Even food may under certain circumstances be eligible for reimbursement. According to Section 20 of the PBA and as further regulated in Section 67 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/who are the payers?

Pricing of medicinal products that are included in the reimbursement system is regulated and the cost of such medicinal products dispensed in pharmacies to patients is to a large extent subsidised by the state. The patient pays some of the costs for subsidised prescription pharmaceuticals, but according to the PBA, a patient's maximum costs are subject to high-cost protection valid for 12 months at a time starting from the date of the first purchase. As of the date of this chapter, the maximum amount is SEK 2,250 (approx. EUR 225). The high-cost protection is calculated based on the base amount set out in the Social Insurance Code (2010:110) (Sw. *socialförsäkringsbalken*). A patient pays the entire cost up to a maximum amount (as of the date of this article SEK 1,125 (approx. EUR 112.5)), 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 with this is to reduce inequality of children's health between groups in society with different financial conditions.

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 are typically paid 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 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 of 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, the appeal will 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 and 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 shall 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 appears reasonable from a medical, humanitarian and socioeconomic perspective, and that (ii) there are no other available pharmaceutical products or treatments, which, when balancing the intended effect and potential harm, is deemed to be significantly more suitable.

TLV shall determine the price 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 as to why TLV grants a restricted reimbursement may be that the pharmaceutical product is only considered 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 current patient group and volume, for instance the number of patients that will need the pharmaceutical product and for how long. Furthermore, TLV considers whether there is a risk that the pharmaceutical product is used outside a potential limitation of the subsidy which in that case risks being a usage that is not cost-effective. TLV has developed a practice on how to apply the criteria for subsidy and pricing. In 2003, TLV issued general guidelines (LFNAR 2003:2, last amended by TLVAR 2017:1) which are intended to guide pharmaceutical companies that plan to apply for subsidy and pricing of a pharmaceutical product, and describes how TLV believes that a health-economic analysis should be conducted. The guidelines are worth considering in the planning and implementation of health economics studies to be used in upcoming applications for subsidy and pricing.

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

There are various pricing procedures for pharmaceutical products, for example, through decisions by TLV, the county councils’ procurement procedures, or free pricing. The pricing of products differs in out-patient and in-patient treatment.

### **Out-patient care**

In outpatient care, the difference between price and reimbursement for pharmaceutical products included in the reimbursement scheme, is the patient’s co-payment (see section “*Who is/who are the payers?*”, “Pharmaceutical Pricing and Reimbursement” above). This means that the state reimburses almost the entire cost.

TLV determines the pharmacies’ trade margin for pharmaceutical products included in the reimbursement scheme, which means that the pharmacies’ purchase price (AIP) as well as selling price (AUP) are regulated. The county councils and pharmaceutical companies may enter into managed entry agreements, which is one of several factors considered when TLV takes decisions on price and reimbursement. Risk-sharing through managed entry agreements has become an increasingly valuable tool to manage uncertainties for certain new pharmaceutical products. Furthermore, they may ensure cost effectiveness and reduce the increasing costs for new pharmaceuticals. Consequently, the discussions between county

councils, pharmaceutical companies and TLV can enable the use of such pharmaceuticals, even when there is significant uncertainty concerning their medical effect and cost-effectiveness. Furthermore, the pharmacies have a right of negotiation which means that they may use prices other than those determined by TLV, for some pharmaceutical products, mainly parallel imported pharmaceutical products.

The pricing of non-prescription (over-the counter) pharmaceutical products can be set freely. The patient pays the entire cost for these medicinal products. Prices are regulated for non-prescription drugs that are included in the reimbursement system, and the patient makes a co-payment. It shall 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 can 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 are decided by TLV and appointed through a monthly auction. The substitution is mandatory and consequently, the pharmacies are obligated to dispense the least expensive pharmaceutical product included in the reimbursement scheme that is available on the market, regardless of the prescribed product.

### **In-patient care**

The prices for in-patient care (hospitals) medicinal products are negotiated in the county council's public procurement processes, which are regulated by the Swedish Public Procurement Act (2016:1145) (Sw. *lagen om offentlig upphandling*). The patient only pays the patient fee that applies for the in-patient treatment concerned, and except such flat fee, the entire price of pharmaceutical products used in in-patient case is reimbursed by the county councils.

Pharmaceutical products used in in-patient care are not covered by the national reimbursement scheme and there is no nation-wide reimbursement list for in-patient pharmaceuticals since county councils decide on which treatments to use and finance them at the regional level.

### Issues that affect pricing

#### **Generic substitution**

As stated above, the MPA approves all medicinal products with regard to their quality, safety and efficacy and the MPA also decides which medicinal products that 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 shall be substituted. Only products that are reimbursed can be substituted. This means that pharmacies are obligated to dispense the least expensive pharmaceutical product included in the reimbursement scheme that is available on the market – regardless of what product is prescribed. Physicians and pharmacists at the pharmacies may only prohibit substitution on medical grounds, as stipulated in Section 21 of the PBA. The purpose of this substitution system is to safeguard the lowest possible cost for both the patient as well as the society.

#### **Ceiling prices**

Generic substitution leads to lower prices due to competitive market forces, which may result in significant price differences between generic substitutes arising. In this situation,



TLV may decrease the maximum accepted selling price within the reimbursement scheme by setting a lower ceiling price for substitutable pharmaceuticals. This is most relevant for the branded original pharmaceutical product that has lost its patent protection.

Each month, TLV analyses prices and sales volumes in order to find groups where the criteria for setting a ceiling price are met. When the prices of a group of substitutable generic pharmaceuticals have dropped by at least 70 per cent of the price that the pharmaceuticals had before generic competition arose, and when generic competition has been ongoing for at least six months, TLV sets a ceiling price.

The new fixed ceiling price is 65 per cent of the price that the pharmaceuticals had before 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.

### **Price reduction after 15 years**

From 1 November 2014, there are new rules for the pricing of some older drugs (see TLV's regulation TLVFS 2014:9). The change is based on changes in the PBA and means that TLV will reduce the price of pharmaceutical products by 7.5 per cent when becoming 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?*", "Pharmaceutical Pricing and Reimbursement").

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, the immigration constitutes the largest demographic change and primarily increases the population that is of working age.

An ongoing public inquiry appointed by the Swedish Government (see further "Emerging Trends" below), *inter alia*, discusses the fact that shared resources available for financing pharmaceuticals are insufficient to meet all needs and therefore priorities must be made. As the population grows, ages and gets more chronic diseases, while the innovations within the pharmaceutical industry increase 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 large focus on the pricing and reimbursement of pharmaceutical products and the Government has 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 the pharmaceutical products benefits was passed from the state to the county councils. Since the introduction of the system, the conditions for the healthcare organisation have changed as well as the types of pharmaceutical products that reach the market. The system has been developed in order to meet the change. However, some parties, such as patients, companies and county councils, describe them as complex, difficult to grasp and, in some parts, not transparent. The inquiry includes investigation of the division of responsibility between the state and county councils regarding the financing of pharmaceutical products and analysis of how the pharmaceutical products shall be priced and reimbursed. The full public inquiry is to be presented on 1 December 2018.

In 2014, a three-party negotiation process between the county councils' negotiation delegation, TLV and the pharmaceutical company in question, as well as managed entry agreements for pharmaceutical products covered by the reimbursement scheme, was 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 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.

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.

### **Successful Market Access**

For successful market access in Sweden, it is crucial to obtain an understanding of the quite unique Swedish value-based pricing model and the considerations involved in assessing applications for inclusion of pharmaceutical products in the reimbursement scheme. This is true for marketing of original drugs, generics and parallel imports alike. An understanding of the model will also facilitate effective participation in public procurement by the county councils for in-patient use.

If an application for listing in the reimbursement scheme is rejected by TLV, the company may consider attempting to enter into three-party negotiations with the county councils' negotiation delegation and TLV in order to get another opportunity for reimbursement of its products. For such a negotiation process to be successful, it is beneficial to understand the different factors that will be considered by the county councils and TLV. As an alternative, or if the three-party negotiation fails, companies can also appeal the rejected decision to have the case tried by the administrative courts, or either go about putting the drug on the market without reimbursement (an option that is always available) or resubmit the application to TLV (e.g. including a more comprehensive health economic analysis) for a second-round evaluation.

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# Switzerland

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## Abstract

Every resident in Switzerland is mandatorily obliged to be covered by basic healthcare insurance which provides for a wide range of services. Persons with lower incomes are in principle granted reductions on the premiums payable for such basic healthcare insurance. Thus, every resident in Switzerland is granted access to affordable healthcare.

In general, therapeutic products are only reimbursed if they are listed on the so-called specialty list. In order to be listed thereon, a medicinal product must be admitted by the competent Swiss authority and has to satisfy the criteria of effectiveness, functionality and economic efficiency, based on which the maximum price for the therapeutic product in question is determined.

## Market Introduction/Overview

### Size, demographics

Switzerland has one of the most expensive healthcare systems. In 2016, the healthcare costs amounted in total to 80.7 billion Swiss francs (increase of 3.8% compared to 2015), among which approximately CHF 13.2 billion were paid for healthcare goods, including therapeutic products in hospitals. Compared to the general domestic product (GDP), the healthcare spending represented 12.2% in 2016 (an increase from 11.9% in 2015 to 12.2% in 2016). Every resident in Switzerland paid on average 803 Swiss francs per month for the healthcare system in 2016 (*cf.* [www.bfs.admin.ch](http://www.bfs.admin.ch); last visited on 6 May 2018).

In 2016, the total value of goods and services exported from Switzerland amounted to 210.5 billion Swiss francs, whereas the value of imported goods and services amounted to 173.5 billion Swiss francs. A positive balance of 36.9 billion Swiss francs in favour of Switzerland resulted therefrom. The most important part of Switzerland's imports and exports were chemical and pharmaceutical products, which constituted 44.3% of the exports (94.3 billion Swiss francs) and 25.1% of the imports (43.6 billion Swiss francs). Compared to 2015, the export of chemical and pharmaceutical products increased by 11% (*cf.* Annual Report on Swiss Foreign Trade 2016 of the Federal Customs Administration, available under the following link: [www.ezv.admin.ch](http://www.ezv.admin.ch); last visited on 6 May 2018).

According to the Association of research-based pharmaceutical companies in Switzerland (Interpharma), in 2016 more than 83% of the total pharmaceutical sales were reimbursable therapeutic products. The remaining part was non-reimbursed products. Most of the reimbursable therapeutic products were subject to prescription (*cf.* Interpharma, Swiss Healthcare and Pharmaceutical Market, 2017, p.40).

Over 422,000 people in Switzerland worked in the healthcare industry and the pharmaceutical sector in 2016. This corresponds to approximately one in twelve of the working population (*cf.* Interpharma, Swiss Healthcare and Pharmaceutical Market, 2017, p.18).

In Switzerland there is a very high density of hospitals which offer a wide range of medical services. In 2016, 283 hospitals and birth houses and 1,570 homes for elderly and care were registered in Switzerland. 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 allowed to dispense medicines themselves (*cf.* Interpharma, Swiss Healthcare and Pharmaceutical Market, 2017, p.18). Contrary to certain countries, such as the USA, most of the 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 endeavours to strengthen the international position of Switzerland with several initiatives, such as the 'Masterplan for the promotion of biomedical research and technology' of 2013 (for further information, *cf.* [www.bag.admin.ch](http://www.bag.admin.ch) and below section "Emerging Trends"). Also, 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 product and how are drug prices set?" in "Pharmaceutical Pricing and Reimbursement").

#### Healthcare system, access to care

The Swiss Federal Office of Public Health ("**FOPH**") is responsible for public health in Switzerland. In particular, the FOPH is coordinating Switzerland's health policy and supervises the compulsory health insurance. Further, the FOPH is involved in the 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 diseases. The responsibility for these tasks is 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 from moving to Switzerland or from his/her birth (article 3 para. 1 HIA). Any such person may freely choose among the insurers, which are authorised pursuant to the AHV to offer basic health insurances (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 offer currently basic mandatory insurance and optional loss of earnings insurance.

The insurers offering compulsory health insurances must treat all insured persons equally. In particular, they are not allowed to decline a request for basic health insurance and must offer to all insured persons the same range of benefits. Insureds are free to change the insurer by giving notice three months before the end of a calendar semester (article 7 para. 1 HIA).

The cantons are required to ensure compliance with compulsory insurance. If a person domiciled in Switzerland does not timely conclude a basic health insurance, the canton of its domicile has to allocate such person to one of the insurers (article 6 HIA). Consequently, every resident in Switzerland has a basic health insurance.

Compulsory health insurance reimburses the costs for the services of healthcare providers regarding diagnosis and treatment of diseases and their consequences (articles 25 para. 1 and 35 HIA). This includes all examinations and treatments carried out by doctors or physicians as well as chiropractors. Further services include, *inter alia*, laboratory analyses, therapeutic products, aids and equipment prescribed by medical doctors (article 25 para. 2 HIA). The aforementioned shows that the catalogue of services covered by compulsory health insurance is quite extensive.

In case of congenital diseases, basic health insurance pays the same costs as in case of disease, if such costs are not covered by the invalidity insurance (art. 27 HIA). As regards accidents, the corresponding healthcare costs will be covered by basic health insurance, provided that no accident insurance is in place (articles 28 and 1a para. 2 lit. b HIA). Furthermore, healthcare costs related to maternity are also borne by the health insurance (article 29 HIA).

In addition to the 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 the mandatory basic health insurances have to be approved yearly 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 on the premiums. Herewith it shall be guaranteed that every resident in Switzerland is given access to affordable healthcare.

#### Incidence and prevalence of disease

Since 1992, the Federal Statistical Office (“FSO”) undertakes every five years a public consultation regarding the health status of the population, the health determinants, the diseases and their consequences, the healthcare system, including the number of doctor appointments, and health insurance (so-called Swiss Health Status Consultation). The fifth consultation took place in 2012, the results of which may be consulted online under the following link: [www.portal-stat.admin.ch](http://www.portal-stat.admin.ch) (last visited on 6 May 2018).

According to the FSO, 82.8% of the population assess their health as being good or very good. 31.9% of the population declare having a chronic health problem. 72.5% are sufficiently physically active, 28.2% smoke, 5% consume cannabis and 13% drink alcohol on a daily basis. At the age of 70, 66% still assess their health as being good or very good (cf. [www.admin.bfs.ch](http://www.admin.bfs.ch); visited last on 6 May 2018).

Compared to 2007, the persons having consumed a painkiller in the course of a week further increased from 20% to 23% in 2012. Further, 9% of the Swiss population took a psychotherapeutic product in the course of the week preceding the consultation done by the FSO. Generally speaking, more female than male and more elderly than young people take painkillers or psychotherapeutic products (cf. [www.admin.bfs.ch](http://www.admin.bfs.ch); last visited on 6 May 2018).

The hospitalisation ratio per 1,000 residents was at 121.0 and the infant mortality was at 3.6‰, in 2016. The most common causes of death in Switzerland are diseases of the circulatory system (32% of the deaths in 2015) and cancer (26% of the deaths in 2015). According to the Swiss Cancer Report 2015 published by the FSO, cancer has become a chronic illness. In 2015, 317,000 people in Switzerland were living with a cancer diagnosis. This is twice as many as 25 years ago. Every year approximately 17,000 people living in Switzerland die from the consequences of cancer. Pursuant to said report, it is expected that around 40% of the Swiss population will be diagnosed with cancer at any point in their lifetime. The main reason for this increase is due to the fact that the population is getting older. However, in comparison to the other European countries, Swiss incidence rates are still average for men and even low for women, except for melanoma, which have a high incidence rate in Switzerland (nevertheless, mortality rates for melanoma are very low). As regards survival rates across all types of cancer, Switzerland's five-year survival rates are among the highest in Europe (cf. for more details, Swiss Cancer Report 2015 of the FSO, available under the link: [www.bfs.admin.ch](http://www.bfs.admin.ch); last visited on 6 May 2018).

## 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") 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 on 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 (categories C and D, respectively) they are subject to prescription. Over-the-counter therapeutic products are classified into category E. More specifically, pursuant to articles 23 to 27 of the Swiss Federal Ordinance on Medicinal Products of 17 October 2001 ("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 medical consultation (category C);
- non-prescription drugs that require previous consultation (category D); and
- non-prescription drugs that may be bought without further consultation (category E).

Irrespective of whether therapeutic products are subject to prescription or not and save for a few exceptions, they can only be brought on the market if authorised by the 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 valid for five years. During this period, Swissmedic may in the event of altered circumstances, on its own initiative or upon request, adapt such marketing authorisation or revoke it (article 16 para. 2 TPA). On request, Swissmedic renews the authorisation for further five-year periods if the requirements are still fulfilled (article 16 para. 4 TPA).

