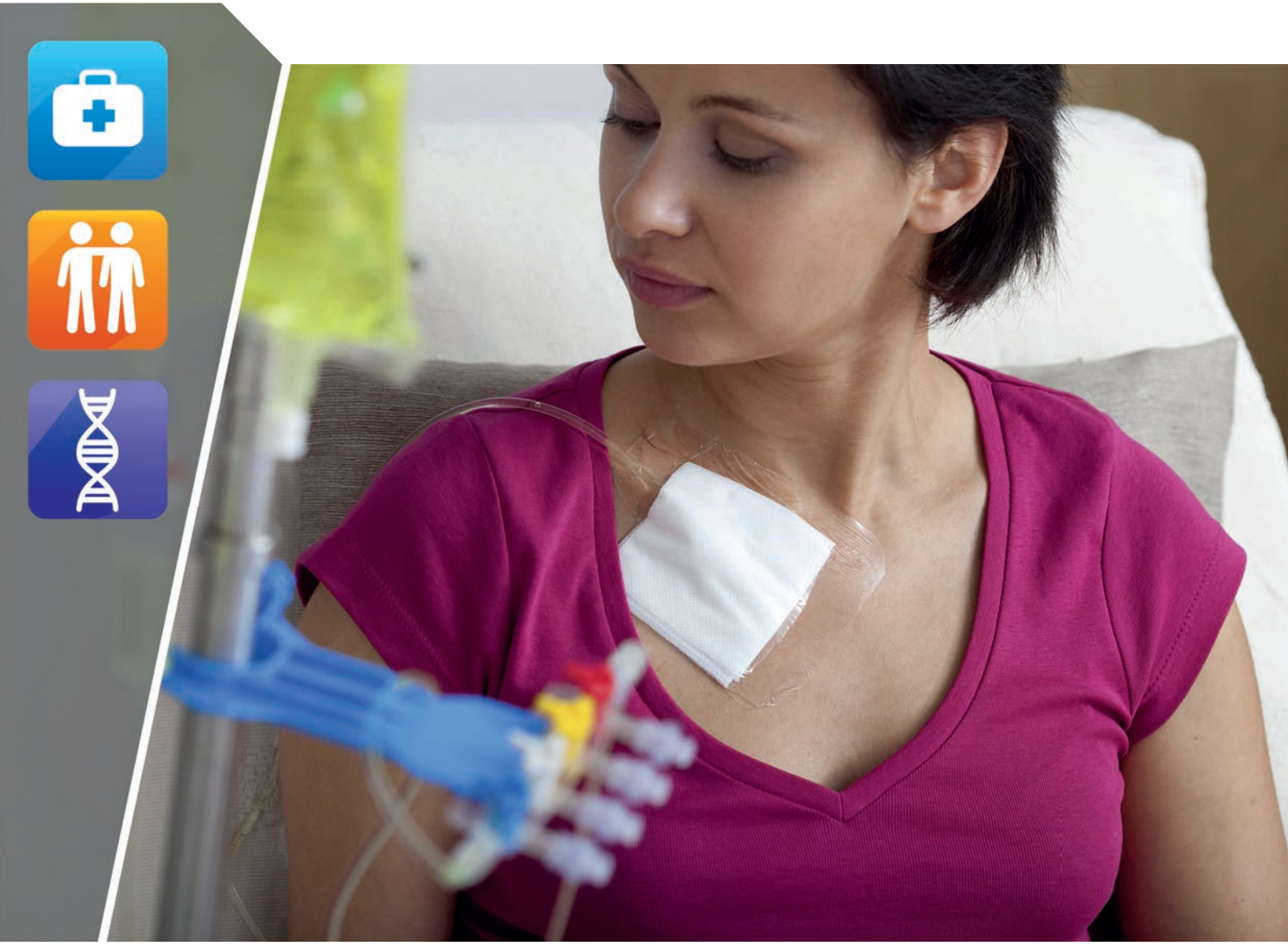
OECD Health Policy Studies

Pharmaceutical Innovation and Access to Medicines



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Foreword

Medicines have delivered tremendous progress in recent decades. They have improved survival and quality of life for many patients and changed the course of diseases such as HIV, certain cancers and more recently, hepatitis C. As a key element of preventive, curative and palliative care, appropriate use of medicines can prevent costly complications and help avoid downstream health care costs. These advances have been brought to us by a global industry whose research and development to sustain this innovation, borne mainly by private enterprises and investors, is costly, time-consuming and risk-prone.

Despite this, policy makers and other stakeholders have become increasingly concerned about the outputs of the pharmaceutical innovation system. Many new drugs, often targeting small populations, enter the market with very high prices, making affordable access to them difficult for both payers and patients. The arrival of very effective but expensive drugs with high budget impact - such as those for hepatitis C - have left countries ill-prepared to respond to this challenge. At the same time, the expected market rewards for the development of new drugs for unmet medical needs – such as new antimicrobials and some drugs for rare diseases – are sometimes insufficient to incentivise the needed R&D. Finally, R&D costs and pricing structures are often opaque, raising legitimate questions about the value offered by some increasingly costly new treatments.

Over time, these issues have affected the trust some payers and other stakeholders have in the pharmaceutical innovation system. Strengthening stakeholders' understanding of how the pharmaceutical market works, and moving the debate from a 'panic' reaction to high prices to a more comprehensive assessment of how the market can be made to work better for patients, payers and producers, is necessary to a future system that delivers the right innovations, to the right patients, at the right prices.

The OECD received a request from France in 2016, subsequently confirmed by Health Ministers of its member countries, to assess the best available evidence, and to identify policy options to address these challenges. In preparing this report, the OECD Secretariat undertook wide-ranging and extensive stakeholder consultations – with policy-makers, the pharmaceutical industry, patient groups, health professionals, and NGOs – and received invaluable contributions from many national and international experts in pharmaceutical policy.

This report identifies a web of interrelated factors that often make health systems unable to ensure patients have appropriate access to innovative medicines at reasonable cost. Given the complex context, the report does not present firm policy recommendations. Rather, it identifies a number of key policy options for policy makers to consider in order to improve the current system, in promoting access while continuing to provide appropriate incentives for developing the next generation of products. These policy options are guided by five objectives: i) to increase the value of pharmaceutical spending;

ii) to ensure access to medicines in countries with different levels of development; iii) to support a system with transparent and well-established rules; iv) to foster competition in on-patent and off-patent markets; and v) to promote better dialogue among stakeholders. Some options – such as harmonisation and cooperation in regulation and health technology assessment – require international cooperation, while others – such as defining transparent criteria for coverage and pricing policies or optimising the use of managed entry agreements – are within the remit of individual countries. We trust this report will contribute to informed and constructive dialogue among stakeholders, and support a shared objective of encouraging the continued development of innovative medicines that bring value to health systems and societies.

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In preparation of this report, the OECD Secretariat engaged in extensive consultations with a broad range of stakeholders and experts. The Secretariat organised two meetings with a high-level expert group advising its work, a consultation with experts from national governments, three consultations with the Business and Industry Advisory Committee to the OECD (BIAC), a consultation with the Trade Union Advisory Committee to the OECD (TUAC), a consultation with representatives of civil society (including, among other organisations, non-government organisations, professional associations, patient associations and academics), as well as an online consultation open to the general public. Meetings were also held with groups representing patients, healthcare providers, insurers, business, and NGOs. We would like to thank all contributors to these various consultations for their valuable input. Finally, this work benefited from financial support from France.

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Acronyms and abbreviations

AHRQ	Agency for Healthcare Research and Quality (United States)
AIFA	Agenzia Italiana del Farmaco (Italian Medicines Agency)
AMC	Advance market commitment
AMR	Anti-microbial resistance
APEC-LSIF	Asia-Pacific Economic Cooperation - Life Sciences Innovation Forum
ASM	United States Census Annual Survey of Manufacturing
ASP	Average sales price (United States)
AUD	Australian dollars
AZT	Zidovudine also known as azidothymidine
BERD	Business Enterprise Expenditure on R&D
BRDIS	Business R&D and Innovation Survey
CAPM	Capital Asset Pricing Model
CDF	Cancer Drug Fund (United Kingdom)
CEA	Cost effectiveness analysis
CED	Coverage with evidence development
CEESTAHC	Central & Eastern European Society of Technology Assessment in Health Care
CEPS	Comité économique des produits de santé (Economic Committee for Health Products, France)
CML	Chronic myeloid leukaemia
CMS	Centers for Medicare & Medicaid Services (United States)
CoE	Cost of Equity
CoK	Cost of Capital
COMET	Core Outcome Measures in Effectiveness Trials
COMP	Committee on Orphan Medicinal Products (EMA)
DAA	Direct acting anti-viral
DALY	Disability-Adjusted Life Years
DDD	Defined daily dose
DMARD	Biological Disease-Modifying Anti-Rheumatic Drug
DMT	Disease Modifying Therapy
DNDi	Drugs for Neglected Diseases Initiative
DRG	Diagnosis-related group
ECDS	Eastern Caribbean Drug Service
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries & Associations
EHR	Electronic health record