#### Who is/Who are the payer(s)?

In order to benefit from the reimbursement of therapeutic products by the compulsory health insurance, the respective products must be listed by the FOPH on the so-called specialty list (article 52 para. 1 lit. b HIA). The specialty list may be consulted online under the following link: [www.spezialitätenliste.ch](http://www.spezialitätenliste.ch) (last visited on 5 May 2018).

If a therapeutic product is more than 20% more expensive than a third of all therapeutic products listed on the specialty list with the same composition, the insured has to pay 20% of the costs exceeding the deductible (article 38a of the Ordinance on the Benefits of the Mandatory Health Insurance of 29 September 1995 [**“OBHI”**]; *Verordnung des EDI über Leistungen in der obligatorischen Krankenpflegeversicherung, KLV*).

Furthermore, reimbursement may be obtained from the 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*, the 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 (**“OCD”**). In order to obtain funding from the invalidity insurance, the insured person has to file an application to the invalidity insurance.

Consequently, non-listed therapeutic products have to be paid by the consumers themselves.

#### What is the process of securing reimbursement for new pharmaceutical product and how are drug prices set?

First of all, an application for a therapeutic product to be listed on the specialty list has to be filed with the FOPH. In order to be listed thereon, a therapeutic product must be approved by Swissmedic and must satisfy the criteria of effectiveness, functionality and economic efficiency (article 65 para. 1 and 3 of the Ordinance on Health Insurance [**“OHI”**]; *Verordnung über die Krankenversicherung, KVV*). Based on these criteria, the FOPH determines the maximum price for the therapeutic product in question. The approval process has recently been expedited and should not exceed 60 days from the date of marketing authorisation (article 32 OBHI).

In order to assess the effectiveness of a therapeutic product, the FOPH relies in principle on the same documents, which were used by the applicant for the approval of Swissmedic. However, the FOPH may demand that further documents are submitted (article 32 OBHI). As regards the criteria of functionality, the FOPH examines the impact, composition and possible side effects of the therapeutic product in question (article 33 OBHI). Finally, a therapeutic product is deemed economically efficient, if the indicated therapeutic



effect is reached most cost efficiently (article 65b OHI). The FOPH bases the evaluation of a therapeutic product's economic efficiency on two aspects: on the one hand on a comparison with the prices in foreign reference countries, which are Germany, Denmark, Great Britain, Netherlands, France, Austria, Belgium, Finland and Sweden (so-called *Auslandpreisvergleich*) and on the other hand on an assessment with respect to other therapeutic products (so-called *therapeutischer Quervergleich*). As regards the comparison with other therapeutic products, the FOPH examines the efficiency and costs of the therapeutic product in question compared with other drugs used for the treatment of the same disease (article 65b OHI and articles 34a *et seqq.* OBHI).

The costs for research and development are taken into account for the examination of the economic effectiveness of a product, unless the original therapeutic product in question is a successor product that brings no therapeutic progress. Further, a so-called innovation supplement is granted for a maximum of 15 years for therapeutic products providing a significant therapeutic progress (article 65b para. 6 and 7 OHI).

The therapeutic products on the specialty list are re-examined every three years as well as after the expiration of the patents in question. As a result of this re-examination, the FOPH may order a reduction of the price for the therapeutic product in question (article 65d and 65e OHI).

### **Policy Issues That Affect Pricing and Reimbursement**

#### Population growth (growth in size of elderly population/growth in populations with chronic diseases)

The life expectancy in Switzerland is among the highest in the world. A newborn in 2016 is expected to reach the age of 81.5 (men) or 85.3 (women). In 2015, people older than 60 years caused approximately the same costs than those younger than 60 years, even though representing less than a quarter of the whole population. For example, among the population over 80 years, 16% lived in retirement homes per 31 December 2016 and 28.1% needed care at home. 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, available under the following link: [www.bfs.admin.ch](http://www.bfs.admin.ch); last visited on 6 May 2018). Given the above, the costs for healthcare will most presumably further rise.

As already discussed herein above, the most common causes of death in Switzerland are diseases of the circulatory system and cancer (*cf.* above section “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 the 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 section “Size, demographics” in “Market Introduction/Overview”). Also, costs and benefits of very expensive treatments, in particular when carried out with regard to old persons, are debated increasingly vehemently.

#### Prohibition of benefits and kick-back

Pursuant to article 33 TPA, it is prohibited to grant, offer or promise material benefits to persons who prescribe or dispense medicinal products, or to the organisations which employ them. Further, it is prohibited for persons who prescribe or dispense medicinal products as well as for the organisations which employ them, to solicit or accept material

benefits. However, material benefits of modest value and which are related to medical or pharmaceutical practice as well as commercially and economically justified discounts on the price are permitted.

In the context of the current revision of the TPA (*cf.* below section “Emerging Trends”), it is planned to further increase transparency and integrity with respect to therapeutic products (*cf.* below section “Emerging Trends”) by clarifying the legal provisions regarding pecuniary benefits and strengthening the implementation of these provisions.

Previously, pharmaceutical companies used to sponsor events and congresses for practitioners. The increasingly stringent regulations have already resulted in a substantial reduction of such sponsoring. It is to be expected that this trend will be favoured by the entering into force of the new ordinance mentioned above.

### **Emerging Trends**

As part of the master plan of the Confederation for strengthening biomedical research and technology, the TPA and the corresponding ordinances are currently under revision. The revision aims at improving the population’s access to therapeutic products and the conditions for biomedical research and industry. The Federal Council transferred the dispatch on the revision of the TPA to the Parliament on 7 November 2012, which accepted the core elements of the Federal Council’s draft, amended part of it and adopted the revised TPA on 18 March 2016. Certain provisions entered already into force ahead on 1 January 2018. With regard to the remaining implementing provisions, a consultation process was conducted in 2017, the results of which are currently being evaluated. It is planned that most of the revised provisions of the TPA and the corresponding ordinances will enter into force on 1 January 2019. However, as a result of the consultation process the implementing provisions relating to integrity, transparency and obligation to pass on discounts need to be amended. The new ordinance on transparency and integrity in the context of therapeutic products will probably be adopted end of 2019 and enter into force on 1 January 2020.

### **Successful Market Access**

In our opinion, the following factors are key to successfully entering the Swiss national market:

- in-depth knowledge of the healthcare legislation in Switzerland;
- taking into account that for certain questions the cantons are competent and not the federal authorities;
- considering that most therapeutic products cannot simply be sold via supermarkets;
- rigorous documentation of the process from research to marketing;
- requests for authorisation in a timely manner and within the time limits; and
- high efficiency and quality.

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# United Kingdom

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## Abstract

The UK has a large and complex healthcare system, under which the National Health Service (“NHS”) funds the vast majority of medicines prescribed to patients.

Reflecting the complexities of the system, 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 context. 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 leaves the price of generic products open to market forces.

Despite price controls and other policies intended to contain spending, NHS drug expenditure continues to grow. This is because of a growing and ageing population, which has increased prescription volumes, as well as the introduction of costlier high tech and rare disease medicines into the UK. Currently, the healthcare system faces significant financial pressure and this creates an increasingly challenging environment for product pricing and reimbursement. In light of this, there is a growing tendency for suppliers and healthcare organisations to enter into innovative or bespoke commercial arrangements to facilitate the availability of a product in the NHS.

## Market Overview

The UK comprises four constituent nations: England; Wales; Scotland; and Northern Ireland. The UK has a population of approximately 65.6 million people, with the vast majority (approximately 55.2 million) resident in England.

The UK has a well-developed healthcare market, in which a large and sophisticated public healthcare system, the NHS, plays a dominant role. The NHS is almost entirely state funded and generally free to patients at the point of need. The structure and organisation of the NHS varies across the four nations of the UK, though most of the main principles and outcomes are very similar. For the sake of simplicity, this chapter focuses primarily on the NHS in England.

In England, the NHS spent an estimated £17.4 billion on medicines in 2016/17, which reflects an average 5% growth rate since 2010/11. Much of this growth is attributable to spending on medicines dispensed in hospitals, which has almost doubled between 2010/11 and 2016/17. Hospital medicines now account for almost half of all NHS drugs spending in England. Historically, the NHS in England has spent approximately three-quarters of its drugs budget on branded products.

When considering pricing and reimbursement in the UK, it is important to recognise the

differences between medicines supplied in NHS “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). The distinction is relevant throughout this chapter, particularly because of the differences in the way the NHS pays for products in each setting.

## **Pharmaceutical Pricing and Reimbursement**

### Regulatory Classification

#### *Classification of Medicinal Products*

The Human Medicines Regulations 2012 create three broad regulatory classes of medicines:

1. prescription only medicines (“POM”);<sup>1</sup>
2. “General Sale Medicines”, which consumers may purchase without a prescription;<sup>2</sup> and
3. “Pharmacy Medicines”, which consumers may purchase without a prescription but only from a pharmacy.<sup>3</sup>

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 Pharmacy Medicine or a General Sale Medicine; (ii) the effect of legislation means the product must fall into a particular category; or (iii) the MHRA, or the European Commission for centrally authorised products, has allocated the product to a category.

In principle, NHS reimbursement is available to all three classes of medicines. However, the NHS increasingly focuses its expenditure on POMs and to that end, NHS England has recently introduced prescribing guidance aimed at dissuading clinicians from prescribing medicines available over the counter (*i.e.*, General Sale Medicines and Pharmacy Medicines).<sup>4</sup>

#### *Eligibility for Reimbursement*

In primary care, any medicinal product commercially available in the UK and prescribed on an NHS prescription form 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 principle are where the NHS has “black listed”<sup>5</sup> a product in the Drug Tariff (the monthly list of reimbursement prices in primary care) or has placed restrictions on the circumstances in which it will reimburse a product (*e.g.*, through the so-called “Selected List” in the Drug Tariff).<sup>6</sup>

In secondary care, eligibility for reimbursement is more localised and there is greater scope for variation. Prescription, treatment and supply often take place within the same NHS organisation (*e.g.*, a hospital), which gives each of those organisations a degree of autonomy over the medicines it funds. CCGs (as defined in section “Who is/Who are the payer(s)?” below), 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 will fund a particular 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/Who 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 some patients (usually, only adults aged under 60 in employment and earning over a certain threshold). The UK has a smaller private healthcare market, funded by patients themselves or through private insurance.

Which NHS organisation is responsible for funding (“commissioning”) a medicine and how it arranges that funding are complex questions, which often hinge on the type of treatment provided and the treatment setting (primary or secondary care). The main payers and payment structures in England are as follows:

- NHS England has responsibility for commissioning primary care in England, though from 2015, many local CCGs (as defined below) have started to partner with NHS England to co-commission primary care services. 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 Clinical Commissioning Groups (“CCGs”).<sup>7</sup> CCGs receive funding from the NHS and it is for them to obtain value for money in terms of the products and services they make available.
- NHS England also commissions Specialised Services (which include treatments for certain cancers, genetic disorders or complex medical or surgical conditions) and Highly Specialised Services for rare diseases (typically to treat around 500 patients per year). These mechanisms allows NHS England to provide centralised funding to high-cost treatments that are not cost-effective in other contexts and may not have a NICE recommendation.

#### 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. As a result, there is no single pathway to securing NHS reimbursement for a new product.

Nonetheless, NICE is often the gatekeeper to reimbursement because a positive recommendation for a product or treatment in NICE guidance obliges NHS England to make funding available for it, usually within three months of that recommendation.<sup>8</sup> A negative recommendation from NICE does not necessarily mean a product is ineligible for reimbursement. However, unless other funding arrangements are in place, it provides commissioners with a basis to resist or delay funding. As a matter of practice, NHS clinicians usually prescribe products according to NICE guidelines.

#### *NICE Topic Selection*

NICE does not appraise each and every new product launched in the UK. NICE would conduct an appraisal if it considers a product is likely to be a significant benefit to patients and be at a significantly different price to the current treatment standard. Manufacturers of new products may make suggestions for an appraisal though UK PharmaScan (an industry horizon scanning directory).

#### *NICE Evaluation*

NICE recommends whether the NHS should fund products or treatments (which NICE refers to as a “technologies”) based on clinical and cost-effectiveness assessments (“Health Technology Assessments” or “HTAs”).

NICE’s approach is to evaluate a technology’s cost per quality-adjusted life year (“QALY”), a health economic concept that seeks to capture the clinical benefits of a technology. In general, NICE will issue a positive recommendation if the incremental cost per QALY

(“ICER”), usually against an existing reference, is 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. It is rare for NICE to give a positive recommendation to a technology whose ICER exceeds £30,000. NICE also has additional discretion where products are used in end-of-life scenarios. NICE has yet to recommend a product where the incremental cost-per-QALY was significantly in excess of £40,000.

NICE’s cost-per-QALY thresholds have remained fixed for a number of years. Inflationary pressures and an increased industry focus on rare diseases and other high-cost treatments mean that it is increasingly difficult to bring certain new products below the thresholds in order to receive a positive recommendation.

#### *NICE’s Budget Impact Test*

Introduced in April 2017, the “Budget Impact Test” provides that any product that NICE has assessed to be cost-effective, but that is likely to cost the NHS more than £20 million in any of the first three years of its use, must be subject to negotiations between the supplier and NHS England to bring the overall cost down. If these negotiations are unsuccessful, NHS England may apply to NICE for its approval to delay funding the product by up to three years, or longer in exceptional cases. This has proven to be a controversial measure: in the second-half of 2017, the Association of British Pharmaceutical Industry (“ABPI”) launched unsuccessful court proceedings to challenge the legality of the test.

#### *Patient Access Schemes*

NICE may recommend a product that might otherwise not meet NICE’s cost-effectiveness criteria, subject to the manufacturer offering a Patient Access Scheme. These are formal pricing agreements, provided for under the PPRS (see section “How are drug prices set? What is the relationship between pricing and reimbursement?” below) between a supplier and NHS England that make the product more affordable (*e.g.*, by way of a price discount, rebates, free-stock or outcome-based pricing). NICE’s Patient Access Scheme Liaison Unit advises NHS England on the feasibility of any proposed scheme.

#### *Managed Access Agreements*

In some cases, NICE recommendations have also taken into account Managed Access Agreements. These agreements to allow 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 Approach to Cancer Drugs and Highly Specialised Technologies*

NICE has certain measures in place to address the challenges of evaluating specialist and high-cost technologies. These include:

- The “Highly Specialised Technologies” (“HST”) appraisal process. HST appraisals use standard NICE assessment procedures but with variations built-in to accommodate treatments for extremely rare conditions. NICE has established a principle that it will automatically recommend funding for HSTs with an ICER of less than £100,000. The HST process is only available to the small number of products that satisfy a number of requirements, including the following:
  - The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS.
  - The target patient group is distinct for clinical reasons.

- The condition is chronic and severely disabling.
- The technology has the potential for lifelong use.
- Cancer Drugs Fund (“CDF”). Following a relaunch in 2016, the CDF operates through a partnership between NHS England, NICE, Public Health England and the Department of Health. It aims to enable faster access to promising new cancer treatments. NICE will recommend a drug for use in the CDF if it has the potential to satisfy the criteria for routine commissioning, but where there is significant 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.

### *NICE Appeals*

Generally, the manufacturer of the product under review, patient groups or clinician organisations who have participated in the assessment may appeal NICE guidance to the NICE Appeal Panel. There are three grounds for appeal:

1. that NICE has failed to act fairly;
2. the recommendation is unreasonable in the 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, recently, 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 the appeal to the NICE appeal panel is unsuccessful, the 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” (for branded products) or in other cases; (iii) the net price at which the contractor purchased the product. The Drug Tariff lists the reimbursement amount mostly for generic products. The NHS reviews these amounts each month, based on a survey of market prices. The NHS list price is set in accordance with the PPRS or Statutory Scheme (see section “How are drug prices set? What is the relationship between pricing and reimbursement?” below).

The concept of a “reimbursement amount” is less relevant in secondary care because the NHS operates *payment by results* model. Under this model, providers receive an amount per patient treated, based on the treatment provided, the length of a patient’s stay, the complexity of their needs, *etc.* In most cases, this does not take the price of individual products directly into account.

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

The Secretary of NHS for Health has a statutory power to limit the price of medicines supplied to the NHS (section 262, NHS Act 2006). Currently, the Secretary of NHS does not exercise these powers for generic medicines. By contrast, branded medicines supplied to the NHS are subject to one of two price control schemes: the Pharmaceutical Price Regulation Scheme (“PPRS”) or the so-called “Statutory Scheme”.

### *PPRS*

The PPRS is a voluntary, non-contractual scheme between companies in the pharmaceutical sector and the Department of Health. The scheme regulates the growth of a company’s sales to the NHS, the profits it makes from those sales, and (to an extent) product prices. In one form or other, the PPRS has been running in the UK since 1957. The current scheme runs for five years from January 2014. Negotiations for the 2019 PPRS are currently underway.



The current PPRS focuses on limiting the overall growth of NHS expenditure on branded medicines that scheme members supply (0% in 2014–15; and 1.8%–1.9% in 2016–18). Members make quarterly rebates to the Department of Health to offset any growth above the agreed limits (“PPRS Payments”). Smaller companies with sales to the NHS of less than £5 million in the previous year are exempt from making PPRS Payments. In 2018, members’ PPRS Payments were set at 7.8% of the value of their net sales of scheme-products.

Under the PPRS, a member may not increase the price of a scheme-product without the prior approval of the Department of Health, which (amongst other things) requires a reasoned justification for the increase and an assessment of the member’s profits. That said, a company may “modulate” prices for specific products (*i.e.*, adjusting certain prices up or down), so long as the net effect is neutral. In order to avoid stifling innovation, members have the freedom to set the price of any “new” products (*i.e.*, those launched in the UK after 1 January 2014) at their discretion.

### *Statutory Scheme*

Manufacturers or suppliers of branded medicines to the NHS who do not participate in the PPRS are, by default, subject to the so-called “Statutory Scheme” (per sections 262–264 of the NHS Act 2006).

Following a 2017 consultation, the Branded Health Service Medicines (Costs) Regulations 2018 (the “2018 Regulations”) came into force on 1 April 2018. The 2018 Regulations amended the Statutory Scheme significantly, which now includes the following features:

- Manufacturers or suppliers must on a quarterly basis pay 7.8% of the net sales income from the supply of branded products to the NHS. This figure is subject to annual review.
- There are also a series of limits on product pricing and price increases, such as:
  - The maximum price of a product that was available to the NHS on 1 December 2013 is capped to the price at that date, subject to any increases agreed in accordance with the Statutory Scheme (including in its previous guise).
  - 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.*

The revisions to the Statutory Scheme bring it more closely in line with the PPRS than before. Previously, some companies had left the PPRS because the Statutory Scheme offered a more favourable environment. At present, one of the main advantages the PPRS possesses over the revised Statutory Scheme is the ability to set prices with more freedom, particularly for new products or as part of price “modulation”.

### Factors that Affect Pricing

A number of factors affect drug pricing in the UK, ranging from pricing and reimbursement policies, commercial negotiations between companies and the NHS and marketplace competition. It is worth noting that the UK list price is often a benchmark for countries that operate reference pricing systems. This can sometimes be an important consideration for companies, particularly if there are opportunities to offer discounts to the NHS without affecting the headline price.

As noted above, companies must price branded products in accordance with the PPRS or the Statutory Scheme. Historically, the general effect of these schemes has been to restrict

price increases for established branded medicines, but provide pricing flexibility for new products. Even so, when pricing new branded products, companies are often conscious to avoid jeopardising formulary listings or reducing uptake. In addition, if a product could be the subject of a NICE appraisal, companies try to fall within NICE's cost-effectiveness criteria, if at all possible. If it is not feasible to meet these criteria, companies might consider methods to provide better value-for-money to the NHS, such as through Patient Access Schemes.

The effect of NHS tendering and other commercial arrangements often reduces the prices that a company actually receives for its products. Hospitals, CCGs and other NHS bodies rely heavily on tenders and rebate agreements to purchase both generic and branded products at discounted levels (*i.e.*, below Drug Tariff and NHS list prices). In particular, there is an increasing use of 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. These "Framework Agreements" are regulated under the UK Public Contracts Regulations 2015.

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 products by their International Non-proprietary Names (INN), wherever possible. 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 rapidly face pressure to reduce their prices. Note, however, that the UK prohibits generic or biosimilar substitution in pharmacies (save for certain hospital pharmacies).

The NHS generally avoids intervening in the market for generic products, relying on market forces to restrict price inflation. However, in the last 12 months, the NHS has experienced severe shortages in supply of certain generic medicines. Reportedly, this is the result of a weakened currency affecting imports and a variety of other supply-side issues. These shortages have led to price increases of many generic products and the NHS has in some cases reflected this by offering a higher reimbursement amount in the Drug Tariff, sometimes on a temporary basis.

### **Policy Issues that Affect Pricing and Reimbursement**

The NHS' medicines policies aim to balance a number of interests, including:

- obtaining value-for-money for taxpayers;
- ensuring there is equitable access to treatment for NHS patients; and
- stimulating innovation in the life sciences industry by reimbursing new products that demonstrate clinical and cost-effectiveness.

However, demographic change, an increase in spending on prescription medicines and budgetary pressure, make it increasingly difficult to maintain this balance.

The UK's population is growing as well as becoming older. The Office for National Statistics projects the UK's population to increase from approximately 65.6 million people in 2016 to approximately 69.8 million people by 2026. In that time, the proportion of the population over the age of 65 would increase from 18% to 20.5%. The rising number of older people has increased the demand for healthcare and the volume of products dispensed, particularly those to treat age-related conditions, such as cardiovascular disease and diabetes.

The NHS' expenditure on medicines in England increased from approximately £13 billion

in 2010/11 to £17.4 billion in 2016/17 (representing an average growth rate of around 5% *per annum*). It is well-accepted that prescription-volume growth linked to demographic change is a major contributing factor. Another reason is an increase in high-cost innovative medicines launched in the UK and reimbursed by the NHS (such as orphan, ultra-orphan and biologic medicines). As a result, while the price control mechanisms in the PPRS and Statutory Scheme have delivered savings on established medicines, it has proven difficult to contain the overall NHS drugs spend.

While NHS spending on medicines rose by approximately 5% *per annum* between 2010/11 and 2016/17, investment into the NHS has failed to keep pace, growing by approximately 1.5% *per annum* over the same period. This is largely because of Government austerity in response to a challenging economic climate. Many politicians and commentators consider that the funding gap is unsustainable and have called for a new funding settlement for the NHS.

### Emerging Trends

The NHS is constantly evolving and there are a number of new initiatives, policies and other changes that will impact pricing and reimbursement in the future. Some of these are below:

- The severe pressure on NHS budgets is likely to result in additional policies to restrict the price the NHS pays for products. The renewal of the PPRS in 2019 will be a key milestone. NICE's Budget Impact Test will stimulate some companies to offer the NHS discounted prices for new products. The use of Patient Access Schemes is also likely to continue increasing, as fewer new products meet NICE's cost-effectiveness criteria.
- Linked to this, the NHS is likely to continue making greater use of tendering (particularly Framework Agreements) and other commercial arrangements to derive better value for money.
- In terms of commissioning, the NHS has recently introduced a new "Accelerated Access Review" pathway. In essence, this will mean that up to five products a year that have the potential for transformative impact will benefit from simplified and simultaneous regulatory approval, NICE assessment and commercial negotiation. The aim is for this pathway to be cost-neutral to the NHS.
- The NHS' prescribing policies are likely to continue to encourage clinicians to consider lower-cost treatments (such as generic and biosimilar medicines) and to restrict the prescription of products available over the counter. For example, NHS England's 2017 Commissioning Framework for Biosimilars sets a target 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.
- In future, the NHS is likely to demand far greater information from companies related to product pricing (e.g., costs or wholesaler discounts). In particular, the Health Service Medical Supplies (Costs) Act 2017 gives the Secretary of State wide ranging powers to demand a variety of information from all stages in the medicines supply chain. Authorities are likely to use this information to derive better value for money in areas where there has traditionally been price opacity (e.g., generics).
- Recently, pharmaceutical product pricing has faced growing scrutiny from the UK Competition and Markets Authority ("CMA"). In particular, the CMA has investigated alleged anti-competitive conduct and suspected unfair pricing. This has primarily related to allegations that manufacturers of generic products that are not subject to pricing controls in the PPRS and Statutory Scheme have inappropriately increased prices of products for which there is no meaningful competition. Going forwards,

competition law considerations are likely to affect the stance that suppliers take to pricing.

### Successful Market Entry

Formulating a successful strategy for market entry will depend on the type of product in question and its place in the NHS' complex architecture. The following are some general points to consider:

- **NICE appraisal.** A company should investigate whether its product could be subject to a NICE appraisal and if so whether it could meet NICE's cost-effectiveness criteria. The company could also explore qualifying for Highly Specialised Technology status or the Cancer Drugs Fund. For high-cost products, the company should consider the possibility of offering a Patient Access Scheme.
- **Specialised Commissioning Categories.** Falling within the scope of Specialised Services, Highly Specialised Services, or the Accelerated Access Review would increase the likelihood of a high-cost product receiving NHS funding.
- **Commercial Negotiations with the NHS Customer-Base.** Companies should consider what their optimal pricing and discount strategy would be in the procurement space. This is particularly important if a product's main use is in secondary care.
- **Understanding NHS Prescribing Policies.** In the UK, market penetration is often a greater concern for companies than market entry. The NHS' prescribing policies (both local and national) have a significant impact on the uptake of a new product. Understanding these is therefore important.

\* \* \*

### Endnotes

1. Regulation 5 of the Human Medicines Regulations 2012.
2. *Id.*
3. Regulation 5 and Regulation 220 of the Human Medicines Regulations 2012.
4. "Conditions for which over the counter items should not routinely be prescribed in primary care: Guidance for CCGs, NHS England, 29 March 2018.
5. Per Schedule 1 to the NHS (General Medical Services Contracts) (Prescription of Drugs, etc.) Regulations 2004.
6. Per Schedule 2 to the NHS (General Medical Services Contracts) (Prescription of Drugs, etc.) Regulations 2004.
7. Pursuant to the Health and Social Care Act 2012.
8. Per 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.

### Acknowledgment

The authors acknowledge the contribution made to this chapter by Raj Gathani. Raj is an Associate in Covington & Burling LLP's London office. Raj's practice includes advising a variety of clients on UK pricing and reimbursement matters. He takes a particular interest regulation of UK pharmacy businesses, having spent eight years in that industry prior to joining Covington & Burling LLP.

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# USA

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## Abstract

The cost of prescription drugs in the United States is substantially more than any other country in the developed world, but treatment outcomes and the quality of care lag behind other countries. Efforts to reform the system, to improve quality and reduce cost face an uphill battle to build any consensus in the current highly divided social and political environment. Despite this volatile context and the barriers to change that it creates, continued growth in US healthcare spending is unsustainable.

The high cost of prescription drugs makes newspaper headlines every day. Although more than 80 per cent are dispensed in lower cost generic form, a small but growing number of new, highly effective specialty brands are driving a rate of growth in drug spending that exceeds the rate of inflation. In response, health insurance plans are shifting cost to their members in the form of higher deductibles or coinsurance that increase the individual's financial exposure.

Some reform efforts have survived the otherwise toxic social and political environment: An additional 8.7 million Americans have been able to purchase prescription drug coverage as a result of the implementation of the Affordable Care Act ("Obamacare"). And, passage of the 21<sup>st</sup> Century Cures Act has helped accelerate FDA's regulatory review process, allowing new drugs to come to market more quickly, and at lower cost.

But challenges remain: List prices for prescription drugs do not reflect what most people pay for these drugs. Manufacturers set higher list prices, and then offer rebates and other discounts to the Pharmacy Benefit Managers ("PBMs"), but rebate amounts are confidential. In response, a growing number of states have passed transparency laws that require drug companies to report drug price increases. But while these new laws appear to be having a moderating influence on drug price increases, it remains unclear whether this is more than a temporary effect.

It is unlikely that the US Congress will be able to work together to advance any essential changes to prescription drug pricing policies in the foreseeable future, but the reform effort will continue at the federal regulatory, state, and local levels. Prescription drug manufacturers that plan to enter the US market must build and continuously refine sufficiently robust evidence to persuade PBMs and health plans of the clinical and economic value of their products. Successful access to the US market demands continuous evidence development, early and ongoing communication with purchasing decision makers, and tools that customers can use to measure and report the impact of product use on treatment outcomes and the cost of care.

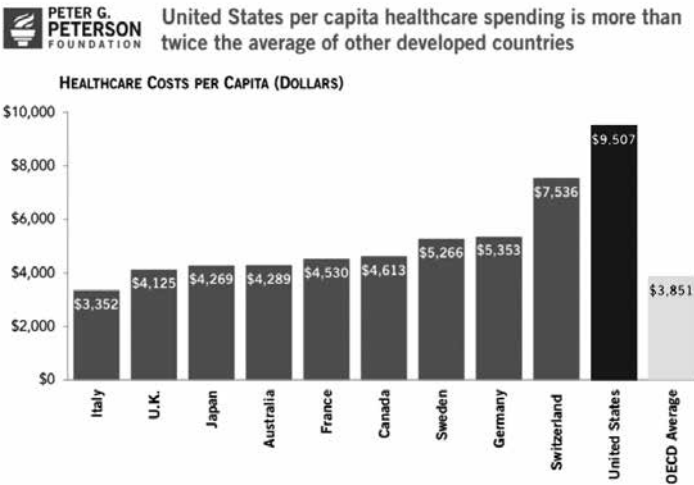
## US market overview

### A. The problem: The high cost of healthcare

Each year, the United States spends more on healthcare than any other country in the world,<sup>1</sup> yet access to care and the quality of services provided lag far behind other nations.<sup>2</sup> In 2016, the United States spent nearly twice as much as 10 other high-income countries on medical care but performed less well on important population health measures. A recent study found that the US had:<sup>3</sup>

- the highest percentage of adults who were overweight or obese (70 per cent vs. 56 per cent);
- the lowest life expectancy of the 11 countries studied (79 years vs. 82 years); and,
- the highest rate of infant mortality (5.8 deaths per 1000 live births in the US vs. 3.6 per 1000).

The high cost of prescription drugs in the US is the single largest reason for differences in overall healthcare spending between the US and other high-income countries. On a *per capita* basis, Americans spent approximately \$9,500 on their healthcare in 2016, compared to an average of \$5,400 in peer nations. Of that amount, \$1,443 was spent on prescription drugs vs. a range of \$466 to \$939 in other countries. For several commonly used medications, the American price was more than double the price in the country with the next highest cost. Overall, spending on prescription drugs represented 15 per cent of all healthcare spending, or approximately \$329 billion.<sup>4</sup> This amount is expected to grow to between \$370 billion and \$400 billion by 2021.



Source: Organization for Economic Cooperation and Development, OECD Health Statistics 2017, Compiled by PGDF.  
 Note: Data are for 2015 or latest available. Chart uses purchasing power parities to convert data into U.S. dollars.

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Figure 1: *Per Capita Healthcare Spending in the US vs. Other Nations.*

See: [https://www.pgpf.org/chart-archive/0011\\_health-outcomes](https://www.pgpf.org/chart-archive/0011_health-outcomes)

Four billion prescriptions were filled at US outpatient pharmacies in 2011, representing on average more than 12 prescriptions per person each year. Nearly 70 per cent of Americans routinely take at least one prescription drug, and more than half of Americans take two.

Half of those who take prescription drugs to help manage chronic diseases do not take their

medications correctly,<sup>5</sup> exposing the broader healthcare system to the higher downstream costs of acute healthcare interventions that are needed when less expensive preventive care has not been consistent or successful.

## 1. Prescription drug costs drive healthcare spending

A recent report found that manufacturers have raised outpatient prescription drug prices in the US an average of 31 per cent (median increase is 9 per cent) during the second quarter of 2018 alone. Most of the recent price increases are well above the current US inflation rate of less than 3 per cent. For many of the drugs, this is the second price hike in six months. For example, Pfizer raised the cost of Viagra (sildenafil citrate) by 9 per cent in January and another 9 per cent in July. A 30-pill bottle of the drug is now listed at more than \$2,200.<sup>6</sup>

Pfizer said that the list prices of its drugs do not reflect what most patients or insurance companies pay. Novartis has also raised prices on some products, but noted that the actual costs of its drugs have decreased in recent years when discounts and rebates are taken into account.

Between 2007 and 2013, annual increases in spending on prescription drugs in the US were flat, in part because a number of commonly used medications had come off patent and began to be dispensed in generic form. Then, in 2014, spending spiked by 12 per cent over 2013 levels because several extremely high-priced but effective drugs came to market. By 2014, Americans spent \$11 billion on these specialty drugs for treatment of hepatitis C alone. This represents about one-third of the \$32 billion in increased spending across all prescription drugs combined.<sup>7</sup> Spending on specialty drugs continued to increase another 15 per cent to \$121 billion in 2015.

Beyond the growth of the specialty drug market, entities across the supply chain are increasingly contracting and consolidating both horizontally and vertically. For example, each of the three largest PBMs maintains some form of common ownership with large retail chains and/or specialty pharmacies. Similarly, the three largest wholesale distributors own and operate specialty pharmacies and physician practices. Extensive consolidation has reduced transparency in the financial relationships among payers and other participants in the drug supply chain.