EHRRG	Electronic Health Records Research Group
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
ESRD	End stage renal disease
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
EUR	Euro
FDA	Food & Drug Administration (US)
FFS	Fee for Service
FOSYGA	Fondo de Solidaridad y Garantia (Colombian Solidarity and Guarantee Fund)
FTEs	Full-time equivalents
GBP	Pounds Sterling
GCC/GPP	Gulf Cooperation Council / Group Purchasing Program
GDF	Global Drug Facility
GDP	Gross domestic product
GICS	Global Industry Classification Standard
GP	General practitioner
GVA	Gross value added
HAS	Haute Autorité de Santé (France)
HCV	Hepatitis C virus
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
HS	Horizon scanning
HTA	Health technology assessment
HTAi	Health Technology Assessment International
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonization
ICT	Information and communications technology
ICTRP	International Clinical Trials Registry Platform
IGDRP	International Generic Drug Regulators Programme
IHSP	Italian Horizon Scanning Project
IMI	Innovative Medicines Initiative
INAHTA	International Network of Agencies for Health Technology Assessment
INN	International non-proprietary name
IPRP	International Pharmaceutical Regulators Programme
KCE	Federaal Kenniscentrum voor de gezondheidszorg (Belgian Healthcare Knowledge Centre)
LCA	Least costly alternative
LIS	Legemiddleinnkjøpssamarbeid (Norwegian Drug Procurement Cooperation)
LMICs	Low- and middle-income countries
LoE	Loss of exclusivity
LSDP	Life Saving Drugs Program (Australia)
MA-PD	Medicare Advantage - Prescription Drug plan (United States)

MCDA	Multi-criteria decision analysis
MEA	Managed entry agreement
MPP	Medicines Patent Pool
MRFF	Medical Research Future Fund (Australia)
NAICS	North American Industry Classification System
NAS	New active substance
NCE	New chemical entity
NDA	New drug approval
NGO	Non-government organisation
NHS	National Health Service (United Kingdom)
NICE	National Institute for Health & Care Excellence (United Kingdom)
NIH	National Institutes of Health (United States)
NIHR	National Institute for Health Research (United Kingdom)
NME	New molecular entity
NOK	Norwegian Krone
NPV	Net present value
NSF	National Science Foundation
NTD	Neglected tropical disease
OECD	Organisation for Economic Co-operation & Development
OFT	Office of Fair Trading (United Kingdom)
OHDS	Observational Health Data Sciences and Informatics
OMPs	Orphan medical products
OTC	Over the counter
P&T	Pharmacy and therapeutics
P4P	Pay for performance
PAH	Pulmonary arterial hypertension
PAHO	Pan American Health Organisation
PANDRH	Pan American Network for Drug Regulatory Harmonization
PaRR	Policy and Regulatory Report database
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PBM	Pharmacy benefit manager
PBS	Pharmaceutical Benefits Scheme (Australia)
PhRMA	Pharmaceutical Research and Manufacturers of America
PMDA	Pharmaceuticals & Medical Devices Agency (Japan)
PDP	Product development partnership
PFS	Progression-free survival
PPP	Public-private partnership
PPRI	Pharmaceutical Pricing & Reimbursement Information
PPRS	Pharmaceutical Price Regulation Scheme (United Kingdom)
QALY	Quality-Adjusted Life Year
R&D	Research and development
RCT	Randomised controlled trial

RedESTA	Red de Evaluación de Tecnologías en Salud de Las Américas (Health Technology Assessments Network for the Americas)
RFP	Request for proposal
RFT	Request for tender
RoA	Return on assets
SEK	Swedish Krona
SME	Small and medium-sized enterprises
SNA	System of National Accounts
SOF/LDV	sofosbuvir /ledipasvir
SOF/VEL	sofosbuvir/velpatasvir
SPA	Special protocol assessment
SRA	Stringent regulatory agency
SRDR	Systematic Review Data Repository
STAN	Structural Analysis
SVR	Sustained viral response
TFEU	Treaty on the Functioning of the European Union
TKI	Tyrosine kinase inhibitor
TLV	The National Dental and Pharmaceutical Benefits Agency (Sweden)
TNF	Tumour necrosis factor
UKPDS	United Kingdom Prospective Diabetes Study
USD	United States dollars
VHI	Voluntary health insurance
WAC	Wholesale acquisition cost (United States)
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

Executive summary

Introduction

In recent decades, novel medicines have not only improved survival rates and quality of life for many patients around the world, they have also changed the natural history of diseases such as HIV and certain cancers. Anti-retroviral therapies have transformed HIV from a terminal illness to a manageable chronic disease, while the once-daily single tablet regimen has simplified the daily lives of patients. In the last 15 years, the 5-year survival rate for patients with chronic myeloid leukaemia has improved from less than 20% to more than 90%, thanks to the advent of a class of drugs known as tyrosine kinase inhibitors (TKIs). With direct acting anti-virals (DAAs), hepatitis C, once the leading indication for liver transplant, is now curable in more than 90% of treated patients with as little as 8-12 weeks of treatment.

Despite these undeniable advances, both policy makers and other stakeholders in many countries have become increasingly concerned about the outputs of the pharmaceutical innovation system. The prices of many novel drugs make affordable access to them very difficult for both payers and patients; the R&D process is costly and complex; the expected market rewards are sometimes insufficient to incentivise the development of some badly-needed products; the costs and pricing structure of the pharmaceutical market are often opaque; and there are legitimate questions about the degree of innovation and value offered by certain increasingly costly new treatments. Over time, these issues have affected the trust some payers and other stakeholders have in the pharmaceutical sector, and at the same time have prompted concern as to whether existing policies can promote the development of major innovations while ensuring sustainable access. Increasingly, there are calls to reform the system.

In 2017 the OECD received a request from Health Ministers of its then 35 member countries to prepare a report that highlights the main challenges governments and other stakeholders are facing in ensuring appropriate access to novel medicines to all those in need, at a reasonable cost, while maintaining incentives to innovate. The purpose of the OECD report is to provide evidence of how well the current system is performing, based on objective measures and evidence-based analyses, and to assess critically policy options for reforming the system.

While this report focuses on medicines, it is important to place its assessment in the broader context of enhancing value for money in the health system as a whole. Indeed most, if not all OECD countries are facing significant challenges to keep health spending under control. Containing health spending, while enhancing access to, and quality of, health services, requires bold action to reduce the waste that permeates health systems. A recent OECD report on "Tackling Wasteful Spending on Health" (OECD, 2017) highlighted that a significant proportion of health spending in OECD countries is at best ineffective, and at worst, wasteful. It suggested ways to address waste in many areas, notably by improving appropriateness of care, and tackling duplication and inefficient

processes. At the same time, the pharmaceutical sector can play an important role in this general effort to improve value for patients, while exploiting all the potential offered by new technologies.

How is the current system performing?

The pharmaceutical industry plays an important role in a number of OECD economies, directly employing more than 1.2 million people, of whom nearly half a million are in the United States. The industry also represents a significant share (0.8-0.9%) of total employment in countries such as Switzerland, Slovenia and Denmark. Among the sectors with the highest R&D-intensity, the industry invests up to around 40% of its gross value added (GVA) in R&D in Japan and the United States. Pharmaceutical industry R&D accounts for 30% of all private R&D in Switzerland and Belgium, and 24-25% in Slovenia and Denmark. Globally, more than three-quarters of all clinical trials of medicines and other health interventions take place in OECD countries.

Pharmaceutical R&D is risk-prone, costly and time-consuming, and although the contribution of the public sector is significant, much of the risk and costs are borne by private enterprises and investors. Successful development of a new medicine takes an average of 10 to 15 years. The probability of obtaining marketing approval for a drug entering phase I clinical trials ranges from 7% to 45%, depending on the type of drug and approval process. The productivity of pharmaceutical R&D, measured as the amount spent per approved medicine, has declined – as it has in other research-intensive industries, partly because "ideas are harder to find". Only a minority of drugs that gain approval achieve commercial success. Of 466 novel active substances launched in the United States between 1991 and 2009, half achieved life-time sales of less than USD 1.5 billion, and only approximately 10% had sales exceeding USD 10 billion.

Retail pharmaceutical spending accounted for 1.4% of GDP across OECD countries in 2016 and for 2% or more in four countries (Greece, Hungary, the United States and Japan). This share has, on average, remained stable over the past decade, while the share in current health spending has decreased from 19.2% in 2006 to 16.5% in 2016. *Total* pharmaceutical spending is actually 9 to 30% higher than that, taking into account drugs dispensed in hospitals or administered in physician settings. In real terms and on average in OECD countries, retail pharmaceutical spending growth has been declining almost every year from a high of 8% growth in 2001 to negative growth rates after 2009 - due in part to the impact of large numbers of patent expiries and the effects of cost-containment policies - before a rebound to growth in 2014. Over this period, real expenditures in other parts of the health system, such as outpatient and inpatient care, continued to grow.

Pharmaceutical spending can represent good value for money in health systems. Beyond the therapeutic value of new products, many relatively inexpensive medicines delay or prevent disease complications and reduce the use of costlier health services. Non-adherence to treatment has been estimated to cost EUR 125 billion in European countries and USD 105 billion in the United States.

However, sustainable access to innovative medicines is a source of growing concern. The high prices of many new medicines are hitting media headlines, as they did some 30 years ago when new HIV treatments were introduced, and a decade ago with breast cancer therapies. Today, concerns about prices and affordability have been driven by a series of events that have shaken the confidence of both payers and patients, and imposed additional stresses on policy makers trying to find a balance between promoting and

rewarding innovation, ensuring access to medicines, and sustaining the viability of health systems.