Spending on outpatient prescription drugs continues to grow, with more than 15 per cent of the healthcare expenses for a family of four now going for drugs dispensed at the pharmacy. And, these figures do not include prescription drugs delivered in hospitals, outpatient infusion centers, or physician offices. When these other drugs are also included, the total drug spend is more than 20 per cent of the average family's spending on healthcare each year.

## 2. Cost-shifting

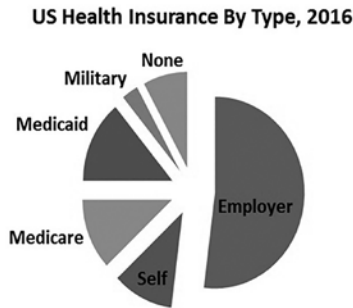
Health insurance plans (also called payers) are increasingly shifting financial responsibility for purchasing drugs to their beneficiaries. The average American's personal financial responsibility for brand name prescription drugs dispensed at a pharmacy has increased more than 25 per cent since 2010, reaching \$44 per prescription on top of the payments made for that prescription by their health insurance plan. Overall, individuals' total out-of-pocket spending increased by 54 per cent from 2006 to 2016, while health plan spending increased at a slower rate of just 48 per cent during that same period.<sup>8</sup>

Continued growth in the cost of outpatient prescription drugs in the US is unsustainable. Healthcare reformers have developed three solutions to lower drug costs, increase quality, and ultimately, reduce overall healthcare spending without limiting access to care.



## B. Solution 1: Reform the US healthcare system

The health insurance market in the US is highly fragmented with state and federal governments and private entities offering a variety of competing options from which Americans choose according to their age, employment status, income level, family size, and geographic location. Figure 2 arrays the primary types of payers that offer health insurance benefits in the US.



*Source: US Census Bureau, September 2017*

*Figure 2: Primary Sources of Health Insurance in the US, 2016*

<https://www.census.gov/content/dam/Census/library/publications/2017/demo/p60-260.pdf>

### 1. Health insurance for more Americans

Since passage of the Affordable Care Act of 2010 (also known as the “ACA” or “Obamacare”),<sup>9</sup> the number of Americans with some form of health insurance has grown to just over 90 per cent of the population.<sup>10</sup> While this number is smaller than in other high-income countries with single payer or government-sponsored healthcare systems, it represents a substantial increase over the number of Americans who had carried health insurance prior to implementation of the ACA, when many people did not have insurance, because (1) they could not afford it, (2) they did not qualify for health benefits because of their employment status, (3) they had a pre-existing health condition that excluded them, or (4) they decided that they did not need it.

### 2. “Obamacare”

Neither US political party had succeeded in previous attempts to expand access to health insurance or reduce the cost or care. But faced with the prospect of losing their majority in Congress, Democrats pushed through two separate health reform bills in 2010 without a single Republican vote. In March 2010, the President signed the bills into law, creating what is now called The Affordable Care Act (“ACA”). The legislation was written quickly, with plans to modify conflicting provisions later. However, Democrats lost their majority in the next election, and subsequent Republican majorities have worked to “Repeal and Replace” the law. Key provisions have also been challenged in court.

The ACA was originally structured around two core provisions:

- **Individual mandate:** To create lower cost options for purchasing health insurance, the ACA required everyone to purchase health insurance or pay a penalty. This was intended to create large “risk pools” of individuals with a broad range of health states so that the higher costs of caring for sicker individuals could be spread over a larger pool of sick and healthy people whose healthcare expenses collectively were lower.

- **Expand Medicaid eligibility:** To qualify for Medicaid benefits, individuals and families must demonstrate household income below a threshold set by the state where they live. That threshold is calculated as a percentage of the Federal Poverty Level (“FPL”) or Poverty Threshold,<sup>11</sup> an amount that is updated annually by the US Census Bureau. In 2018, the poverty threshold is \$12,140 for an individual, and \$25,100 for a family of four.

The ACA required states to expand Medicaid eligibility to those with annual incomes of 138 per cent of FPL (or \$16,753 and \$34,638 for an individual and family of four, respectively.) Thus, individuals and families whose income had previously been too high to qualify for Medicaid would be eligible for health insurance through the expanded Program. The federal government would withhold its financial contribution to any state that refused to expand its programme.

The ACA has driven the most significant changes in the US healthcare system since the creation of the Medicare and Medicaid Programs in 1965. Many important provisions have been implemented. Among others, the ACA:

- **Eliminated exclusions for preexisting conditions:** The ACA made it illegal for health insurance plans to deny coverage on the basis of preexisting health conditions, such as cancer or heart disease. These conditions had previously rendered some individuals essentially “uninsurable,” and forced others to remain at one job, knowing that they or their dependents would not be covered by a new employer’s health plan.
- **Mandated coverage of “Essential Health Benefits”:** The ACA required employers of a certain size to offer health insurance that covered a minimum number of broadly defined “Essential Health Benefits”. These included, for example, pharmacy, women’s preventive healthcare, hospitalisation, behavioural and mental healthcare and other services.

An additional 8.7 million Americans were able to purchase prescription drug coverage in 2014 as a result of the implementation of the ACA.<sup>12</sup> However, the number of newly insured individuals, multiplied by the higher cost of new specialty drugs has added to the growth in drug costs and in the volume of prescription drugs dispensed in retail settings in the US.

### 3. “Repeal and Replace”

While some provisions of the ACA have been broadly popular, such as eliminating the preexisting conditions exclusions, others have caused controversy. For example, some employers protested that they could not afford to provide health insurance for their employees; others refused to cover contraceptive services required under the women’s preventive health benefit on religious grounds.

Ultimately, the dispute made its way to the US Supreme Court, which issued a split decision:<sup>13</sup>

- Constitutional: The “individual mandate” was really a tax,<sup>14</sup> and comprises a valid exercise of Congress’ power to “lay and collect taxes”.<sup>15</sup>
- Unconstitutional: Withholding federal funds from states that refused to expand their Medicaid Programs would violate the law.<sup>16</sup>

### 4. Health system reform: a work in progress...

Other legal challenges were mounted, and Congressional Republicans launched an unsuccessful bid to repeal the ACA and replace it with the American Healthcare Act (“AHCA”).<sup>17</sup> Ultimately, politics has overtaken health policy development.

- **Individual mandate rescinded.** A recent overhaul of the US tax system eliminated the tax penalty that the ACA imposed on individuals who refused to purchase health insurance.<sup>18</sup>

- **Medicaid expansion incomplete.** Thirty-one states and the District of Columbia (Washington, DC) expanded their Medicaid Programs; the 19 remaining states have not.
- **Essential Health Benefits no longer required.** The Trump Administration has issued new regulations permitting the formation of “Association Health Plans” that may not include all Essential Health Benefits.<sup>19</sup>
- **Executive authority stopped implementation.** President Trump has issued a series of Executive Orders to delay or prevent implementation of other provisions of the ACA.

## **C. Solution 2: Reform the regulatory review process for new drugs**

The 21<sup>st</sup> Century Cures Act of 2016 (“Cures Act”)<sup>20</sup> built on reforms that had been introduced through the ACA. The Cures Act endorsed advances in precision medicine, supported research at the National Institutes of Health (“NIH”), and invested in the formation of young, emerging scientists, among other important provisions.

Importantly, the Cures Act also authorised funding to accelerate new drug discovery, encouraged development of non-traditional clinical trial designs, promoted the use of “Real World Evidence,” and required the FDA to reform its regulatory review processes for innovative drugs and biologics.

### **1. The US Food and Drug Administration**

The Food and Drug Administration (“FDA”)<sup>21</sup> is responsible for the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. It oversees the safety and security of the US food supply, cosmetics, dietary supplements, products that give off electronic radiation, and tobacco products. Headquartered outside of Washington, DC, it has local and regional offices around the country, and around the world. FDA was established in 1906 by the Food and Drugs Act,<sup>22</sup> and expanded by the Food Drug and Cosmetic Act<sup>23</sup> of 1938 (“FD&C” or often, simply “the Act”).

Federal law requires that a drug be the subject of an approved marketing application before it can be legally transported or distributed across state lines.

FDA’s Center for Drug Evaluation and Research (“CDER”) is responsible for evaluating new prescription and nonprescription drugs before they enter the market to ensure that they work correctly, and that the health benefit of using the drug outweighs any known or potential risk.

### **2. Accelerating the regulatory review and approval process**

Once preclinical testing has been completed on a new drug candidate, the manufacturer initiates a series of interactions with FDA to secure approval to sell the product on the US market.

#### **a. Request a “Pre-IND” consultation**

FDA encourages manufacturers to arrange a Pre-IND meeting before submitting an Investigational New Drug (“IND”) application. This is a preliminary meeting with FDA reviewers to discuss the potential design, endpoints, experimental methods, etc. of clinical research intended to demonstrate the safety and effectiveness of the investigational new drug candidate in humans. Communication between the manufacturer and FDA generally takes the form of written comments that may be supplemented by teleconferences or meetings. FDA may recommend research strategies to accelerate the drug review process, including use of modeling and simulation, real-world evidence, and other tools for collecting and evaluating product safety information in real-time.

## **b. Submit an Investigational New Drug (“IND”) application<sup>24</sup>**

The IND provides formal notice to FDA that a manufacturer intends to initiate human clinical studies of a potential new drug. Manufacturers must comply with certain safeguards of the IND process, including engaging an Institutional Review Board (“IRB”), securing informed consent from study subjects, distributing the drug through qualified channels, maintaining adequate manufacturing facilities, submitting safety reports, etc. The sponsor must wait 30 calendar days from the date it submitted the IND application before initiating clinical trials.

## **c. Register the study at ClinicalTrials.gov<sup>25</sup>**

ClinicalTrials.gov (<https://clinicaltrials.gov/>) is a searchable database of government and privately-funded clinical studies conducted in the US and around the world. For each listing, the database identifies the target disease/condition, describes the intervention, provides a summary of the clinical study protocol, the locations and contact information for study sites, and other information. As a condition of IND approval, manufacturers must register certain types of studies<sup>26</sup> and keep the registration current.<sup>27</sup> Civil monetary penalties of up to \$10,000 a day may be levied for failing to register.

## **d. File the appropriate application for marketing approval**

FDA has created review processes for both innovator and follow-on products. Detailed information on each of these regulatory pathways is found on the FDA website.

### *i. New Drug Application (“NDA”)*

Manufacturers of novel, single source drug candidates submit an NDA to provide information on the scientific and clinical testing conducted on the new drug candidate, a statistical and clinical analysis of study findings, proposed indication(s) for use, information about the manufacturer, and a survey of the relevant peer reviewed literature. Manufacturers generally submit individual modules of the NDA electronically when they have been completed.

A complete index of guidance documents addressing the new drug application process may be at: <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm>.

### *ii. Abbreviated New Drug Application (“ANDA”)*

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act, more commonly known as the “Hatch-Waxman Act”,<sup>28</sup> to open a shorter approval pathway for generic copies of already approved reference drugs. Under Hatch-Waxman, manufacturers may file an Abbreviated New Drug Application (“ANDA”) for a drug product that is identical, or bioequivalent to a brand/reference drug in dosage form, strength, route of administration, quality, performance characteristics, and intended use. Although generic drugs are chemically identical to their reference products, they are typically sold at substantial discounts from the branded price and often drive price reductions for the brand as well.

An overview of guidance documents addressing the abbreviated new drug application process for new generic drugs may be found at: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm>.

### *iii. Therapeutic Biologic Application (“BLA”)*

Large molecule biologics are regulated by FDA through the Center for Biologics Evaluation and Research (“CBER”). These products include monoclonal antibodies,

cytokines, growth factors, enzymes, immunomodulators, thrombolytics, proteins and other non-vaccine immunotherapies.

Information about the regulatory review process for innovator biologic products may be found at: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm>.

iv. *Abbreviated Biologic License Application (“ABLA”)*

The Affordable Care Act created a new abbreviated regulatory pathway for biological products that are demonstrated to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product through the Biologics Price Competition and Innovation Act (“BPCI”), part of the ACA.<sup>29</sup> Under BPCI, manufacturers submit an abbreviated Biologic License Application (“ABLA”) to demonstrate that the follow-on product is biosimilar if data show that, among other things, the product is “highly similar to or interchangeable with an already-approved biological product”.

More detailed information on the regulatory pathway for biosimilars may be found at: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm>.

**e. Register and pay User Fees**

In the late 1980s, individual drug reviews often took years to complete because FDA lacked adequate funding to hire the staff needed to review drugs in a timely manner. In response, Congress authorised FDA to collect “User Fees” from manufacturers for each new NDA or ANDA submitted, to provide the agency the funding needed to hire review staff to review submissions more quickly. FDA committed to accelerate review times and provide annual reports on their performance.

The first Prescription Drug User Fee Act (“PDUFA”), passed in 1992, authorising FDA to collect fees from companies that produce certain human drug and biological products. The law is reauthorised by Congress every five years. The sixth reauthorisation (“PDUFA VI”)<sup>30</sup> was signed into law on August 18, 2017 to help fund FDA drug review through September 2022. Parallel user fee programmes have been created for generic drugs (“GDUFA”), biosimilars (“BsUFA”) and medical devices (“MDUFA”).

**f. Secure FDA approval for new drug**

FDA review staff look for “substantial evidence”<sup>31</sup> of efficacy before approving a new drug candidate to enter the US market.<sup>32</sup> Historically, FDA has interpreted this standard to mean that the manufacturer must submit data from at least two rigorous clinical trials (preferably randomised, double-blind, placebo-controlled) that independently show statistically significant and clinically meaningful benefit that outweighs any known or potential risks associated with the product.

In 1992, FDA responded to the AIDS epidemic by creating an accelerated review process to get certain potentially life-saving drugs to market more quickly when no alternative therapy was available. Congress codified the accelerated approval pathways through passage of the Food and Drug Administration Safety and Innovation Act in 2012.<sup>33</sup>

Drugs that qualify for accelerated approval include those that offer a significant benefit compared to available therapies for serious medical conditions where there is unmet medical need, based on preliminary evidence of efficacy. Manufacturers request accelerated review, and if FDA agrees, it will grant approval on condition that the manufacturer commit to

conducting and completing confirmatory “postmarket” studies after the product is approved and in commercial use. There are currently three accelerated review designations:

- **Breakthrough therapy:** FDA may designate a new drug candidate a “breakthrough therapy” if preliminary clinical evidence suggests that the drug offers substantial improvement over existing therapies for serious and life-threatening diseases.
- **Fast track designation** facilitates development, and expedites review of drugs to treat serious conditions and fill an unmet medical need.
- With **Priority review**, FDA’s goal is to take action within six months.

FDA approved 46 new drugs in 2017, the largest number of new drug approvals in more than 20 years. Of these, 37 per cent were approved with “Breakthrough therapy” designation.

#### g. Fulfil postmarket obligations

As FDA works to accelerate the review process to bring new drugs to market sooner, it has required manufacturers to conduct additional studies after approval to confirm the safety and effectiveness of their new drugs. While numerous manufacturers had previously failed to meet their postmarket study commitments, viewing these studies as an unnecessary regulatory burden and expense, FDA has recently become stricter in enforcing compliance. Despite the additional expense, manufacturers often leverage postmarket data for use in reimbursement negotiations.

#### h. Promote product according to approved “label”

The Food, Drug and Cosmetic Act requires manufacturers to promote their new drug products according to the approved label. The label is the primary tool that communicates information regarding safe and effective use of the product, and must include approved prescribing information, adequate directions for safe use and any applicable safety warnings.<sup>34</sup> Labeling is not simply the information contained on a drug container, but rather also includes:

*Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs,...reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published...for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor...*<sup>35</sup>

FDA has generally prohibited so-called “off-label” promotion, except in specific situations, such as when clinicians present research or other information to peers at structured scientific meetings, or when clinicians contact a manufacturer to request additional product information. However, several companies have recently challenged FDA’s prohibitions against off-label promotion. In one interesting case, a pharmaceutical company sued FDA, charging that the Agency had denied its right to free speech by not allowing it to present truthful and not misleading information to customers that was not included in the product’s (Vascepa®, icosapent ethyl, Amarin) approved labeling. The company won the case against FDA.<sup>36</sup>

Recognising the importance of this information to the payer community, in 1997 Congress created a safe-harbor to permit manufacturers to communicate “healthcare economic information” (“HCEI”)<sup>37</sup> proactively to “a formulary committee, or other similar entity,” provided the HCEI is based on “competent and reliable scientific evidence” (“CARSE”) and “directly relates” to an approved indication.

#### D. Solution 3: Reform the reimbursement system for outpatient prescription drugs

An individual’s health insurance typically reimburses some or all of the cost of prescription drugs.

## 1. Employer-sponsored plans

More than half of Americans purchase private (or “commercial”) health insurance through their employers. The employer either contracts with a third party administrator to manage its own health plan (a “self-funded” plan), or purchases coverage from a private health insurance company (“fully insured”). In both cases, the employer pays half of the monthly cost of the benefit, and the employee uses pre-tax dollars to pay monthly premiums that make up the other half. The employee also pays any out-of-pocket costs at the point of sale. Employers are reluctant to change benefit design or opt for health plans that might be perceived as limiting employees’ choices, especially as employers are increasingly concerned with recruiting and retaining talent. Because employees are most sensitive to increases in prescription drug copayment amounts which they pay at the pharmacy counter, a recent study found that deductibles and coinsurance increased from 2006 to 2016, but copayment spending dropped by 38 per cent in that period.<sup>38</sup> In an effort to make the benefit appear more affordable, actual cost increases were shifted to other less visible expense categories.



*Figure 3: Typical Cost-Sharing for Employer-Sponsored  
(Private) Health Insurance Plan – 2018*

## 2. Government-sponsored plans

Government-sponsored health insurance became available in the US after 1965, when Congress passed the Social Security Act<sup>39</sup> authorising creation of the Medicare and Medicaid Programs. These programmes are administered by the Centers for Medicare and Medicaid Services (“CMS”).<sup>40</sup>

### a. Medicare: Federal health insurance for the elderly and disabled

Medicare is a federal health insurance plan for persons 65 years of age and older, for individuals who are younger than 65 with certain disabilities, and for persons with end-stage renal disease (“ESRD”). It was originally created as a hospital insurance plan (“**Part A**”) with optional health insurance to cover physician services (“**Part B**”), but was later expanded. Under “Traditional Medicare,” the beneficiary pays a monthly premium<sup>41</sup> adjusted for income. Once he or she has met an annual deductible,<sup>42</sup> Medicare pays 80 per cent of charges and the beneficiary pays 20 per cent up to a cap. The beneficiary can choose to see any doctor or visit any hospital. The vast majority of US providers accept Medicare payment, and in doing so, agree not to “balance bill” Medicare beneficiaries for covered services.<sup>43</sup>

Medicare Advantage (“**Part C**”) was added to the Program in 1997.<sup>44</sup> Under Part C, private health insurance companies contract with the government to provide Medicare benefits. Today, more than 2,000 regional plans located around the country offer beneficiaries a range of different benefit structures, which may offer a greater number of options at a lower cost

than traditional Medicare. Depending on where they live, most beneficiaries are eligible to join at least one of more than a dozen different plans, with one or more plans that offer a “Zero Premium” option.

A voluntary outpatient prescription drug plan (“**Part D**”)<sup>45</sup> was added to the Medicare Program in 2003. Like Part C, Part D is also managed by private health insurers under contract with the federal government.<sup>46</sup> A beneficiary may enroll in traditional Medicare (Part A and B) and then purchase the prescription drug benefit (Part D). To do so, the beneficiary pays an additional monthly premium to participate in Part D. Then, after meeting the annual deductible amount, pays a percentage of the cost of outpatient drugs until reaching the “catastrophic coverage” level where Medicare pays 100 per cent of drug costs. Cost-sharing resets again to zero at the beginning of the following calendar year.<sup>47</sup>

*Table 1: Medicare Part D Outpatient Prescription Drug Benefit: Benefit Structure and Cost-Sharing for CY 2019*

| Phases of Coverage | Cost-Sharing Obligations  | Total Spending Out-of-Pocket                                | Total Spending |
|--------------------|---|---|----------------|
| Deductible         | Patient: 100%<br>Up to deductible   | \$0–415   | \$0–415        |
| Initial Coverage   | Patient: 25%<br>Up to \$3,820   | \$415–\$3,370<br>Deductible plus 25% of<br>\$3,820          | \$415–\$3,820  |
| Coverage Gap       | <b>Brand Name</b><br>Patient: 25%<br>Manufacturer: 70%<br>Plan: 5%<br><b>Generic</b><br>Patient: 37%<br>Manufacturer: 63%     | \$1,370–\$5,100<br>Patient Pays up to Out-<br>of-Pocket Gap | \$3,820–£8,140 |
| Catastrophic       | <b>Brand Name</b><br>Patient: Greater of<br>5% or \$8.50 copay<br><b>Generic</b><br>Patient: Greater of<br>5% or \$3.40 copay | \$5,100 and up  | \$8,140 and up |

*Source: Minority Staff, Senate Finance Committee. June 2018*

Medicare pays for physician-administered outpatient drugs under Part B and for other prescription drugs under Part D. About 43 million (72 per cent) of the 60 million people with Medicare have purchased outpatient prescription drug coverage under Part D. Beneficiaries who qualify for both Medicare and Medicaid (the “Dual Eligibles”, generally low-income seniors) automatically receive prescription drug coverage through Part D.

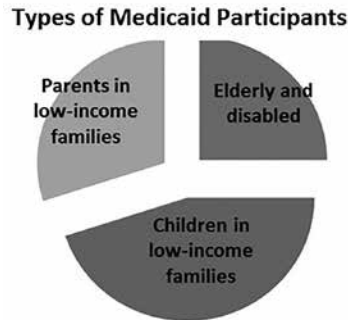
**b. Medicaid: Joint federal/state health insurance for persons with low incomes, families, and for women and children**

Medicaid is a joint federal-state programme that pays for healthcare services and long-term care for low-income individuals, including pregnant women, children, their parents, the elderly and disabled. The federal portion varies by state, but has historically averaged about 57 per cent. Almost half of Medicaid enrollees are children in low-income families, and just under one-third are the parents of those children or low-income pregnant women. The elderly and disabled constitute the remaining quarter of enrollees.



States administer their Medicaid Programs according to federal guidelines that specify a minimum set of services that must be provided to certain categories of low-income individuals. In order to sell their products to government-sponsored health insurance plans, drug manufacturers must enter into rebate agreements with the federal government to ensure that Medicaid receives a net price that is consistent with the lowest, or “Best Price”<sup>48</sup> for which the manufacturer has sold the product to any customer. In exchange for rebates, state Medicaid Programs agree to cover that manufacturer’s products with certain limitations.<sup>49</sup> States collect rebate payments on a quarterly basis.<sup>50</sup>

State governments spent 31 per cent of their total annual budgets, or \$929 billion, on healthcare and social services combined in 2015. By 2025, spending for these same services is expected to reach \$1.6 trillion, or 38 per cent of budget, assuming no significant policy action is taken in the meantime. Because 49 of 50 states are required by law to balance their annual budgets, (Vermont is the exception,) state legislatures will face increasing pressure to manage drug prices aggressively.



*Figure 4: Medicaid Program by Beneficiary Type*

**3. Structuring health plan benefits**

Health insurance plans are typically structured into two parts: a medical benefit, which covers hospitalisations, doctor’s office visits and other physician and professional services, and outpatient clinic admissions; and a pharmacy benefit which covers outpatient prescription drugs, and may also cover other services, such as distribution of durable medical equipment (“DME”).



See: <http://www.milliman.com/mmi/>

*Figure 5: Healthcare Spending for a US Family of Four, 2018*

#### 4. Pharmacy benefit managers (“PBMs”)

Pharmacy benefit managers (“PBMs”) administer prescription drug benefits for health insurance plans and employers using a range of tools intended to increase clinical quality and appropriateness, provide decision support, and reduce cost. The PBM:

- negotiates contracts (rebates) with drug manufacturers and pharmacies;
- processes claims;
- develops and maintains drug formularies;
- performs drug utilisation reviews;
- manages clinical decision support programmes targeted to specific disease states; and,
- may operate pharmacies, including mail-order and specialty pharmacies.

Decisions on formulary design, cost-sharing for beneficiaries, and the size and scope of pharmacy networks are made on a contract-by-contract basis with the specific health plan or employer.

PBMs generate revenue by negotiating rebates with drug makers for preferred formulary placement for their drugs. This translates into broader market share for their products than for their competitors.<sup>51</sup>

PBMs receive fees for processing and dispensing drugs for plan sponsors, and operating their own mail-order and specialty pharmacies. PBMs also retain the margin, or “spread” between the amount they charge their customers (i.e., the health plan) to manage the benefit and the amount paid to pharmacies for dispensing prescriptions.

Pharmacies contract with PBMs to establish a payment rate for each prescription, plus a dispensing fee. Pharmacies collect patients’ copays and send them to the PBM. Some independent pharmacies still negotiate directly with wholesalers to purchase prescription drugs, but the number of independent pharmacies is declining.

Patients remit copays (a fixed dollar amount) or co-insurance (a per cent of the cost of the drug) to the pharmacy, and make monthly premium payments to their health plan for their prescription drug benefit.

##### a. Prescription drug formularies: Employer-sponsored plans

A formulary is a list of the prescription drugs that the PBM agrees to reimburse when they are prescribed for a member who meets specified criteria. A formulary system is a standard process used to develop, review, and update policies regarding the use of drugs, therapies, and drug-related products and identifies those that are most medically appropriate and cost-effective for a given patient population.<sup>52</sup>

Formularies are structured into levels or “tiers.” **Covered generic drugs**, sometimes called preferred generics, are typically placed on Tier 1. These are the least expensive drugs for the PBM/health plan and require the lowest patient copayment. **Preferred brand drugs** for which no generic equivalent is available are assigned to Tier 2. **Non-preferred brands** and **specialty drugs** may be assigned to Tier 3 or 4. To create incentives for beneficiaries to use generics and preferred brands, PBMs will often charge much higher copays for non-preferred products. **High cost specialty drugs** and **biologics** are typically assigned to the lowest tiers on the formulary (i.e., Tier 3, 4, or even 5) for which the plan pays only a small amount, thus shifting the financial responsibility for the high cost of these drugs from the employer or health plan to the members themselves.

Formulary structures are becoming more complex over time. While the three-tier flat-dollar copay structure was standard in the PBM industry in 2008, with a 68 per cent use rate, today it is used by only 44 per cent of plans (a 24 per cent decrease over eight years). Four-tier

formulary designs are taking its place, typically placing higher cost specialty drugs on the fourth tier. Four-tier structures, with either flat copay (the same dollar amount is paid for any drug on that tier) or coinsurance (a percentage of the drug cost to the PBM), are currently used by 28 per cent of plans, compared with just 8 per cent of plans in 2008.<sup>53</sup> Many plans, including Medicare Part D plans, employ a 5-tier formulary structure.

PBMs update their formularies on a routine basis to account for changes in the commercial availability of brand and generic drugs, and to recognise the value of rebates that they have negotiated with manufacturers (i.e., in recognition of a significant manufacturer rebate, a PBM could move the manufacturer's drug or biologic to a 'preferred tier' on the formulary thus reducing the member's copay/ coinsurance and making the drug more attractive to the member/consumer).

#### **b. Prescription drug formularies: Medicare Part D plans**

Commercial PBMs contract with the Medicare Program to manage the Part D benefit using approved formularies that are required to provide appropriate access to covered drugs, biologics, insulin, certain medical supplies and vaccines included in broadly accepted treatment guidelines. To be approved by the Medicare Program, the formulary must be consistent with best practices in formulary design.<sup>54</sup>

Current rules require that an insurer's Medicare drug list cover at least two drugs (unless only one drug is available) for a particular category or class, as these are defined by USP or another body.<sup>55</sup> The two drug minimum requirement must be met through providing two chemically distinct drugs, not two dosage forms of the same drug, or a brand and its generic. More than two drugs for particular categories or classes may be required if additional drugs present unique and important therapeutic advantages in terms of safety and efficacy, and if their absence from the sponsor's formulary would substantially discourage enrollment by beneficiaries with certain disease states.<sup>56</sup>

In addition, a separate provision also requires plans to cover "substantially all" drugs in six drug classes:

- anticonvulsants;
- antidepressants;
- antineoplastics;
- antipsychotics;
- antiretrovirals; and
- immunosuppressants for transplant rejection.

Part D sponsors must also cover treatment of opioid dependence when medically necessary.<sup>57</sup>

The Centers for Medicare and Medicaid Services ("CMS") reviews the specific drugs, and the tiering strategies employed in each formulary to identify any strategies that are significantly different from common practices for managing drug benefits so that these can be evaluated before being approved.

The PBM must limit the number of formulary changes made over the course of a plan year, provide notice of any such changes to beneficiaries and their physicians, limit changes in therapeutic classifications, and provide a transition process for new beneficiaries.<sup>58</sup>

#### **c. Prescription drug formularies: Medicaid plans**

Coverage of prescription drugs is an optional benefit in state Medicaid Programs, though all 50 states and the District of Columbia currently provide a drug benefit. If states provide drug coverage, they are required to cover all drugs of manufacturers that have entered into rebate agreements with CMS when prescribed for a medically accepted indication. They may only subject a covered outpatient drug to prior authorisation, or exclude or otherwise restrict coverage if the prescribed use is "off label".

In 2012, when direct acting antiviral drugs (“DAAs”) were approved for treatment and cure of Hepatitis C (“HCV”), clinical efficacy was found to be extremely high, with cure rates of 95 to 100 per cent being reported. Despite this, because the cost of a full course of treatment can range from \$16,000–\$94,000 per patient, some state Medicaid plans had begun to deny coverage on the basis of the drug’s high cost. In response, Medicaid Drug Rebate Program officials and CMS sent a series of notices to states to remind them of their statutory responsibility to cover these drugs, especially because of their significant clinical efficacy and elimination of additional downstream costs associated with progression of untreated disease.<sup>59</sup>

## Pharmaceutical Pricing and Reimbursement

Changes in the US healthcare market, driven by an accelerating pace of drug discovery and practice innovation have produced new, highly effective treatments for complex medical conditions. However, the discovery process, together with the growing number of individuals with prescription drug coverage have converged to drive dramatic growth in prescription drug costs.

The Pharmaceutical Research and Manufacturers of America (“PhRMA”), a trade association for makers of pharmaceutical products, released an August 2016 report that put the costs of developing innovative drug therapy into context.<sup>60</sup> Among other things, it identified the changing economies associated with drug development in the current market and observed that appropriate use of expensive drug therapy can reduce the total cost of medical care dramatically for some classes of patients.

### A. Setting the list price for prescription drugs

Prescription drug pricing is complex, but at bottom, there is a list price set by the manufacturer called the “Wholesale Acquisition Cost” (“WAC”). Average Wholesale Price (“AWP”) has become the *de facto* trade price with a 20–25 per cent mark-up over WAC.<sup>61</sup>

Manufacturers set the list price, or WAC for their products. This is the amount on which rebates, service agreements and price concessions are calculated for negotiating purchase price and payment amounts throughout the supply chain. In theory, manufacturers have great flexibility in setting WAC at any price point they wish, but in reality, their options are constrained by global market dynamics and the competitive environment. Manufacturers take a number of factors into account in setting WAC for a new branded prescription drug, including:

- **Cost of research and development:** The US Government Accountability Office (“GAO”) recently reported that worldwide spending on research and development for single source, branded prescription drugs increased in real dollars from \$82 billion in 2008 to \$89 billion in 2014.<sup>62</sup> The Tufts Center for the Study of Drug Development estimated that total capitalised costs for a single new FDA-approved drug were approximately \$2.6 billion in 2013.<sup>63</sup> Other estimates place the cost of new drug development at between \$648 million and \$2.6 billion.
- **Role of mergers and acquisitions in the research and development pipeline:** Rather than undertake drug development in house, large companies increasingly rely on M&A to obtain access to new molecules and to fill their product pipelines quickly without assuming the cost of clinical labs, research personnel.
- **Marketing costs:** The cost of marketing and promotional activities over the life of the product can far exceed R&D costs, and are factored into calculating WAC.
- **Competitive position in market:** Manufacturers of new, single source products with patent protection have maximum flexibility in setting the initial WAC and changing

price over time, though pricing of any other drugs in the same class that have already been launched to the market often sets a ceiling for WAC for subsequent market entrants.

**CASE STUDY:** When **Gleevec (imatinib mesylate, Novartis)**, a highly effective treatment for leukemia, first came to market in the US, its list price was about \$26,000 a year. Today, there are several highly-effective drugs in the same family on the market with an annual list price of about \$150,000 each. What happened is that each new entrant cost more than its predecessors, which then also increased their prices to meet the higher price point. When the first generic version entered the market in 2016, its list price was only slightly less, about \$140,000. This phenomenon is sometimes called “**sticky pricing**”.

## 1. Novel pricing models

As manufacturers face increasing pressure to lower drug prices, traditional “price per dose” models are giving way to newer approaches to pricing that more closely link drug price to drug value.