Four main challenges have been identified:

- Despite a slowdown in growth in the 2000s, pharmaceutical spending has nevertheless increased sharply in some therapeutic areas, such as oncology and certain rare diseases where many new medicines target small population groups and command high prices. While these may well address unmet needs, they often have prices that may not be justified by the health benefits they confer.
- Countries may be ill-prepared for the arrival of novel medicines targeting wide population groups. In 2013, the first of a new class of very effective but expensive drugs known as direct-acting anti-virals (DAAs) for hepatitis C created a shock due to the potential budget impact of treating all infected people. Many countries initially restricted access to the most severely affected patients, creating frustration among patients and clinicians alike. Although subsequent entries of alternative products have created competition on prices and allowed payers to expand eligibility to treatment, the initial shock highlighted the lack of readiness of payers for such events.
- In some countries, sudden, large price increases for off-patent medicines have made important treatments unaffordable for patients.
- Finally, innovation is lacking in certain areas of high-unmet need, such as new antimicrobials, non-vascular dementia, and some rare diseases.

Discussions around some of these issues have been difficult in many countries, and have exposed a fifth challenge: that trust between payers, civil society and pharmaceutical companies has been eroded. Rebuilding confidence among all stakeholders on how the pharmaceutical market works is necessary if they are all to work together to ensure that the system delivers the right innovations, to the right patients, at the right prices in the future.

What could be done to make the system work better for all?

In determining how to address these challenges, this report is guided by five broad principles:

1. **Increasing the value of spending on medicines.** The overall objective is to ensure that maximum value is obtained from the expenditure made. This could lead to reduced (or curtailed) expenditure on low value items and/or increased expenditure on high value items; it may mean seeking to reduce prices (to ensure a desired level of cost effectiveness) or varying payment methods; or it may involve varying the ways in which certain products are deployed within the health care system. While payers may wish to reward innovation explicitly in order to encourage further, effective private investment in research and development (R&D), at the same time they may wish to send clear signals intended to guide investment toward the kinds of innovations that reflect *their* priorities.
2. **Ensuring access in countries at different levels of development.** The most effective way of ensuring that patients in countries at different levels of development can access innovative treatments is to apply differential (or tiered) pricing. Under this paradigm, more affluent countries pay higher prices than

poorer countries and firms are able to earn sufficient profits in affluent countries to make further investments in R&D.

3. **Supporting a rules-based system.** The development and application by public payers of transparent criteria for determining willingness to pay for added health benefits could enable developers to know in advance what level of reward they might expect.
4. **Fostering competition in both on-patent and off-patent markets.** More competition would improve the efficiency of pharmaceutical spending and provide incentives to innovate. On-patent competition is not always possible, even where there are multiple therapies for the same indication, but could be facilitated with appropriate procurement and payment policies.
5. **Promoting better communication and dialogue between payers, policy makers, pharmaceutical companies, and the general public** would increase trust among stakeholders and improve alignment of industry R&D with societal priorities. Policy debates and decisions need to be informed by authoritative information on industry activities, R&D costs and forthcoming products.

This report assesses a number of policy options against these principles. Given the complexity of the pharmaceutical system, there can be no quick fixes, and most – if not all – options offer advantages and disadvantages. It is a matter for countries – individually and in some cases collectively – to decide how these should be balanced. This report does not advocate or recommend any of these policy options; rather, its purpose is to inform a policy debate and facilitate the aggregation of policies into packages that improve the system, so that valued innovations can be developed that are both accessible and affordable. The policy options are described under five broad headings. The underlying analysis supporting these options is presented in the remainder of this report.

A. Involve stakeholders in joint efforts to reduce the costs of R&D and accelerate market access

While companies are continuously seeking efficiency gains in their R&D processes, regulators could work on harmonising approval requirements, accelerating and streamlining evaluation processes, supporting information and work sharing, and in some cases, engaging in mutual recognition across national agencies. Such efforts have the potential to reduce the costs of R&D, promote both faster access for patients and earlier returns for manufacturers. However, to enhance financial sustainability for payers, any such measures would need to be accompanied by reduced prices and concomitant improvements in the value proposition.

- **Harmonising regulatory requirements, and encouraging mutual recognition.** This measure has the potential to reduce the number and costs of clinical trials. The challenge lies in gaining agreement among agencies on appropriate methods and outcome measures.
- **Accelerating market access for medicines with significant potential benefit.** The US Food & Drug Administration (FDA) and the European Medicines Agency (EMA) have already implemented various approval pathways to accelerate access to market for treatments for unmet medical needs. These processes work quite well, though some experts have expressed concerns about manufacturers' compliance with requirements for the submission of post-marketing studies of

medicines approved through these routes. Ensuring compliance and availability of appropriate patient information are essential for this to work for the benefit of patients, payers and industry

B. Increase spending efficiency

Increase spending efficiency in all parts of health systems, including the value and efficiency of spending on both novel and existing medicines. In the pharmaceutical sector, policy makers could consider:

- **Facilitating cooperation in health technology assessment (HTA)**. Many countries use HTA to inform coverage and pricing decisions. HTA is a complex undertaking, requiring appropriate resources and skills. OECD countries have very different capacities in HTA and duplication of effort is widespread. There is thus a rationale for promoting international co-operation in HTA activities, though arguably this may only be feasible at regional level and among countries with similar standards and patterns of care. It also requires agreement among HTA agencies on methods and approaches to be used. Collaboration and cooperation in HTA can potentially reduce administrative costs for agencies and compliance costs for manufacturers, and accelerate access to treatment. However, economic aspects of HTA will always need to be evaluated at national level, informed by local data on burden of disease, resource utilisation, and patterns and costs of care.
- **Encouraging cooperation in price negotiations, contracting or procurement.** Already occurring to some extent (for example, the BeNeLuxA agreement in Europe, the South America/PAHO arrangements), this could increase the bargaining power of buyers, enhance competition among sellers, and impose greater discipline in negotiation and pricing processes through improving the information available to buyers. The idea is to reduce transactions costs in determining prices and/or assessing benefits, thereby benefiting participant countries (by increasing their negotiating power) and manufacturers (by reducing transactions costs). However, countries may need to be of similar income level and/or willingness to pay in order to protect the principle of tiered pricing, or additional agreements will be needed as to how prices should vary across countries.
- **Assess the performance of medicines in routine clinical practice and adjust coverage conditions and prices.** Health system capacity to assess the performance of new technologies in routine practice is increasing. Routinely collected data could be harnessed to evaluate the effectiveness of medicines outside the clinical trial context, and to assess comparative performance. These assessments could inform not only clinical practice guidelines, but also coverage and pricing. This would increase efficiency and value in pharmaceutical spending. The main constraint is methods development; observational studies do not always provide the information needed to assess the impact of a single product.
- **Promoting competition in on-patent markets.** Competing health insurers or pharmacy benefit managers typically use formulary management to foster competition in on-patent markets. Price concessions from pharmaceutical companies are negotiated in exchange for "preferred status" on their formularies; this is associated with lower patient contributions and thereby encourages use of

these medicines. Monopsonist purchasers often do not exploit competition in on-patent markets. Tendering is widely used in off-patent markets or/and for hospital purchases, but is uncommon among patented products. One exception is Norway, which is now tendering by indication in on-patent markets (e.g. medicines for treating hepatitis C). While tender outcomes allow for multiple suppliers – to ensure physicians and patients retain some therapeutic choice and to maintain multiple suppliers in the market – company bids determine which medicine is recommended as the first-line treatment.

- **Exploring bundled payments for episodes of care, for example in oncology**. Such payments offer a single payment, based on the expected costs of a bundle of services used for a clinically-defined episode of care. They are expected to incentivise providers to use the most cost-effective treatment for a given pathology and to negotiate procurement prices with companies. Payments per episode of care are being piloted in oncology in the United States. While thus far these have shown encouraging results in terms of both efficiency and quality of cancer care overall, they do not necessarily give rise to savings in drug costs.
- **Promoting competition in off-patent markets.** Competitive off-patent markets can deliver savings without loss of benefit for patients, by moving prices closer to marginal costs of production and increasing penetration of generics and biosimilars through incentives for prescribers, pharmacists and patients. A number of policies can promote uptake of generics and biosimilars, such as encouraging early entry of new suppliers upon loss of exclusivity (LoE) of originator medicines, streamlining marketing approval, encouraging physician prescribing by international non-proprietary name (INN), strengthening the role of pharmacists, and incentivising and educating patients. In addition, price competition can be fostered by appropriate procurement mechanisms, provided several manufacturers are active in each market segment. Mechanisms to influence the prices of generics could use competitive processes, such as tendering, that aim to balance short- and long-term savings, sustain competition and prevent manufacturers from gaining market dominance, which could lead to higher prices or shortages in the longer run. Sole-supplier arrangements should be avoided, as they can lead to market exit of suppliers, risking security of supply and creating monopolies that might increase prices in the long run. Finally, countries could also implement a system to monitor market dynamics and allow purchasers to report sharp price increases when they occur.