### a. Indication-specific pricing

Manufacturers may charge different prices for the same drug according to the indication for which it is used, so that the drug may be priced higher where treatment alternatives are fewer, or where treatment produces significantly better outcomes than existing alternative therapies.<sup>64</sup>

Sildenafil (Pfizer) received separate FDA approvals and unique drug codes for Viagra, sildenafil indicated for erectile dysfunction, and Revatio, sildenafil indicated for pulmonary arterial hypertension

Manufacturers can only negotiate reimbursement contracts for FDA-approved indications. Drugs that have significant off-label uses, even when supported by research, guidelines and compendia, are unlikely to be suitable candidates for indication-specific pricing since a decision would have to be made regarding which price to be used for off-label uses. Manufacturers could not enter into contract negotiations that give the perception of promoting off-label use.

### b. Outcomes-based pricing

Manufacturers of high cost specialty drugs may negotiate rebate agreements with customers according to the anticipated clinical outcomes associated with their drug(s) when taken as prescribed by individuals or subgroups of members. Such agreements can be very attractive to potential customers, but they may present financial and regulatory risks for both parties. To de-risk these types of agreements, the parties should exchange detailed information on drug performance, including data not on the label, and on the health status of the insured population. Manufacturers are cautioned to ensure that any data exchange is not viewed as off-label promotion. The number of outcomes-based pricing agreements has grown significantly in recent years. Table 2 presents a list of select agreements that have been publicly announced.

*Cont'd overleaf*

Table 2: Select list of publicly reported outcomes-based pricing agreements

| Manufacturer(s)      | Payer(s)                               | Drug (Indication)                         |
|----------------------|--|---|
| Amgen                | Cigna<br>CVS Health<br>Harvard Pilgrim | Repatha (cholesterol)                     |
| Sanofi and Regeneron | Cigna                                  | Praluent (cholesterol)                    |
| Amgen                | Harvard Pilgrim                        | Enbrel (rheumatoid arthritis)             |
| Eli Lilly            | Harvard Pilgrim                        | Forteo (osteoporosis)                     |
| Eli Lilly            | Harvard Pilgrim                        | Trulicity (diabetes)                      |
| Novartis             | Aetna                                  | Entresto (cardiovascular)                 |
|                      | Cigna                                  |   |
|                      | Harvard Pilgrim                        |   |
|                      | Humana                                 |   |
| Novartis             | Humana                                 | Gilenya (multiple sclerosis)              |
| Merck                | Aetna                                  | Januvia and Janumet (oral diabetes drugs) |
|                      | Cigna                                  |   |
| P&G and Sanofi       | Health Alliance                        | Actonel (osteoporosis)                    |
|                      | Medical Plans                          |   |
| AstraZeneca          | Harvard Pilgrim                        | Brilinta (acute coronary disease)         |
| AstraZeneca          | Harvard Pilgrim                        | Bydureon (diabetes)                       |

Source: Sachs, Bagley 2018

### c. Drug licences

A drug licensing model offers the option of flat monthly or annual payment based on clinical appropriateness, similar to software licensing where the customer pays a fixed amount for a specified number of installations. A license-based model for antibiotics could reduce the financial disincentives associated with antibiotic development, such as low sales volume that occurs when providers try to use antibiotics sparingly to reduce the risk of drug resistance.

### d. Drug mortgages

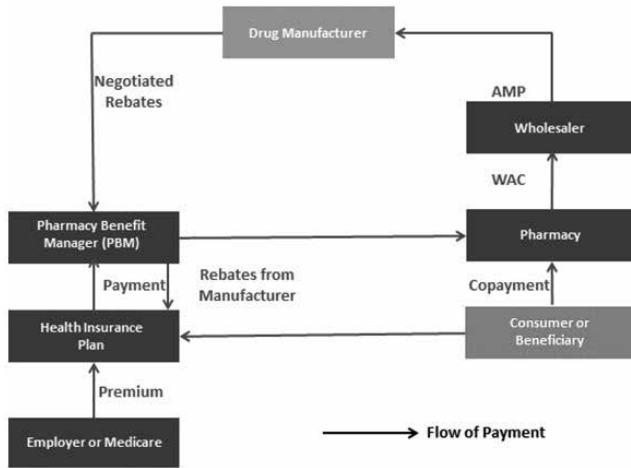
Drug mortgages spread out payment over time. For example, direct-acting antivirals (“DAAs”) can cure Hepatitis C with an eight- to twelve-week course of treatment. But while the benefits of the cure accrue over a lifetime, under current models, the costs of the drugs (\$16,000–\$94,000) are recouped within a much shorter eight- to 12-week window of treatment, making the drugs unaffordable to some health plans.

### e. Buy-and-bill

For physician-administered drugs, healthcare providers use a buy-and-bill model in which a provider purchases the drug directly from a manufacturer or distributor, administers it to a patient, and then submits a claim to the health insurance plan for payment for the drug itself plus a separate payment for administering the drug.

### B. The flow of payment for outpatient prescription drugs

Generally, the manufacturer sells an outpatient prescription drug to a wholesale distributor at a list price set by the drug maker (WAC), minus discounts negotiated between the parties, typically 2 to 5 per cent. This discounted price is the Average Manufacturer Price (“AMP”).<sup>65</sup> Additional discounts of 1 to 2 per cent may be added to AMP for prompt payment, volume purchases, etc. The distributor then sells the product to a pharmacy at a price marked up to be roughly equivalent to WAC. A beneficiary buys the drug at the pharmacy after paying some form of cost-sharing (coinsurance or copayment) set by the his/her insurance plan. The insurance plan outsources management of its drug benefit to an intermediary, the PBM. The PBM negotiates with the pharmacy to set the copayment and service fees that the pharmacy receives for dispensing the medication.



Source: Congressional Budget Office

Figure 6: Flow of money through US Drug Channel

## 1. Manufacturer rebates to PBMs and health plans

Throughout the supply chain, participants exchange rebates, discounts, and other payments to encourage other entities to contract with them or to encourage purchasing a particular drug. For example, a manufacturer may offer a distributor volume discounts, prompt pay discounts, or chargebacks if the manufacturer contracts directly with a pharmacy or healthcare provider. A manufacturer may also grant financial incentives or concessions to a PBM or pharmacy.

Manufacturers typically provide three types of rebates to PBMs:

- **Formulary rebates** are given in exchange for placing a manufacturer's product on the plan's formulary. They can be a substantial source of savings, anywhere from 0.5 to 0.75 per cent of WAC. Manufacturers may offer even larger rebates if their products are placed on a preferred tier, or if their product is not subject to prior authorisation or other utilisation management. The rebate agreement may also require the plan to discourage use of competitor drugs by demanding that the plan impose a higher copay to purchase a competitor's product.
- **Market-share rebates** reward plans or PBMs for higher use of the rebated product than competing therapies.
- **Price protection rebates** are newer arrangements that compensate plan sponsors and PBMs if WAC rises beyond an agreed-upon percentage or dollar threshold. These rebates mitigate the risk of financial losses as drug prices go up.

## 2. Manufacturer discounts to distributors

The majority of outpatient prescription drugs are distributed through one of three companies, McKesson, AmerisourceBergen, or Cardinal Health. Sometimes referred to as the "Big Three", they collectively control between 85 to 90 per cent of the US market.

Distributors have greater leverage in negotiations with manufacturers of multiple-source (generic) drugs because these manufacturers compete to gain a distributor's business. Thus, distributors often secure lower prices from manufacturers when purchasing generics, increasing the spread between the price at which distributors pay and sell a product. For this reason, distributors' profits are higher when handling generic drugs (\$8 for every \$100 spent on a drug at a retail pharmacy) than they are for brand name drugs (\$1 for every \$100).

Another key financial arrangement between manufacturers and distributors is the “chargeback” used to compensate distributors after a drug maker negotiates directly with a third party in the supply chain (such as a pharmacy or healthcare provider), rather than going through the distributor. Under these arrangements, distributors may distribute drugs from a manufacturer to a pharmacy or provider and then “chargeback” the difference between a manufacturer’s contracted price with a third party and the distributor’s invoice price. Chargeback arrangements make up a substantial portion of distributors’ net sales.

In the past two decades, distributors have reinvented their business models by charging manufacturers for additional services they provide, including packing and shipping drugs, data management, periodic retail demand information, current inventory levels, and reimbursement support services. In turn, manufacturers have developed performance-based incentives and discounts to encourage distributors to enter service contracts with them.

### 3. Manufacturer discounts to pharmacies

Manufacturers also negotiate directly with certain pharmacies and pharmacy chains. The market power of a pharmacy plays a key role in these financial relationships. Chain pharmacies that serve a greater number of consumers and hold higher market share are able to negotiate more favourable financial arrangements with manufacturers. These large chains stand in contrast to smaller pharmacies, which are less able to exert the necessary leverage to negotiate substantial price concessions. Pharmacies also exert greater leverage when negotiating for generic rather than brand name drugs. This is mainly because, unlike plan sponsors and PBMs, pharmacies do not control or select the brand name drug ultimately dispensed to the consumer. In contrast, for generic drugs, pharmacies select which product to stock from all available generic versions of a drug. As a result, generic manufacturers may offer discounts and rebates to pharmacies to encourage pharmacies to stock their product for consumers. Thus, while a drug’s list price (“WAC”) may be a good indicator of the price pharmacies pay for brand name products, pharmacies frequently pay below WAC for generic drugs.

### 4. Manufacturer rebates to Medicare

The Medicare Program is the single largest purchaser of outpatient prescription drugs in the US. As such, if Medicare were to negotiate directly with manufacturers, it could exert significant pressure on them to demand deep discounts for purchasing their products, causing potentially major disruption to the global research-based biopharmaceutical industry ecosystem.

In fact, Medicare does not negotiate directly with pharmaceutical manufacturers. Rather, Medicare applies one of two different methods, one for drugs taken orally, the other for physician-administered drugs:

- **Medicare pays for orally-administered outpatient prescription drugs under Part D.** Private health insurance plans and PBMs that have contracted with the federal government to administer the Medicare Part D benefit negotiate acquisition costs for outpatient prescription drugs independently. While they have sufficient size in their own right to negotiate attractive discounts with manufacturers, they do not negotiate as a block on behalf of the Medicare Program.
- **Outpatient prescription drugs administered by a physician are paid under Part B:** Medicare pays for Part B drugs, that is, drugs administered by a physician or other healthcare professional, on the basis of a statutory formula: “ASP + 6”. Each quarter, manufacturers report a weighted average of the sales prices offered to customers in each channel. This includes discounts applied. Medicare then takes the reported Average



Sales Price (“ASP”) and adds 6 per cent. As product pricing and discounting varies from month to month, Medicare payment also varies.

### **C. Specialty drugs**

Eighty-five per cent of health insurance plans in the US classify certain drugs as “specialty drugs” because they (a) are very expensive (often more than \$670 a month), (b) require special handling in the supply chain (e.g., temperature or shelf life), (c) must be administered by a healthcare provider, and/or (d) have significant side-effects that require counseling.

Specialty drugs make up only 1–2 per cent of outpatient drugs prescribed, but represent 40–50 per cent of drug spending, making them an important target for payers and policy makers. Current trends suggest that specialty drug spending will total \$350 billion by 2020, or about 9 per cent of US spending on all healthcare-related services.

Since passage of *Hatch Waxman* in 1984, creating an abbreviated approval process for generic drugs, the practice of prescribing and/or dispensing lower cost generics has grown to represent about 86 per cent of all prescription drugs dispensed annually. However, any savings associated with generic substitution is being washed out by significant growth in both the number and the cost of new specialty drugs.

### **D. Orphan Drugs**

Orphan drugs are a class of products intended to treat rare diseases and disorders, defined as conditions that affect fewer than 200,000 people. Because of their more limited markets, the US Government created incentives to encourage manufacturers to develop these products, including tax credits for certain clinical testing, exemptions from certain user fees, and an extended period of market exclusivity totaling seven years.

### **E. Employer/PBM strategies to reduce drug spend**

There are significant differences between drug prices set by a manufacturer, and the amount actually paid for its drugs in the US market. Manufacturer rebates to PBMs and pharmacies, government-mandated discounts that manufacturers must offer to Medicare and Medicaid, cost-sharing arrangements between employers or health plans and their employees/beneficiaries all contribute to a complex web of confidential business agreements between and among players in the distribution channel for outpatient prescription drugs in the US. Employers and health plans actively participate in negotiating their purchase prices for individual drugs, but they have also developed strategies to manage the overall cost of the drug benefits that they provide to their members. Current strategies include:

#### **1. Substitute lower cost drugs**

PBMs may recommend or require that lower cost alternative drugs be dispensed in place of more expensive drugs when they are available and clinically appropriate.

##### **a. Generic substitution**

Some PBMs encourage or require pharmacies to dispense the generic version of a brand name drug if a generic is available and both the prescriber and state law permit substitution.

Generic drugs have the same active ingredient, strength, dosage form, and route of administration as an NDA-approved brand name drug and share the safety and efficacy data of the reference drug. While they may be sold under different names than the reference brand, the FDA considers generic drugs to be “bioequivalent”, or “therapeutically equivalent” to the reference product.<sup>66</sup>

Since the 1990s, the use of generic drugs has grown dramatically, and while generic drug prices have themselves begun to increase over the last several years,<sup>67</sup> their use can still

produce significant cost savings. In 2002, 40 per cent of prescription drugs dispensed at retail pharmacies were generics. By 2015, that number had increased to about 78 per cent. Today, nearly 85–90 per cent of all prescription drugs sold in the US are generics, and the Association for Accessible Medicines, the trade association of generic pharmaceutical manufacturers, estimates that generics have saved consumers and the healthcare system \$1.5 trillion in the past decade alone.<sup>68, 69</sup>

## **b. Biosimilars substitution**

The Biologics Price Competition and Innovation Act of 2009 (“BPCI”)<sup>70</sup> amended the Public Health Service Act,<sup>71</sup> to create a new regulatory approval pathway for follow-on biologic products similar to the abbreviated new drug application (“ANDA”) process created by Hatch Waxman.

Biologics, such as human growth hormone, injectable treatments for arthritis, and stem cell therapy are much more complex than traditional chemically-synthesised drugs. Because they are manufactured from living organisms by programming cell lines, they are not identical, and thus are not technically “generic” biologics.<sup>72</sup> Rather, biosimilars are *“highly similar to or interchangeable with”* a reference product approved under a biologics license application (“BLA”).<sup>73, 74</sup> A product is biosimilar if it is:

- highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
- there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product.

Some biosimilars are also considered to be “interchangeable” if they can be expected to produce the same clinical result as the reference product in any given patient, and the risk in terms of safety or diminished efficacy of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of using the reference product without such alternation or switch.<sup>75</sup>

The BPCI statute appears to allow PBMs to manage the cost of biological products by either excluding the more expensive reference biological product from the formulary, or implementing automatic edits requiring a beneficiary to use the less expensive biosimilar agent first, and only progress to use of the reference product if there were a lack of clinical efficacy or drug-related adverse event. It appears likely that PBMs would also implement rigid prior authorisation rules for beneficiaries to access branded biologics when a biosimilar is available.

## **2. Apply a “pay-for-value” formula**

A number of independent organisations (i.e., with no ties to pharmaceutical manufacturers, employers or health insurance plans) have developed “value formulas” to provide systematic evaluation of the potential benefit of a new prescription drug or medical technology at various price points to a population of “covered lives”. These formulas are intended to help employers, health insurers, and PBMs set the amounts they are willing to pay for the drugs they purchase.

One such organisation is The Institute for Clinical and Economic Review (“ICER”),<sup>76</sup> a non-partisan research organisation that evaluates the clinical and economic value of prescription drugs and other healthcare innovations objectively. ICER analyses clinical data and convenes key stakeholders at public meetings to translate this evidence of value into policy decisions that may help inform new product coverage and pricing determinations.

The ICER model includes steps such as:

- Objective evaluation of the clinical and economic evidence to account for potential benefit across a lifetime. This includes potential downstream cost offsets for new treatments that might take many years to be seen, and so that care options that might increase spending for one type of service (e.g. drugs) while reducing other spending (e.g. hospital costs) receive full credit for cost offsets and are not penalised in any way.
- Evaluation of the comparative clinical effectiveness of different treatment options through review of available evidence and judgment of the net health benefit of each.
- Acceptance of multiple forms of evidence, including high quality randomised controlled trials (“RCTs”), but also observational analyses based on cohort studies, patient-reported data, and long-term registries, and the so-called “gray literature”.<sup>77</sup>
- Consideration of other factors, including the ability to return to work, family and caregiver burden, impact on the public health, or on other aspects of the health system or society.
- Acknowledgment of the role of contextual considerations, such as severity of the condition, whether other treatments are available or other ethical, legal or societal priorities.

### 3. Enter into risk-based contracts<sup>78,79,80</sup>

Some payers negotiate risk-based contracts with pharmaceutical manufacturers under which the purchase price of certain high cost drugs is tied to treatment outcomes, i.e., how well a drug works for specific segments of their member population. Such “value-based” deals are becoming more common, especially with very expensive specialty drugs. For example, when FDA approved Spark Therapeutics’ Luxterna (*voretigene neparvovec-rzyl*) in 2017 for treatment of retinal dystrophy, the drug cost \$850,000 a year. Spark offered employers and health insurance plans extended financing and rebates when no clinical improvement was observed.

#### a. Impact of risk-based contracting on “Best Price”

Risk-based contracting presents potential challenges to compliance with complex Medicaid Best Price provisions. Manufacturers are reluctant to consider risk-based contracts because they fear that the variety of price concessions and services in a risk-based contract arrangement could lower a drug’s best price, increase the manufacturer’s Medicaid rebate obligations, and become a disincentive to pursuing such arrangements. (Note: this is not the average lowest price. A single rebate to a single customer could trigger Best Price.)

Regulators urge manufacturers to consult the regulations on determining Medicaid best price when negotiating value-based prices, and should “continue to document the calculation of best price, including any reasonable assumptions about the impact of their arrangements”.<sup>81</sup>

### 4. Deny reimbursement for expensive therapies

In order to manage the costs of providing health benefits, employers and health insurance plans may place restrictions on certain high cost drugs, even when therapy can be highly effective in the near term and save significant downstream costs.

#### F. Manufacturer strategies to maintain drug prices: Financial assistance to consumers

Because the Wholesale Acquisition Cost (“WAC”) or list price for a drug is the primary input to formulas used to calculate the purchase price of outpatient prescription drugs and the size of rebates offered to both private and government customers, higher WAC can be an important component of a manufacturer’s global market strategy, despite the near term barriers to access that it may create for individual consumers.

To help overcome these barriers, manufacturers commonly sponsor a number of programmes to provide financial assistance directly to the individuals who purchase their products.

1. Reimbursement support services

Many companies sponsor reimbursement support programmes for prescribers and their patients who have health insurance. These programmes are typically outsourced to third-party vendors that staff call centres from which they provide technical assistance, including insurance benefits verification, prior authorisation, and appeals support. Reimbursement support programmes are generally offered as a service provided at “arm’s length,”<sup>82</sup> and at no cost to the prescriber.

**CASE STUDY:** Reimbursement denied for Hepatitis C cure

A recent study found that government- and employer-sponsored health plans had denied reimbursement for more than 35 per cent of prescriptions for Direct-Acting Antivirals (“DAAs”) written for treatment of Hepatitis C between January 2016 and April 2017. DAA therapy cures about 95 per cent of people with chronic Hepatitis C, a viral liver disease that can cause liver failure or death, affecting about 3.5 million people. It kills 19,000 a year, according to the Centers for Disease Control and Prevention (“CDC”). However, one course of treatment with Harvoni is the same as the annual Medicaid cost for 29 people.

Examples of DAA drugs, which first became available in 2014, include:

| Drug  | Manufacturer | List price for course of therapy | Estimated price per pill |
|---|--------------|----------------------------------|--------------------------|
| Harvoni ( <i>ledipasvir/sofosbuvir</i> )    | Gilead       | \$94,500                         | \$1125                   |
| Sovaldi ( <i>glecaprevir/pibrentasvir</i> ) | Gilead       | \$84,000                         | \$1,000                  |
| Epclusa ( <i>sofosbuvir/velpatasvir</i> )   | Gilead       | \$74,760                         | \$890                    |
| Zepatier ( <i>elbasvir/grazoprevir</i> )    | Merck        | \$54,600                         | \$650                    |
| Mavyret ( <i>glecaprevir/pibrentasvir</i> ) | Abbvie       | \$16,700                         | \$200                    |

Table 3: Estimated Price Range for Branded Direct-Acting Antivirals for HCV Treatment

Given the clinical benefits of curing chronic HCV infection, the cost-effectiveness of DAA treatment, and the importance of antiviral therapy to HCV elimination efforts, The high incidence of reimbursement denials adversely impacts strategies for HCV elimination.

Source: Gowda C, Lott S, Grigorian M, Carbonari DM, *et al.* Absolute insurer denial of direct-acting antiviral therapy for hepatitis C: A national specialty pharmacy cohort study. *Open Forum Infectious Diseases*. Volume 5, Issue 6, 1. June 2018, ofy076. <https://doi.org/10.1093/ofid/ofy076>

Manufacturers benefit from offering these programmes to their customers, because, in addition to facilitating access to reimbursement for their products and lowering price-related barriers to access, they are also educating current and future prescribers, patients and health insurance plans, introducing them to the brand and detailing them on its clinical and economic value.

US regulators monitor reimbursement support programmes to ensure that the services offered are clearly delineated and that the offering does not grow into delivering free goods or services in exchange for prescribing or purchasing the drug, which could be viewed as a kickback.<sup>83</sup>

## 2. Coupon programmes

In recent years, PBMs and health plans have tried to guide patients toward less expensive drugs by making them pay a higher portion of a drug's costs when it is "non-preferred" on the formulary, or when a generic is available. Manufacturers have responded by raising the amount of temporary financial assistance they offer to customers through "copay assistance" cards – similar to a debit card – that reduce what consumers pay at the pharmacy. Coupons provide a form of direct financial support to customers regardless of financial means. They can be used to help build brand awareness and can create brand loyalty.

Customers present drug coupons at the point of sale to receive an immediate discount. Figure 7 presents an example of one coupon.



Source: <https://www.mavyret.com/copay-savings-card>

Figure 7: Example of Co-Pay Coupon Presented at Pharmacy

Individuals with government-sponsored health insurance (i.e., Medicare or Medicaid) are not eligible to use coupons because their use could be viewed as creating an illegal inducement to purchase. In addition, some states, including Massachusetts, ban their use when a generic equivalent is available.

Payers and policy makers often criticise coupon programmes for keeping individuals on brand when generics or other less expensive alternatives are available. A recent study found that prescription drug coupon programmes actually increase healthcare spending by billions of dollars a year.<sup>84</sup>

The researchers estimate that for brand-name drugs facing generic competition, coupons boost retail sales by 60 per cent or more and increase spending by \$30 million to \$120 million per drug.

To counter manufacturers' use of coupons, a number of PBMs have recently introduced new "copay accumulator" programmes that segregate funds received from manufacturer coupons so that these amounts do not count toward meeting a member's deductible that must be paid before the pharmacy benefit begins to pay. Using coupons, the manufacturer covers most, or all, of the member's costs for the drug and these payments count towards meeting the deductible. But if the plan is using an accumulator, the member could still have to pay the deductible amount out-of-pocket once the copay card expires or runs out of money.

## 3. Patient assistance programmes ("PAPs")

Patient assistance programmes ("PAPs") provide a vehicle through which manufacturers can offer indirect financial assistance to individuals who use their products. These programmes are generally administered through independent charitable organisations or by foundations established by the manufacturers.

Manufacturers make financial contributions to fund a charity or foundation which disburses funds on the basis of availability and individual need determined according to a set of pre-established criteria.

Individuals apply directly to the PAP to request financial assistance. The programme independently verifies financial need and may provide assistance if the requestor meets pre-specified criteria. The manufacturer cannot direct funds to any individual or group and cannot have access to detailed information about how or to whom their contributions are disbursed.

The U.S. Department of Health and Human Services (“HHS”) Office of the Inspector General (“OIG”) has continually acknowledged that properly structured PAPs can provide important “safety net assistance” to patients with limited financial means who cannot afford necessary drugs. However, these programmes face increasing enforcement scrutiny from regulators and legislators on a state and federal level.

#### **4. Legal risks associated with financial assistance programmes**

The federal Anti-Kickback Statute (“AKS”) prohibits anyone from soliciting, receiving, offering, or paying any remuneration in return for a referral for an item or service that may be paid for by a federal healthcare programme.<sup>85</sup> Nonetheless, the OIG has approved certain independent charitable programmes to help financially needy beneficiaries pay healthcare expenses when the programmes are sufficiently independent from drug manufacturers, and do not violate fraud and abuse laws.

However, the OIG has noted that the AKS could be violated if a donation is made to a PAP to induce it to recommend or arrange for the purchase of the manufacturer’s federally reimbursable items, and if a PAP’s financial assistance to a patient is made to influence the patient to purchase (or induce the patient’s physician to prescribe) certain items”.<sup>86</sup>

In one case, United Therapeutics (“UT”), a Maryland-based biotech company, agreed to pay \$210 million to settle allegations that it violated the AKS and False Claims Act by working through a foundation to pay the Medicare copays of patients taking its drugs. UT had allegedly made numerous donations to a charity, which in turn used the funds to pay the Medicare copays associated with UT’s drug products for thousands of Medicare beneficiaries. The DOJ alleged that the charity routinely gave UT access to data which detailed how much the charity had spent to cover copays for UT drugs. The DOJ also alleged that UT maintained a programme which offered free drugs to financially needy patients, but did not permit Medicare patients to participate, instead referring them to the foundation, thereby funneling claims to the Medicare Program.

As a part of its settlement, UT entered into a five-year Corporate Integrity Agreement (“CIA”) under which they established an Independent Charity Group, agreed to comply with rigorous requirements to ensure that the charity was independent from UT’s commercial enterprise, and allowed government oversight and audits of its donations to PAPs.<sup>87</sup>

### **Policy issues that affect drug pricing and reimbursement**

The Trump Administration has broadly endorsed changes to US policy on outpatient prescription drugs to require greater transparency in price setting, increased competition to drive quality and lower costs, and reduced regulatory burden to shorten time to market.<sup>88</sup>

#### **A. Transparency in setting drug prices**

Federal health policy makers have expressed grave concerns about the rising costs of prescription drugs in the US, but have taken little substantive action because the issue is so

politically charged. The President has “tweeted” about reducing drug prices, and there was early concern that the Administration’s Blueprint for lowering drug prices would include proposals to require drug makers to cut prices or limit their ability to increase them, but it did not.<sup>89</sup> Given deep division in the current political environment, it is unlikely that federal policy makers would be able to reach consensus on these issues in the foreseeable future.

However, a number of states have moved forward to implement new laws to contain prescription drug costs in their states.

For example, in June 2016, Vermont enacted a new law authorising the state attorney general to require manufacturers that had increased drug prices by more than 50 per cent over a five-year period to provide justification for the cost increases. The state then posts this information for public review on an annual basis.<sup>90</sup> By March 2018, Oregon became the ninth state to enact similar legislation.<sup>91</sup>

A total of 16 states have introduced legislation requiring drug manufacturers to report the rationale for drug price increases exceeding 10 per cent or more over a 12-month period. Seven states also cap beneficiary cost-sharing for prescription drugs in employer-sponsored health plans.

## **B. Increased competition**

Medicare currently pays for outpatient prescription drugs that are taken by mouth under Part D, where it uses private PBMs to negotiate rebates with manufacturers, but pays for physician-administered drugs under Part B of the programme. Because Part B payments are calculated on the basis of Average Sales Price (“ASP”) plus some per cent, pricing is less sensitive to competitive market dynamics. Administration officials have talked about moving physician-administered drugs from Part B to Part D, where PBMs could secure more competitive pricing by negotiating manufacturer rebates. This is not a new idea, but would likely draw opposition from manufacturers that would be required to accept discounts on a broader range of products.

## **C. Reduced regulatory burden**

The FDA Commissioner recently committed to accelerating regulatory approval for generic drugs in two ways:

### **1. KASA platform**

FDA intends to create a new review platform, the Knowledge-aided Assessment & Structured Application (“KASA”) platform, to transition generic drug review from a text-based to a data-based assessment. KASA will create a more efficient review process able to identify and correct any deficiencies earlier in the review process, allowing FDA to provide earlier feedback to manufacturers that will, in turn, help reduce the number of cycles of review and increase the number of generic products approved after the first cycle. This would accelerate market entry and increase overall competition.

KASA will also provide a more robust knowledge management system for effective surveillance of product quality and safety.

### **2. Updated labelling**

Generic drugs must have the same labelling as the brand drugs they reference. The manufacturer of the reference product is responsible for updating its product’s label with new safety and effectiveness information. But, when reference drug manufacturers voluntarily withdraw their marketing applications because of generic competition, they also stop updating their label. When this happens, FDA

can no longer confirm that generic labels are identical to the reference products. The Agency intends to encourage reference product manufacturers to keep their labels current to help promote broader use of generic drugs.

### **Emerging trends**

Three important trends are reshaping the US prescription drug market:

- Regulators appear willing to consider a broader range of evidence to support marketing approval and reimbursement for new drugs. If this trend continues, it could shorten the time to market for some products.
- Healthcare providers report that cost-containment has become their most important business priority. If this trend continues, purchasing agreements for expensive new drug therapies may be more difficult to execute, despite evidence of superior clinical efficacy. However, new products that offer tools to help providers contain growing healthcare costs will become more attractive to customers.
- A wave of vertical integration is changing the profile of the overall market. If this continues, it could make it more difficult to identify purchasing decision makers and give them greater leverage in negotiating drug prices. This trend could create new hurdles to successful commercialisation.

#### **A. “Real World Evidence”**

Before approving commercial use of a new drug candidate, FDA has traditionally required manufacturers to provide “substantial evidence” of efficacy from rigorous, well-controlled research on a study population that meets stringent inclusion criteria. While this methodology can provide clear answers to narrowly framed research questions, it also begs questions about product performance in the real clinical practice setting.

Through the 21<sup>st</sup> Century Cures Act, Congress directed FDA to accelerate the regulatory review process by considering the “totality of evidence”<sup>92</sup> on certain new drug candidates, ranging from rigorous clinical trial data to so-called “Real World Evidence” (“RWE”),<sup>93</sup> taken from claims data, longitudinal registries, and records on patients’ satisfaction and social determinants of health. Reviewing different types of data for approval could help drive more rapid adoption of clinical best practices and provide new tools for monitoring safe use.<sup>94</sup>

For example, FDA recently allowed researchers to create a “virtual control group” from a cohort identified through consulting a longitudinal population health registry in Finland for a study of treatment-refractory gastroesophageal cancer patients.<sup>95</sup> Using the virtual cohort allowed the study to be completed more quickly, and at lower cost, than if researchers were required to accumulate a randomized control group prospectively.

#### **B. Cost containment**

A recent survey of 146 US-based health system executives conducted by the Advisory Board Company<sup>96</sup> found that, while annual revenue growth continues to be an important business objective, cost containment has now become their primary strategic focus. With annual expense growth of 7 per cent but revenue gains of only 6 per cent, nearly two-thirds of respondents reported that preparing the organisation for sustainable cost control was their top aim, followed by adopting innovative approaches to expense reduction and diversifying revenue streams.

Health system CEOs recognise that changes reimbursement, consolidation of traditional players in the drug channel and the entry of nontraditional players like Amazon, sustainable



cost containment becomes all the more urgent. These priorities will apply across the organisation and affect drug pricing negotiations and purchasing decision-making. Manufacturers should evaluate novel pricing and contracting models discussed elsewhere in this chapter to help them differentiate from competitors.

### **C. Market consolidation through vertical integration**

The PBM market is highly concentrated, with three PBMs (CVS Health, Express Scripts, and OptumRx) accounting for 85 per cent of the total market, giving them significant leverage to negotiate deep rebates with manufacturers. In the current system, the size of specific manufacturer rebates and the percentage of the rebate passed on to the employer or health plan is confidential. This encourages manufacturers to set artificially high list prices, which they reduce through rebates to specific customers.<sup>97</sup>

To gain access to this information, large commercial health insurance companies, have recently turned to vertical integration. By moving PBMs in-house, they gain better control over rebate negotiations, and the opportunity to manage the total cost of care across medical and pharmacy services.<sup>98</sup>

This trend may create hurdles for new product adoption because:

- Purchasing decision making is centralised at the corporate level.
- Evidence thresholds for coverage and reimbursement are higher.
- Larger, vertically-integrated entities have greater market share and, therefore, more leverage in rebate negotiations.

### **Successful market access**

The US is the largest pharmaceutical market in the world. Arguably, it is also the most fragmented, and among the most difficult to enter and compete in successfully. Manufacturers should always take a global view when planning to enter specific markets to leverage investments made and assets developed in one market to help accelerate successful entry into subsequent markets. Presented below are 10 principals for successful market access.

#### **1. Know the customer**

Someone once observed that “When you’ve seen one market, you’ve seen one market. . .” Indeed, every healthcare and pharmaceutical market is unique.