C. Determine willingness to pay for new treatments and health benefits

Governments and public payers could benefit from determining how much they are willing to pay for new treatments or for health benefits. Transparent and procedurally fair processes for defining willingness to pay might help to ensure that coverage and pricing decisions are understood and accepted by all parties. They could also increase the returns from current spending, better align spending with public priorities, improve the bargaining power of national authorities and payers, and provide greater predictability of decisions to the industry. Policy makers could consider:

- **Defining explicit criteria for coverage and pricing.** Willingness to pay for a given drug may legitimately vary across countries and across therapeutic areas (e.g. higher willingness to pay for severe or rare diseases). Criteria considered could include not only cost-effectiveness (to reflect value), but also budget impact

and equity considerations. When determining a 'value-based willingness to pay', countries might also need to consider how the benefits of a new medicine compare with the benefits obtained from the same amount of additional spending on other health interventions or services – particularly when those healthcare services are being funded from the same revenue source. Value-based pricing is appealing in that it enables industry to be rewarded for the most effective medicines and ensures that the development of medicines with low value is not over-compensated. A rules-based process to making coverage and pricing decisions could also provide for resolution mechanisms when negotiations fail to reach agreement (e.g. as in Germany).

- **Special rules when the budget impact is high.** The general principle of pharmaceutical pricing should be to reward good value. But occasionally – as with sofosbuvir (Sovaldi®), a medication used for the treatment of hepatitis C – the combination of extremely high therapeutic value and significant burden of disease led to a potentially explosive budget impact for payers, with negative effects on access. The set of criteria referred to in the previous point could include particular rules, defined in advance, on how to behave in such (albeit generally rare) situations. For example, payers could propose a capped budget and negotiate with the company to supply, within that expenditure cap, all those needing treatment (as was the case in Australia with hepatitis C treatments, for example). They could also propose that payments be phased over several years, in order to accommodate budget cycle constraints. Such policies do not undermine the need to reward innovation appropriately, since the total returns in such cases may still be very high. However, by determining the magnitude and phasing of large expenditures in advance, greater certainty is provided to both manufacturers and payers. Governments and other payers could, for example, begin to consider how they would manage the advent of one or more effective treatments for a highly prevalent condition such as Alzheimer's disease.
- **Optimising the use of Managed Entry Agreements.** Performance-based managed entry agreements are used in many countries but their implementation has not always been ideal, with difficulties in outcome measurement and high administrative overheads. Such agreements could be better utilised, by being limited to products whose effectiveness or cost-effectiveness is highly uncertain at the time of launch, and where the additional evidence can shed light on their value. Outcomes could be better defined and measured, and results shared with the scientific community, prescribers and patients. Ideally, agreements should be designed to incentivise firms to demonstrate the performance of their products. This could, for example, involve setting initially low default prices or partial payments, with price increases or additional payments made if and when evidence demonstrates that pre-defined performance targets have been met. Such agreements have the potential to increase the knowledge base for medical products, and to ensure payers pay for value. They should not, however, supplant randomised control trials as the primary source of evidence from which to assess efficacy, effectiveness, and cost effectiveness.

D. Develop new push and pull incentives for innovation

New push and pull incentives could be developed to encourage innovation in areas of high unmet need, such as antimicrobials, non-vascular dementia and rare diseases. Options include:

- **Developing push incentives targeting product development** addressing unmet medical needs and attaching access conditions to public funding of R&D. The public sector already contributes to R&D funding through various mechanisms (R&D tax credits, direct funding of basic research or of clinical trials, Public-Private Partnerships and Product Development Partnerships). It could prioritise investment in research that is unattractive to the private sector. Where the public sector contributes substantially to the development of specific products, affordable access could be assured through voluntary licencing or patent buy-outs.
- **Exploring alternative pull incentives to encourage R&D addressing unmet medical need.** This is particularly necessary to tackle antimicrobial resistance and rare diseases. The existing system of rewards based on volume of sales cannot work for new antimicrobials, and countries need to explore other mechanisms such as market entry rewards, prizes and advance market commitments.
- **Reviewing orphan drug policies to target more closely areas of unmet medical need.** The number of medicines and indications available to treat rare diseases has been increasing over time. While this is good for patients with rare diseases, orphan designation (with associated advantages) is sometimes granted for products with multiple other indications that generate 'blockbuster' revenues. The development of precision medicine implies that indications will target increasingly small populations, making them potentially eligible to receive advantages arising from orphan drug policies. These advantages often come at a cost to taxpayers, through reduced or absent evaluation fees, tax credits, and extended market exclusivity in some countries. Current trends suggest that these costs will increase, without necessarily spurring development of the types of medicines for which these advantages were originally intended. It may be useful to assess whether existing orphan drug policies are delivering the right incentives and outcomes, and to assess alternative options.

E. Strengthen the information base to better inform policy debates.

Despite the complexity of assessing with precision the costs incurred in successful and unsuccessful product development, both payers and the general public need a better understanding of the costs involved in developing new medicines, how these costs are incurred, and the magnitude of the returns investors and companies earn from these activities. Payers also need intelligence about company pipelines to prepare for the impact of forthcoming treatments on both systems and costs, particularly transformative treatments with high costs and budget impact. Progress in this domain requires action on a broad front, including:

- **Publishing authoritative information on industry activities and the risks, costs and returns from R&D, to better inform policy decisions.** Policy debates are often confounded by contradictory data and polarised views on the role and performance of the industry. Divergent views are legitimate, but the publication of relevant and authoritative information could inform a more constructive debate.

The OECD could mobilise its wide expertise (including in health, innovation and technology and finance) and its privileged relations with governments and industry to develop consensus on relevant indicators and data collection (e.g. primary data collection as well as the use of existing databases).

- **Increasing price transparency in pharmaceutical markets.** Levels of price opacity in pharmaceutical markets are high and increasing, both within and between countries, in part due to the proliferation of confidential agreements between the industry and private and public payers. The disconnect between list prices and transaction prices has a number of drawbacks: high list prices serve as an anchor in all price negotiations; they blur international benchmarking, which is used by many countries; analyses of price trends become uninformative, and manufacturers may be criticised for high list prices that do not apply in reality. Full transparency might be difficult to reconcile with tiered pricing, because the pressure from public opinion in countries with high ability and willingness to pay to reduce prices to match those obtained elsewhere, may be intense. To balance these concerns, a first step would be for purchasers to indicate publicly the existence of pricing agreements on specific products. *Ex-post* and transparent rebates for public payers are another option, which would be compatible with both value-based and tiered pricing.
- **Improving horizon scanning activities and encouraging co-operation at regional level**. A number of countries have recently engaged in horizon scanning activities to better prepare for market launches and adoption of new technologies, sometimes involving regional co-operation. International co-operation in horizon scanning could help improve methods and sharing of information on the R&D pipeline and forthcoming treatments, as well as information on dates of patent expiries and loss of market exclusivity. Companies would benefit from countries being better prepared for the diffusion of new treatments.

Chapter 1. Medicines in health systems and society

This chapter begins by highlighting the benefits medicines bring to patients and health systems. It then describes recent trends in pharmaceutical expenditure and financing, and the different approaches to coverage and pricing used in OECD countries. Finally, it discusses key challenges currently faced by policy-makers – the growing launch prices of new medicines; assessing the value for money of spending in certain therapeutic areas; anticipating the arrival of high cost effective medicines for highly prevalent diseases; sharp price increases in off-patent products; and the potential misalignment of current incentives for development of treatments for rare diseases.

The statistical data for Israel are supplied by and under the responsibility of the relevant Israeli authorities. The use of such data by the OECD is without prejudice to the status of the Golan Heights, East Jerusalem and Israeli settlements in the West Bank under the terms of international law.

Introduction

This chapter reviews the role of medicines in health systems and society, and sets pharmaceutical spending levels and trends in a broader context. It describes the role of governments and other payers in financing these expenditures, as well as pharmaceutical policies related to coverage and pricing of medicines. Lastly, it highlights some of the current challenges in pricing and affordability of medicines. The key findings may be summarised as follows:

- Innovations in medicines have not only improved survival rates and the quality of life for many patients, but have also changed the nature of diseases like HIV and cancer. Pharmaceutical spending often represents good value for money in health systems. Many medicines prevent disease complications and the use of costly health services. Non-adherence to pharmaceutical treatment is estimated to cost EUR 125 billion in European countries and USD 105 billion in the United States.
- In 2016, *retail* pharmaceutical expenditure accounted for 16.5% of current health expenditure, on average, in OECD countries. This represented 1.4% of GDP on average, exceeding 2% of GDP in only four countries (Greece, Japan, Hungary, and the United States). *Total* pharmaceutical spending is estimated at between 9% and 30% higher, taking into account drugs dispensed in hospitals or administered in physician settings.
- Since the onset of the global financial and economic crisis, per capita retail pharmaceutical expenditure has been declining on average in OECD countries by 0.5% per year in real terms, contrasting with 2.3% growth seen during the period 2003-2009. This is largely due to patent expiries of "blockbusters" and cost-containment policies implemented by governments. Conversely, over this period a majority of countries saw continued real expenditure growth in outpatient, inpatient and long-term care, albeit at slower rate than previously.
- Governments or largely publicly-funded health insurance schemes finance nearly 55% of retail pharmaceutical spending in OECD countries and an even higher proportion of expenditure in hospitals. Most OECD countries regulate the price of pharmaceuticals, at least for some market segments, either directly or through defining the conditions for coverage by public payers or social insurance schemes. They use a mix of several instruments, the most common being international benchmarking (basing the price a country pays for a medicine on what other countries are paying) and the use of health technology assessment (HTA) (which may include consideration of economic aspects, such as the cost-effectiveness of the new treatment relative to existing therapies).
- Finally, this chapter highlights a number of challenges countries face regarding the affordability of medicines. First, policy makers, patients and clinicians are increasingly concerned about drug pricing trends; these raise concerns about the future sustainability of health spending and the value of some high-cost new treatments; payers may be ill-prepared for the arrival of new treatments for diseases or conditions of high prevalence; high prices can compromise access; and incentives for the development of orphan medicines have had varying effects.

Pharmaceutical treatments bring significant benefits to patients and society

Medicines play a significant role in the health care system and in society. Approximately half of all adults in OECD countries take prescribed medicines regularly (see for example Chaplin, 2015; National Center for Health Statistics, 2017). Vaccines and antimicrobials that prevent or treat communicable diseases have had a large and measurable effect on the life expectancy of the population as a whole. Many medicines improve the quality of life of patients with chronic diseases – alleviating or preventing pain, disfigurement, functional decline, disability, and premature death. They can have a substantial effect on productivity and prevent absenteeism due to ill-health, and in many cases, can reduce downstream healthcare costs by preventing avoidable complications or delaying disease progression.

Antimicrobials and vaccines have been pivotal in extending life expectancy and reducing the burden of communicable and vaccine preventable diseases. In 2003, Ehreth estimated that globally, vaccination prevented almost 6 million deaths annually, and higher vaccination rates could save another 3 million children's lives (Ehreth, 2003). Antibiotics have not only saved patients' lives, but have also played a role in achieving major advances in medicine and surgery. They have successfully prevented or treated infections in patients undergoing chemotherapy; in those suffering from chronic diseases such as diabetes; in patients who are immunosuppressed (e.g. being treated for autoimmune disorders such as rheumatoid arthritis); and in those undergoing complex procedures such as organ transplant, joint replacement, or cardiac surgery (Ventola, 2015).

Pharmaceutical innovations have changed the management of HIV and more recently, have transformed the treatment of hepatitis C. Life-expectancy post-HIV infection has improved dramatically since the early 1990 due to anti-retrovirals. The life expectancy of treated HIV-positive individuals is now close to that of the general population in the United States and Canada (Lacey et al., 2014). Combined with increased screening and prevention efforts, anti-retroviral treatments have led to a decline in the number of deaths from HIV/AIDS in Australia, Canada, France, Spain and the United States, from a peak in the mid-1990s, by 84% to 90% through 2013-14 (OECD, 2018).

Box 1.1. What is an innovative medicine?

"Innovative" and "innovation" are widely used terms but are rarely defined explicitly. For the purposes of this report a medicine may be described as innovative if it:

- meets a previously unmet or inadequately met, substantive (i.e. non-trivial) health need
- offers enhanced effectiveness (e.g. greater efficacy, reduced toxicity or both) or other incremental benefit (e.g. a substantive improvement in patient convenience) relative to existing therapeutic alternatives.

Conversely, a product that is new or novel, but does not offer additional benefit over existing therapies would not *per se* be considered innovative (Morgan, Lopert and Greyson, 2008; Bruen et al., 2016).

As recently as five years ago, the available treatment options for hepatitis C were associated with debilitating side effects, and achieved sustained viral responses (SVR) in only half of the patients over a course of treatment lasting up to 48 weeks

(Shepherd et al., 2004). Today, a number of treatment options are available offering cure rates of more than 90%, with minimal side effects, in as little as 8 weeks (Asselah, Marcellin and Schinazi, 2018). A study estimated that the implementation of a one-time birth-cohort screening and the use of the new treatments could avert 78 800 cases of liver cancer, 9 900 liver transplants and 126 500 liver-related deaths in the United States by 2050 (Kabiri et al., 2014).

Prescription medicines are a key component of chronic disease management guidelines to reduce the mortality and morbidity burden of many non-communicable diseases. Outcomes for patients with diabetes and cardiovascular disease have improved substantially over the last few decades (OECD, 2015a, 2017a). Across the industrialized world, age-adjusted mortality rates from ischemic heart disease and stroke had declined to about one third of their 1960s baseline by the year 2000, catalysed by advances in both prevention and treatment, including significant declines in cigarette smoking, better hypertension control, widespread use of statins to reduce cholesterol levels, and the development and use of thrombolytics and stents in acute coronary syndromes to limit or prevent infarction (Mensah et al., 2017).

In the United States the age-adjusted annual heart disease mortality rate fell by more than 50% from 1950 to 1996, and by a further 22% from 1990 to 2013 (Mensah et al., 2017). Similar declines were recorded in nearly all regions of the world, particularly in North America and Western Europe, as well as in Japan, Australia, and New Zealand. Coronary heart disease mortality rates in England and Wales decreased by more than 50% between 1981 and 2000. Medical and surgical treatments contributed approximately 21% of total life-years gained during the period, of which 32% were attributable to secondary prevention in patients post myocardial infarction or revascularisation; 13% to heart failure treatments; and 9% to anti-hypertensive therapies (Unal, Critchley and Capewell, 2004; Unal et al., 2005). Cutler, McClellan and Newhouse (1998) estimated that nearly 30% of the decline in 30-day mortality due to heart attacks between 1975 and 1995 could be attributed to pharmaceuticals. A large US study of myocardial infarction in patients aged 65 and over found that mortality had declined by 3% per year between 1995 to 2004, and attributed the observed improvement primarily to increased use of cardiovascular medications (e.g. statins, beta blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, antiplatelet drugs) post discharge (Setoguchi et al., 2008). Finally, the United Kingdom Prospective Diabetes Study (UKPDS) established that retinopathy, nephropathy, and possibly neuropathy can be reduced in people with type 2 diabetes by lowering blood glucose levels through intensive pharmacological therapy. The impact of better glucose control has resulted in life expectancy improving substantially in people with type 1 and type 2 diabetes over recent decades (Miller et al., 2012; Home et al., 2014).

The momentum of biomedical research in rare diseases has resulted in new treatments that have dramatically improved outcomes for patients for whom treatment options had been limited. Ivacaftor, a drug used to treat cystic fibrosis in people with certain mutations present in 4–5% of cases has shown broad benefits of treatment across most outcomes assessed, including lung function and patient reported outcome measures, such as physical and social functioning, health perceptions and vitality (Whiting et al., 2014; Quittner et al., 2015). A decade ago, patients with pulmonary arterial hypertension (PAH) had limited treatment options and many required a lung transplant as their condition worsened. The last decade has seen large gains for these patients with the development of endothelin receptor antagonists. Macitentan, approved in 2013, has been shown to slow disease progression and reduce morbidity from PAH (Pulido et al., 2013). Fifteen years

ago, the treatment of chronic myeloid leukaemia (CML) was dramatically transformed by a new class of medicines known as tyrosine kinase inhibitors (TKIs). Imatinib was the first of several TKIs, and was approved by the FDA in 2001. In patients with CML, the estimated 5-year survival rate has improved from a historical level of less than 20%, to >90% in the TKI era (Woessner, Lim and Deininger, 2011; Kantarjian et al., 2012).

Cancer mortality rates have been declining and five-year survival rates for most cancers have improved over recent decades, reflecting improvements not only in prevention and early detection, but also in treatment. Sun et al. (2010) estimated that overall survival increased by 3.9 years for all cancer combined in the United States between 1988 and 2000, with variations across cancer sites. Survival gains ranged from 0.5 years for pancreatic cancer to 3.5 years for non-Hodgkin's lymphoma and 3.6 years for breast cancer.[1] Improvements in treatment explained about 81% of these survival gains on average. More recently Dubois and Kyle (2016), using data from 11 countries over the period 1990-2011, showed that every new cancer medicine in a country was associated with a decline in cancer mortality of 8% for men and 9% in women. New cancer medicines such as novel immunotherapies offer better survival rates and provide patients with options that in many cases may be more tolerable, thus improving their quality of life. Immune checkpoint inhibitors (nivolumab, pembrolizumab, and atezolizumab) have achieved better survival rates than chemotherapy for patients with advanced non-small-cell lung cancer (Kim, Kim and Kim, 2017). Additionally, many emerging therapeutic options can be taken orally, which can help reduce patients' time in clinics or hospitals.

Prescription medicines not only improve health outcomes for individuals but can also reduce costs in other parts of the health system, by reducing utilisation of health care services, especially hospitals. Khan and Socha-Dietrich (2018) reported that non-adherence may cost European governments as much as 125 billion euros annually in excess health care services and in the United States, USD 105 billion per year of avoidable hospitalisations alone (New England Health Care Institute, 2009; IMS Institute for HealthCare Informatics, 2013; Iuga and McGuire, 2014). Patients with chronic diseases who are non-adherent to their medicines use more secondary care services, such as outpatient care, emergency department visits and hospitalisations, than adherent patients. A large observational study of patients with diabetes, hypertension, high cholesterol and congestive heart failure found that, for all four conditions hospitalisation rates were significantly higher for patients with low medication adherence. Higher levels of adherence were found to be associated with significantly fewer annual inpatient hospital days (Roebuck et al., 2011). Combining the increases in pharmaceutical spending with the decreases in medical spending, average cost-benefit ratios from adherence for the four conditions examined were 1:13 for hypertension, l:9 for congestive heart failure, 1:9 for diabetes, and 1:3 for hyperlipidaemia. Thus just one extra USD spent on medicines for adherent patients with congestive heart failure, high blood pressure, diabetes and high cholesterol can generate between 3 to 13 USD in savings on emergency department visits and inpatient hospitalisations (Roebuck et al., 2011 quoted in Khan and Socha-Dietrich, 2018).