The US healthcare market may be better described as “markets,” because practice patterns, incidence and prevalence of disease, access to healthcare services, rates of health insurance coverage, and benefit design vary widely from one region of the US to another, suggesting that the profile of a typical customer will vary just as widely. For that reason, successful entry requires intensive listening, not just market research. Understanding how customers articulate the issues they face and the vocabulary they use to describe their unmet need should influence product design and evidence planning.

For example, a physician-administered drug that requires two intramuscular injections over a 48-hour period may face adoption hurdles if health insurers will only reimburse one office visit during that time period. Similarly, an economic model demonstrating the long term cost-effectiveness of using an expensive new drug is unlikely to persuade a hospital operating room purchasing manager who is focused on reducing near term product acquisition costs.

Successful products fit within clinical best practices and reimbursement policies. Evidence of treatment outcomes will be more persuasive if it demonstrates product value using the same language and the same measures that the customer used to articulate unmet need.

## 2. Engage stakeholders sooner, and frequently

Manufacturers should identify and engage stakeholders across the product lifecycle as early and as frequently as possible, keeping applicable regulatory restrictions on product promotional activities in mind. Thus, peer reviewed journal articles, scientific poster presentations and discussions with patient advocacy groups on new research to address unmet medical needs all present opportunities for appropriate engagement with these stakeholders to build their interest and educate them about new products. In fact, manufacturers should proactively develop and refine an “end-to-end” evidence strategy to provide opportunities for ongoing engagement with key stakeholder groups about new product value.

FDA has recognised the importance of this type of customer engagement, and has recently released guidelines on the types of communication with stakeholders that are permitted because they comply with FDA regulations on promotional activities for prescription drugs. For example:

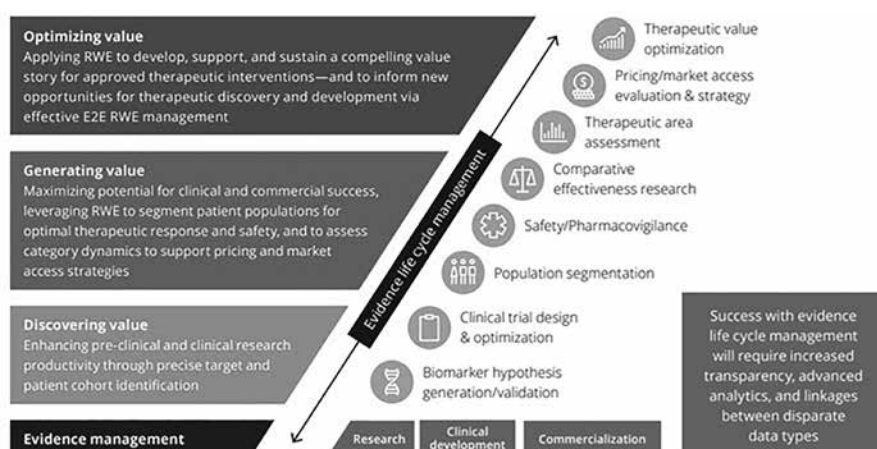
- In its guidance on medical product communications, FDA indicated that manufacturers are permitted to provide information to PBMs and health plans about unapproved products and unapproved uses of approved drug products if that information is “truthful and not misleading.” The Agency commented further that this type of communication could eventually help accelerate coverage and payment decision making after the products have been approved.<sup>99</sup>
- Similarly, in its guidance on communicating with payers, formulary committees and other entities,<sup>100</sup> FDA noted that providing healthcare economic information that pertains to the economic consequences of treating, preventing, or diagnosing a disease to PBMs and health plans before approval is also permitted. Early discussion with potential customers about the anticipated economic benefits of using a new product may improve customer “readiness” to make the purchase by giving them time to develop internal financial models they need to be able to purchase the product, thus shortening the overall sell cycle.
- Finally, through the Cures Act,<sup>101</sup> Congress directed FDA to provide guidance on the types of healthcare economic information that can be provided to customers through distribution of evidence dossiers, reprints from peer-reviewed journals, software packages comprising a model with user manual, budget-impact models, slide presentations, payer brochures, etc.

In general, FDA anticipates that PBMs, health plans and other entities will review this information through deliberation as part of their process of clinical and financial oversight of selecting appropriate drugs for coverage and reimbursement.

FDA also advises manufacturers that present such information to identify and clearly acknowledge any weaknesses or limitations of the data. While drug companies may prefer not to do so, these frank observations about data quality demonstrate the company’s understanding of the importance of robust evidence and often lead to the PBM/health plan being more willing to take subsequent meetings with the company.

## 3. Build an evidence plan

Successful market entry demands continuous, “end-to-end” evidence development and strategic communication across the product lifecycle. As the drug company listens deeply to customers’ needs and responds with effective solutions, it should develop and communicate new, robust evidence of clinical effectiveness appropriate to each stage of product commercialisation. Deloitte’s life sciences and healthcare consulting practice, ConvergeHEALTH recently developed a useful graphic to help demonstrate the importance of continuous evidence development, presented here as Figure 8.



Source: Deloitte analysis

Figure 8

#### 4. Conduct a thorough legal and regulatory assessment, including an analysis of the risk of regulatory noncompliance and trends in enforcement

Drug companies should conduct an in-depth assessment of the legal and regulatory landscape in the markets they target for new product entry. In the US, a complex web of federal and state laws, licensing requirements, mandatory coverage regulations, inconsistent coverage and formulary placement by PBMs and health plans, etc. will all be relevant factors to consider.

Companies already familiar with US market dynamics through their experience with other commercial products should nonetheless confirm their understanding of specific requirements applicable to the new product class and intended use. If competitors have already entered the market with similar products, analysis of publicly available information on their product and any legal or regulatory hurdles that they may have faced would be instructive.

For example, if the government were to change the way Medicare pays for physician-administered drugs by moving them into Part D, how would that affect pricing for a product that is currently reimbursed at an appropriate rate under Part B? Drug companies should conduct these types of risk analyses early in the product commercialisation cycle.

#### 5. Understand changing market dynamics

Continued focus on improving treatment outcomes while also reducing cost is forcing stakeholders throughout the drug channel to bring innovative solutions to their customers; innovation that eventually sparks both new competition and new regulation. Drug makers that proactively monitor these market dynamics will be well-positioned to set the standard for future innovation by introducing new products and services that meet the changing needs of customers within a changing regulatory environment.

For example, renal dialysis has become a major area of growth in the US because the prevalence of diabetes and other kidney diseases has exploded. Now the seventh-leading cause of death in the country, diabetes affects 30 million Americans, or more than 9 per cent of the population. Another 84 million Americans have pre-diabetes, a condition that can lead to Type 2 diabetes within five years. More than 1.5 million new cases of diabetes are diagnosed each year.<sup>102</sup>

Trends suggest that an increasing number of people require kidney dialysis earlier in their lives and for a longer period of time. Because the Medicare Program has reduced payment for dialysis in the hospital, fewer and fewer hospitals are offering these services.

Renal dialysis is treatment-intensive, requiring about four hours a day, three times a week.

By monitoring market dynamics, dialysis providers Fresenius and DaVita anticipated the need to deliver affordable, intensive services at convenient times and locations for a rapidly growing population, and have opened smaller facilities located in the community, in shopping centers and strip malls that are more convenient for patients to get to, relatively inexpensive to build, and profitable to operate.

## **6. Develop a network of advocates among thought leaders and patients; engage them as “partners,” not “customers”**

Increasingly, drug companies need strong support from clinical thought leaders and from the patient community to advocate for accelerated approval and broad commercial availability of expensive new drugs.

Following is one remarkable example. In 2016, Sarepta Therapeutics submitted a new drug application (“NDA”) for Exondys 51 injection (eteplirsen) for the treatment of progressive muscle wasting associated with Duchenne muscular dystrophy.

As part of its routine drug review and approval process, FDA convened a clinical advisory panel to study the data submitted in the NDA and recommend whether it should be approved for commercial use. Panel meetings are open to the public. At the Exondys meeting, the panel recommended that the drug not be approved because the available evidence was insufficient to demonstrate the drug’s effectiveness. While not required to do so, FDA generally follows the recommendations of their advisory panels.

Members of the Duchenne patient advocacy community were furious and engaged in heated debate with the panel both at the meeting and in the press.

Despite the panel’s recommendation, and at least in part because advocates from the Duchenne patient community had objected so strongly, FDA ultimately approved the drug for commercial use, with the caveat that the company collect additional postmarket data.

Sarepta priced the product at \$300,000 for a one year supply. Even though the number of patients is very small, health plans refused to pay such a high price for the drug, creating a situation where the drug was available, but not affordable. In response, clinical thought leaders and patients and their families met with health plans repeatedly to appeal the decision to refuse payment. Because of this intensive advocacy work, an increasing number of health plans will now pay for the drug.

## **7. Provide tools to measure and report product-related treatment outcomes**

Drug manufacturers should develop tools to help their customers measure and report the clinical and economic impact of product use. Was the product clinically effective? Did its use reduce downstream treatment costs? Despite its high price, was the product cost-effective?

If the manufacturer can provide an easy-to-use tool to capture and analyse this data in a manner that customers can use, they can report it to formulary committees, health plans and other stakeholders. In addition, the manufacturer can use this real world evidence to support price setting decisions and to strengthen its position in rebate negotiations with PBMs.

## **8. Consider new models for pricing and contracting**

Increasingly, PBMs and health plans ask drug companies to assume some or all of the financial risk associated with ineffective treatment. Especially in cases of ultrahigh cost

specialty drugs, PBMs and health plans have demanded these arrangements as a condition of purchase. In these cases, manufacturers sell the product at full cost and then rebate the agreed amounts for the number of cases where specific treatment outcomes were not achieved.

Proposing new pricing and contracting models can help differentiate products from their competitors, but there can be risk associated with their use. For example, how is an episode of care defined? What is the appropriate performance metric? Is the treatment population comparable to the population(s) that the drug company has studied? Will the treatment effect be comparable?

Manufacturers should examine new pricing and contracting models and may be forced into accepting these types of agreements in order to access the market, but successful risk-based contracting demands careful analysis of multiple factors and sharing a considerable amount of data between the parties.

## 9. Take the long view, then take the short view

Successful market access strategies require commitment to and investment in developing assets that the company can leverage to adapt to new market dynamics and shorten the time to reach peak sales. By understanding or anticipating the clinical and economic evidence, the level of experience with product use in real world medical practice, the clinical and patient advocates needed to be successful, companies can work backwards from the ultimate goal to plan a process to develop such assets in efficient, priority order. For example, a company may intend to enter the US market (the “long view”), but find that, despite the ability to commit significant time and money, the regulatory and competitive hurdles are too high to overcome. Rather than waste these resources, the company might target smaller markets with lower barriers to enter first (the “short view”) where it can build the assets (data, experience, customer relationships) necessary to enter US market later. This type of process can significantly shorten the time that the company would otherwise have needed to achieve market share.

## 10. Do not underinvest

As a corollary to the principal above, the company that chooses to enter smaller, less complex markets first must nonetheless invest sufficient resources to be successful in those markets, and to generate an early revenue stream that builds the confidence needed to leverage the assets developed there in subsequent complex markets.

\* \* \*

## Endnotes

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14. 26 USC § 7421.
15. Art 1 § 8, cl 1.
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18. 26 USC § 5000(A)(a).
19. US Department of Labor. Definition of “Employer” under Section 3(5) of ERISA-Association Health Plans. 83 Fed Reg 28912. June 21, 2018. *Available at:* <https://www.federalregister.gov/documents/2018/06/21/2018-12992/definition-of-employer-under-section-35-of-erisa-association-health-plans>.
20. 42 USC § 201.
21. The FDA website, [www.fda.gov](http://www.fda.gov) provides access to detailed information on US regulations, guidance documents for industry on FDA policies and procedures, information about the safety and effectiveness of specific products, and directions for reporting adverse health events related to the use of specific medical products, cosmetics, foods or tobacco.
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23. 21 USC 9 § 301-399(d).
24. 21 CFR § 312.34.
25. 21 USC 301 *et seq.*
26. Checklist for evaluating whether a clinical trial or study is an Applicable Clinical Trial (“ACT”) under 42 CFR 11.22(b). *Available at:* [https://prsinfo.clinicaltrials.gov/ACT\\_Checklist.pdf](https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf).
27. 42 USC 282(j).
28. 21 USC § 355(j) *et seq.*
29. 42 USC § 1301 *et seq.*
30. 21 USC § 379g(3).

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32. Or, in the case of a generic drug application (“ANDA”), evidence of bioequivalence to an approved reference drug.
33. 21 USC 301 *et seq.*
34. 21 CFR § 201.100(d).
35. 21 CFR § 202.1.
36. See: *Amarin Pharma Inc. v. FDA*, 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015).
37. Any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components of the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug. Such analysis may be comparative to the use of another drug, to another healthcare intervention, or to no intervention.
38. *Id.*
39. 42 USC § 1395 *et seq.*
40. Detailed information on both the Medicare and Medicaid Programs, including regulations, operating manuals, coverage, coding and payment information for healthcare products and services can be found at the CMS website: <https://www.cms.gov>. CMS is headquartered in Baltimore, MD.
41. An amount paid on a monthly basis to qualify for Medicare and other health insurance plans.
42. An amount paid by the beneficiary out of pocket before the health insurance plan begins to cover healthcare expenses.
43. Medicare providers agree to accept a discounted Medicare payment as payment in full for covered services. As such, they may not “balance bill”, or charge the beneficiary for their fees above what Medicare has paid.
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45. 42 USC § 1395w-101 *et seq.*
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47. When Part D was first passed in 2003, the benefit was structured with a so-called “donut hole” in drug coverage in order to reduce the overall cost of implementing the programme. Initially, the beneficiary (1) paid for outpatient prescription drugs out of pocket until meeting an annual deductible amount. Then, (2) he or she entered the “initial coverage period” during which they paid a percentage of drug costs up to a cap. (3) At this point, they entered the “coverage gap” where they were responsible for 100 per cent of drug costs until they reached (4) catastrophic coverage where

Part D paid 100 per cent of charges. The Affordable Care Act requires the federal government to close the coverage gap in phases. It will be eliminated in CY 2020, when the beneficiary will pay 25 per cent co-insurance for outpatient prescription drugs.

48. ‘Best price’ means, with respect to a single-source drug or innovator multiple-source drug of a manufacturer (including the lowest price available to any entity for any such drug of a manufacturer that is sold under a new drug application approved under section 505(c) of the Federal Food, Drug and Cosmetic Act), the lowest price available from the manufacturer during the rebate period to any wholesaler, retailer, provider, health maintenance organisation, nonprofit entity, or governmental entity within the US”.
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## Glossary

**Actual acquisition cost (“AAC”).** Defined in federal regulations (42 CFR 447.502) as a state Medicaid agency’s determination of the pharmacy providers’ actual prices paid to acquire drug products marketed or sold by specific manufacturers.

**Average manufacturer price (“AMP”).** The average price paid to the manufacturer for the drug in the United States by wholesalers for drugs distributed to retail community pharmacies and retail community pharmacies that purchase drugs directly from the manufacturer. The calculation of AMP excludes the prices paid by certain payers (e.g., Department of Veterans’ Affairs, Department of Defense, or Federal Supply Schedule) and providers (e.g., hospitals, long-term care facilities, mail order pharmacies, or managed care organisations) and certain discounts to wholesalers (e.g., prompt pay or *bona fide* service fees). In the February 2016 final Medicaid drug rule [CMS-2345-FC], CMS provides detailed technical guidance related to the calculation of AMP.

**Average wholesale price (“AWP”).** List price from a wholesaler to a pharmacy. AWP for drugs are reported by pharmaceutical manufacturers and published in commercial clearinghouses such as Redbook, MediSpan, First DataBank, and Elsevier Gold Standard.

**Best price.** The lowest price available to any wholesaler, retailer, provider, or paying entity excluding certain governmental payers such as the Indian Health Service, Department of Veterans’ Affairs, Department of Defense, Public Health Service (including 340B), Federal Supply Schedule and Medicare Part D plans.

**List price:** Most often the wholesaler acquisition cost (“WAC”) is reported as the list price of a medicine. Typically, this price influences the final price paid at the pharmacy, but is often not the exact price. Intermediary markups and the design of the individual’s health insurance plan influences the actual price paid by the individual and the insurance plan.

**Outpatient prescription drug.** Drug obtained with a prescription and typically dispensed from a retail or other outpatient pharmacy. Outpatient prescription drugs do not include drugs provided as part of or incident to and in the same setting as inpatient and outpatient hospital services, hospice services, dental services, nursing facility and intermediate care facility services, and physician services (e.g., physician administered drugs).

**Wholesale acquisition cost (“WAC”).** Price paid by a wholesaler for a drug purchased from the wholesaler’s supplier, typically the manufacturer of the drug. WAC amounts may not reflect all available discounts, such as prompt-pay (cash) discounts.

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