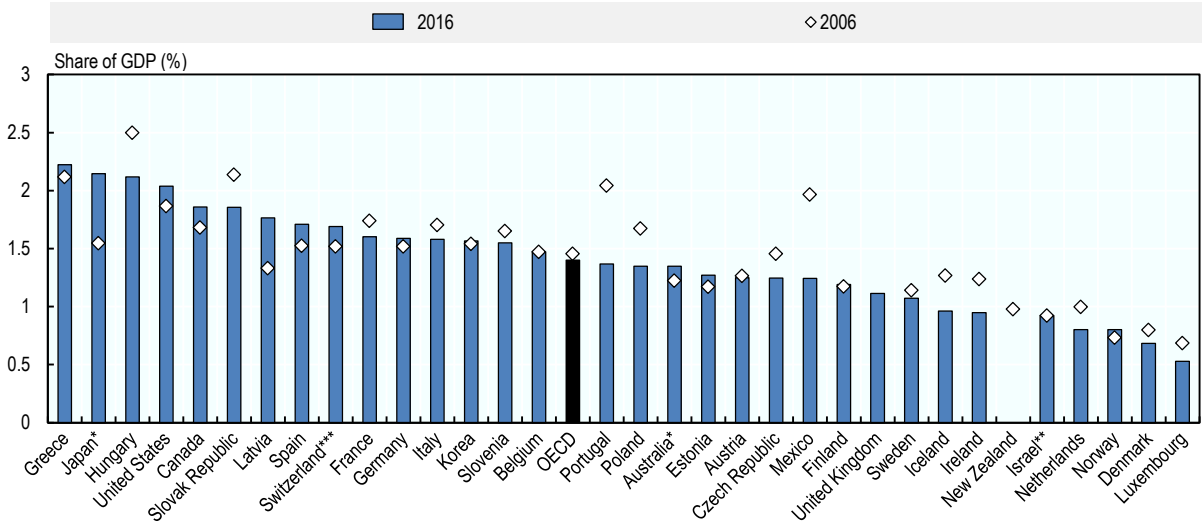
Over the past decade, retail pharmaceutical spending as a share of GDP has been relatively stable in most OECD countries

Retail pharmaceutical spending[2] accounted for 1.4% of GDP across OECD countries in 2016 and has on average remained stable over the past decade. The share of spending in GDP decreased significantly in Mexico, Portugal, Hungary, the Slovak Republic, and

Poland, and increased significantly in Japan and Latvia (Figure 1.1). Retail pharmaceutical expenditure, however, does not provide a full picture of spending for pharmaceuticals. Total expenditure on pharmaceuticals is higher when expenditures for pharmaceuticals used in inpatient care are taken into account (see Figure 1.2). These expenditures account for less than 10% of total pharmaceutical expenditures in some countries (e.g. Korea or Germany) but for 30% or more in countries like Israel, Portugal and Denmark.

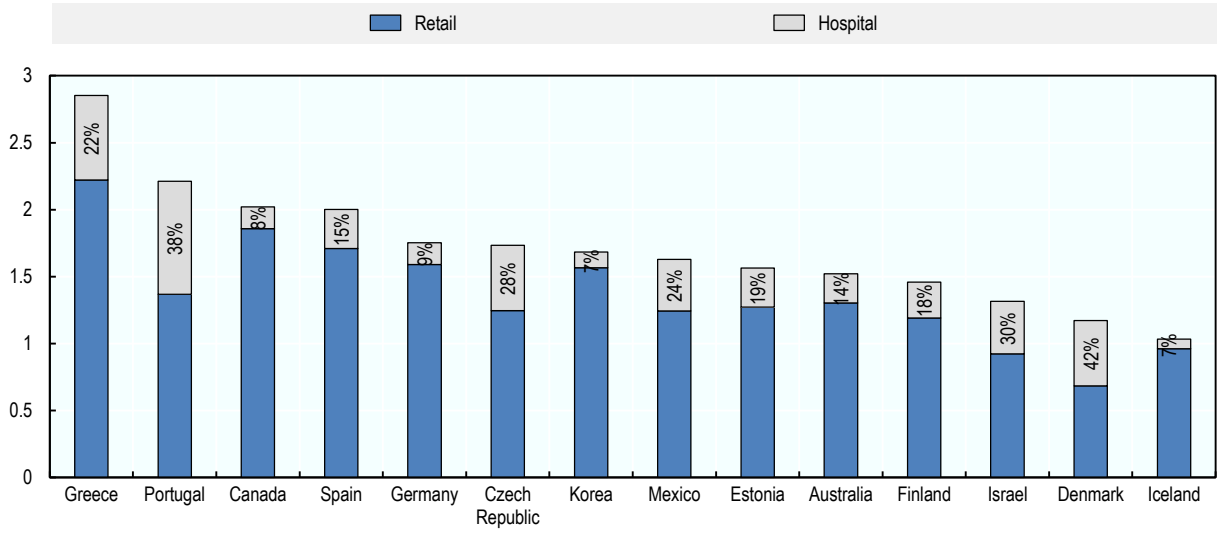
Retail pharmaceutical spending was 16.5% of current health spending in OECD countries in 2016, a decline from 19.2% in 2006. In real terms and on average in OECD countries, retail pharmaceutical spending growth has been declining almost every year from a high 8% growth in 2001 to negative growth rates after 2009, before a rebound to growth in 2014 (see Figure 1.3). Over this period, real expenditures in other parts of the health system, such as outpatient and inpatient care, continued to grow.

Figure 1.1. Retail pharmaceutical expenditure, as a share of GDP, in 2006 and 2016



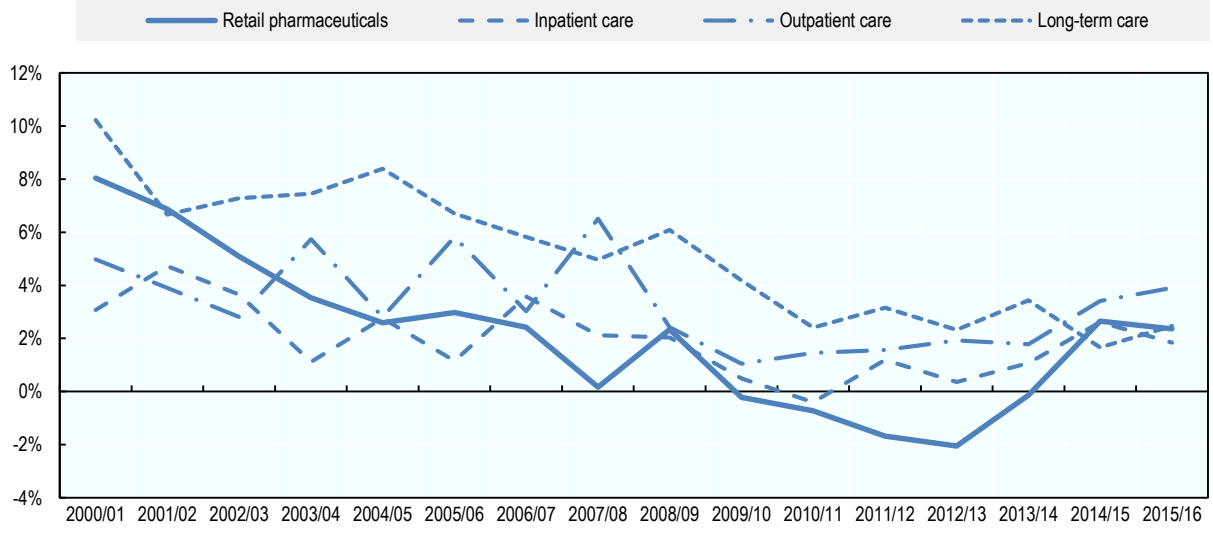
Notes: Retail pharmaceutical expenditure includes medical non-durables, but does not include medicines administered in hospitals.
* latest year available 2015; ** 2014; *** first year available 2010
Source: OECD (2018), *OECD Health Statistics* (database), http://dx.doi.org/10.1787/health-data-en.

Figure 1.2. Total expenditure on pharmaceuticals[1] (retail and hospital[2]), as a share of GDP, in 2016



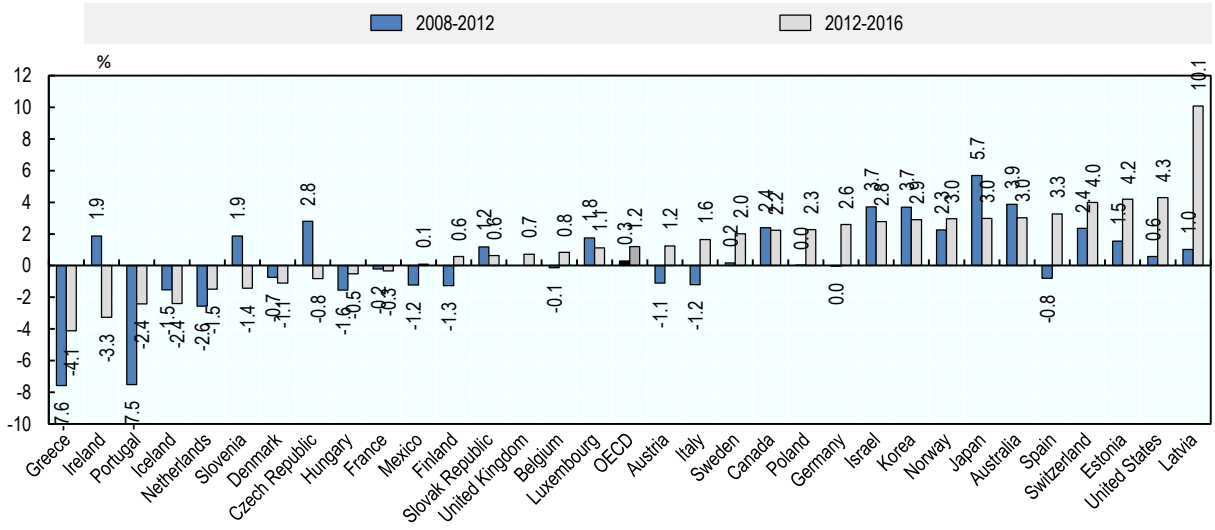
Note: 1. Including medical non-durables. 2. May include spending on pharmaceuticals in other health facilities.
Source: OECD (2018), *OECD Health Statistics* (database), http://dx.doi.org/10.1787/health-data-en.

Figure 1.3. Growth rates of health expenditure for selected services, in real terms, OECD average, 2000-16



Note: Retail pharmaceuticals exclude the costs of pharmaceuticals used as part of an inpatient episode.
Source: OECD (2018), *OECD Health Statistics* (database), http://dx.doi.org/10.1787/health-data-en.

Figure 1.4. Average annual growth in retail pharmaceutical expenditure[1], in real terms, 2008-12 and 2012-16 (or nearest period)



Note: 1. Includes medical non-durables.
Source: OECD (2018), *OECD Health Statistics* (database), http://dx.doi.org/10.1787/health-data-en.

In individual countries, spending trends vary. Since 2008, real spending in retail pharmaceuticals has declined in one third of OECD countries, while it has continued to grow, sometimes moderately, in other countries (Figure 1.4). These trends are explained by both cost-containment measures adopted in the aftermath of the economic crisis and by patent expiry of top-selling products (Belloni, Morgan and Paris, 2016).

"Specialty medicines" account for one-third of pharmaceutical spending

"Specialty medicines" account for an increasing share of global pharmaceutical sales[3] (see Box 1.2). According to QuintilesIMS, the share of specialty medicines increased from 20 to 35% of pharmaceutical sales in the United States between 2007 and 2016; from 15-25% to 35-45% in the five largest European markets; and from 12-16% to 18-35% in South Korea, Japan, Canada and Australia. The proportion of specialty medicines is expected to further increase (QuintilesIMS Institute, 2016).

The growing share of expenditure attributable to "specialty medicines" arguably reflects the combined effects of therapeutic progress and market dynamics (e.g. loss of market exclusivity and generic competition). For example, Figure 1.5 shows changes in market shares by drug class from 1995 to 2015 in France. In the 1990s, anti-hypertensives and other drugs for cardiovascular diseases accounted for about 20% of pharmaceutical spending. Today, despite a continuous increase in consumption, they represent only a small proportion of spending (about 5%). In contrast, expenditures in oncology, autoimmune disorders and hepatitis C were much smaller in the early nineties with fewer, and less expensive treatments, and have grown steadily in the last ten years.

Although the increasing share of "specialty medicines" in pharmaceutical spending has raised concerns about the sustainability and efficiency of pharmaceutical spending, it should not be seen as a problem *per se*. As long as new products bring benefits to patients and represent value for health systems, paying for them may be a good investment.

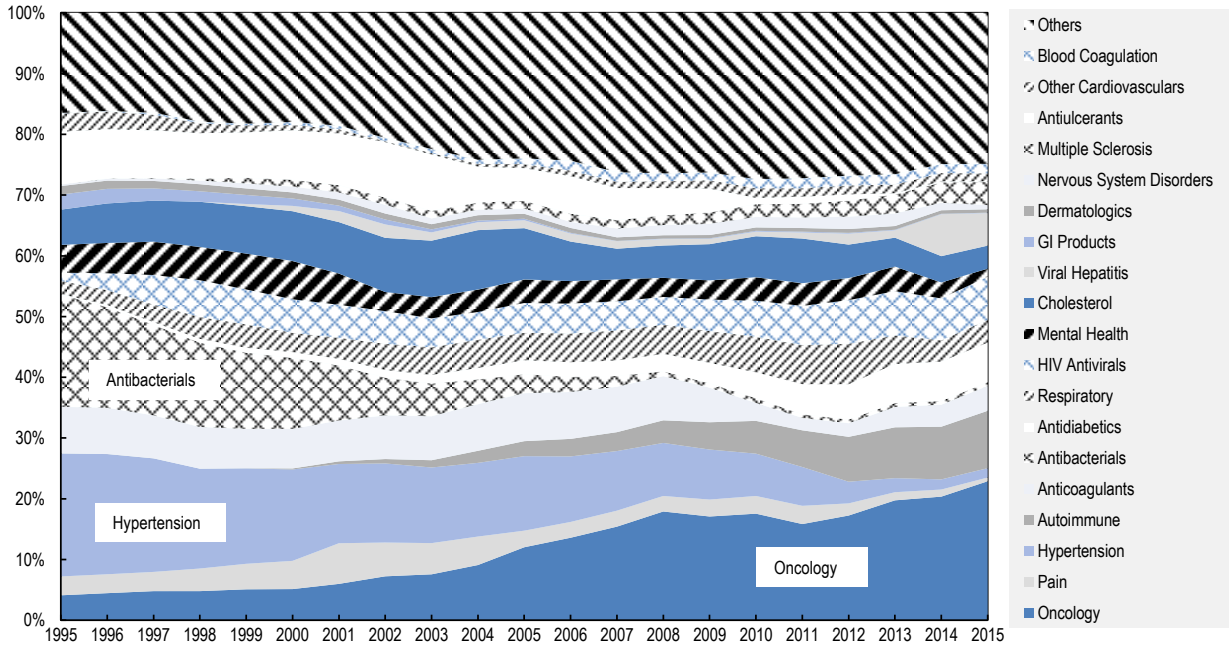
Box 1.2. Specialty medicines – definition

"Specialty medicine" is a term mainly used in the United States. However, there is no standard definition and the scope of drugs included in this group varies across stakeholders (ASPE, 2016). That said, the term usually refers to injectable and non-injectable drugs that are typically used to treat chronic, complex conditions and may have one or more of the following characteristics: a requirement for frequent dose adjustment or intensive clinical monitoring; intensive patient training and compliance assistance; limited distribution; and specialised handling or administration. Specialty medicines are mainly used in cancer, rheumatoid arthritis, haemophilia, HIV/AIDS, psoriasis, inflammatory bowel disease and multiple sclerosis.

Several definitions also include price as a key criterion. For Quintiles IMS, for whom medicines with list prices in excess of USD 6 000 per patient per year are likely to be classified as specialty medicines, the share of pharmaceutical sales[4] (IMS off-invoice data) accounted for by specialty medicines in the United States in 2016 was about 40%, albeit representing a volume of only 1-3% of prescriptions. The proportion was higher in the non-retail market (58%) than in the retail and mail-order market (32.5%) (QuintilesIMS, 2017).

Using the threshold of USD 600 per month (actual price) defined by CMS for inclusion of medicines in the specialty-tier of Medicare formularies, the share of retail expenditure represented by so-called "high-cost drugs" was 22% in 2015 (ASPE, 2016).

Figure 1.5. Composition of drug expenditure by drug class in France 1995-2015



Source: QuintilesIMS MIDAS, Quintiles IMS Institute, September 2016

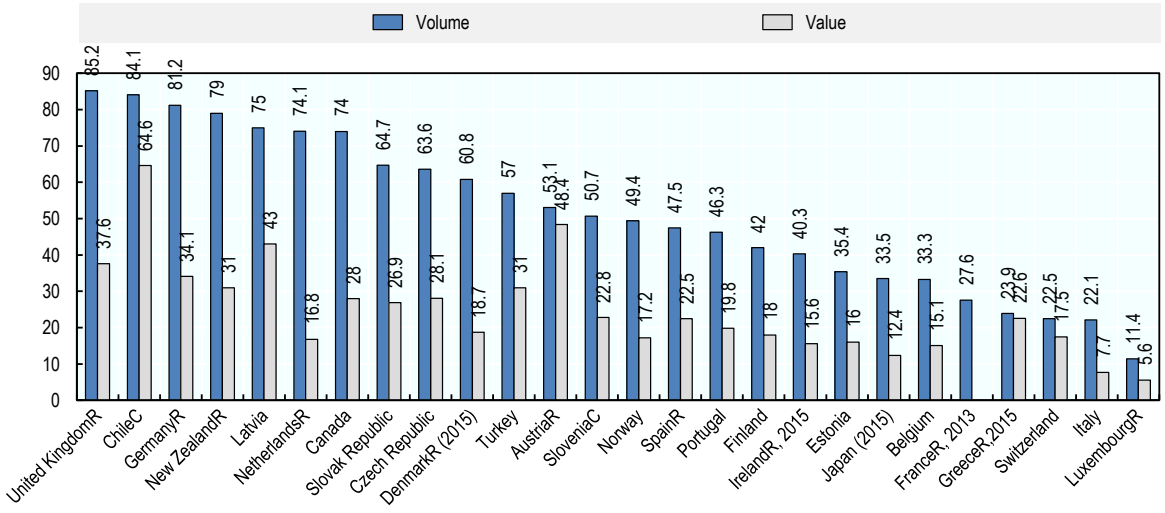
Competition has helped contain pharmaceutical costs and improve access

In pharmaceutical markets, products can compete on quality or prices. Competition in off-patent markets usually reduces prices while both the existence and the effect of competition between patented drugs varies across settings and therapeutic areas.

Competition in off-patent markets drives prices down

Generic entry at the end of patent term offers opportunities to reduce costs without affecting the quality of care. In the United States, for instance, where the generic market is very dynamic, generic drugs generate significant savings, estimated at USD 1.68 trillion in the last decade (Uhl, 2017). Yet, in a number of OECD countries, there remains untapped potential for greater generic competition (see Figure 1.6), due in part to regulation and stakeholder reluctance (see OECD, 2017c).

Figure 1.6. Share of generics in the total pharmaceutical market, 2016 (or nearest year)



R. Reimbursed pharmaceutical market. C. Community pharmacy market.
Note: Depending on sources used by individual countries, "value" in this figure refers to market sales or to pharmaceutical expenditures. Volumes correspond to the number of DDD, or the number of prescriptions/items dispensed.
Source: OECD (2018), *OECD Health Statistics* (database), http://dx.doi.org/10.1787/health-data-en.

Biologic medicines represent a growing proportion of pharmaceutical sales (prescription medicines and OTC) and this share is predicted to increase from 24% in 2015 to 29% in 2022 (EvaluatePharma, 2016). Several biologics have just begun to go off-patent in the past decade and the current size of the biologics market losing patent exclusivity between 2015 and 2020 is significant (IMS Institute for Healthcare Informatics, 2016b). The introduction of biosimilars is at various stages in OECD countries, and it has already and should continue to yield savings for health systems (Belloni, Morgan and Paris, 2016). However, this savings potential is not as high as with small molecule generics, due to longer and costly development and production processes for biologics and biosimilars. Price discounts of biosimilars are thus far in the range of 15-40% versus up to 85% for generics (Paris and Belloni, 2014; FDA, 2015; Harris, 2016; Simon Kucher, 2016; OECD, 2017d).

The uptake of biosimilars has been slow due a number of challenges, such as the complexity of the manufacturing process, which relies on reverse engineering, uncertainty around the timing of market entry (for example due to extensions of market exclusivity granted to originators as incentives for the development of paediatric indications), and both clinical and regulatory constraints on interchangeability and substitution in many countries (Moorkens et al., 2016). Payers, regulators, physicians, and patients have all expressed concern regarding biosimilar substitutability, particularly in light of the issues inherent in the biologics production process itself, and the severity of many conditions treated by biologics (ACS CAN, 2013). Such concerns are beginning to wane, as evidence of early experiences with substitution (and even switching) of biosimilar products has raised no cause for clinical concern (Jørgensen et al., 2017). Biosimilar penetration varies widely across OECD countries, for example from 4% for infliximab in France to 98% for filgrastim in the United Kingdom in 2015 (Simon Kucher, 2016). In 2015, biosimilars had 100% of the epoetin market share in Finland, Hungary, Poland, the Slovak Republic and the Czech Republic, but only 2% in Belgium and 6% in the United Kingdom. For TNF inhibitors, biosimilars had 90% and 82% of the market share in Denmark and Norway respectively, but only 2% in Switzerland and 5% in Belgium and Ireland (OECD, 2017a).

The opportunity for cost savings from increased generic and biosimilar uptake remains substantial. A wide array of policies can increase uptake, such as encouraging early entry, competitive pricing, encouraging physician prescribing, increasing the role of the pharmacists, and incentivising and educating patients (see Chapter 3). According to QuintilesIMS (2016), expected savings from loss of market exclusivity in the United States alone could amount to as much as USD 143.5 billion in the period 2017-2021, substantially more than the USD 91.1 billion achieved between 2012 and 2016.

The impact of competition in on-patent markets varies across settings and therapeutic areas

The effects of competition in on-patent markets on prices and volumes vary across therapeutic classes and across countries. Medicines with similar mechanisms of action and indications are not usually interchangeable but often constitute reasonable treatment alternatives for a given condition. Thus in competitive markets, the existence of multiple products in a homogeneous therapeutic class might be expected not only to drive prices down but also to increase use through expansion of the eligible population and increased promotional efforts. Evidence of the effects of such oligopolistic competition in OECD countries, however, remains unclear. One study of the peptic ulcer and gastroesophageal reflux disease market (mainly H_2-antagonists and proton pump inhibitors) in the United States between 1991 and 2001 suggested that “me-too” drugs competed on price, but also increased use and spending (Arcidiacono et al., 2013). One Canadian study found that manufacturers of brand-name drugs launched between 1994 and 2003 did not compete on price with other products in the same class until there were 4 or more competitors (Lexchin, 2006). Similarly, a study of 458 new molecules launched in Germany between 1993 to 2008 found that the initial two entrants in a new class expanded the market and competed on quality but not on price, while price competition set in with the third competitor. The authors concluded that this pattern was related to prescriber behaviour (Mueller and Frenzel, 2015).[5] In the United States, PBMs (specialists in managing pharmaceutical spending) and health insurers are able to negotiate rebates in some therapeutic classes in exchange for formulary listing, which results in a form of competition. The impact of this competition, however, remains

unclear, as list prices of some on-patent medicines are increasing at a rapid rate and are not directly related to proportional increases in rebates (see below and Visante, 2017).

Recently, competition has reduced the prices of direct antiviral agents (DAAs) for the treatment of hepatitis C. The first entrant, Gilead's sofosbuvir, entered the US market in 2013 at a list price of USD 84 000, with lower prices in other markets as a result of a tiered-pricing strategy defined by Gilead, linking the price of the medicine to the income level and prevalence of the disease in different countries. Between August 2013 and August 2017, five new single-component DAAs and six new fixed-dosed combinations obtained regulatory approval (Unitaid and WHO, 2017). Competition helped lower prices and the last competitor entered the US market in 2017 with a list price of USD 26 400 per treatment course (before discounts), and a monthly price 30% to 60% lower than those of its competitors (Sagonowsky, 2017). The most recent negotiations in OECD countries with regulated pricing also achieved lower prices thus enabling expanded population coverage (see Box 1.6 later in this chapter).

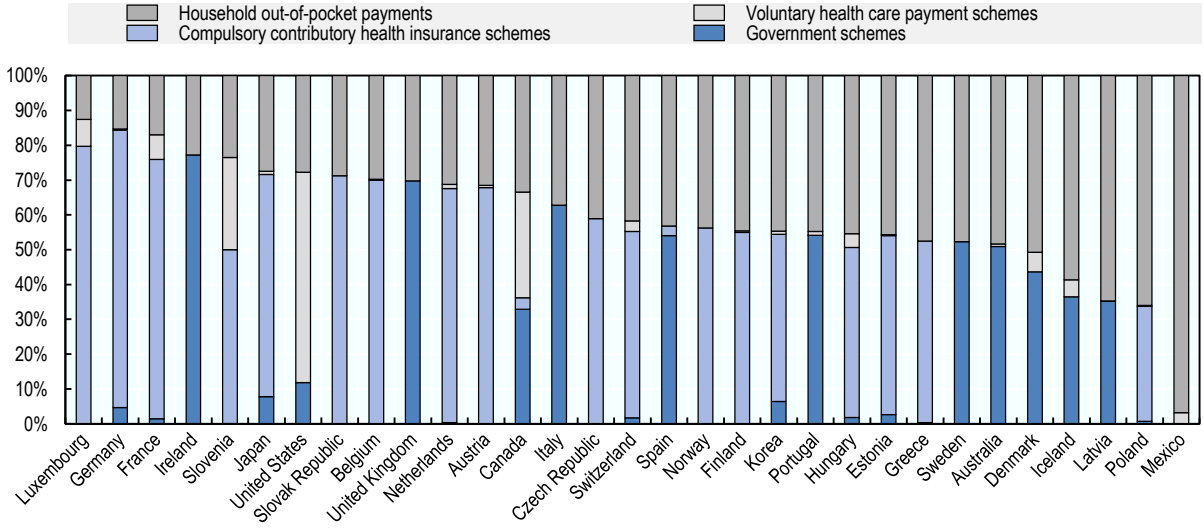
Governments or compulsory health insurance schemes finance nearly 55% of retail pharmaceutical spending in OECD countries on average

In OECD countries, some coverage for prescription medicines is usually included in health coverage schemes. Most OECD countries define positive lists of reimbursed medicines at the central level and assess new medicines before inclusion in these lists. Canada and the United States, where public and private insurers define their own formularies, are exceptions. The United Kingdom and Germany do not use positive lists and medicines that are not excluded from reimbursement by law are paid for as soon as they are authorised for use in the country, although assessment bodies in parts of the United Kingdom may subsequently recommend not to continue funding.

As a result, governments or compulsory schemes finance nearly 55% of retail pharmaceutical spending in OECD countries, albeit with wide variations (see Figure 1.7), and most cover almost all costs of medicines dispensed to inpatients. Private voluntary health insurance schemes finance about one third of retail pharmaceutical spending in Canada, where they cover medicines used in outpatient care for a large share of the population. VHI also finances nearly one quarter of pharmaceutical spending in Slovenia, where it covers co-payment gaps left by basic health insurance.

Households financed 40% of retail pharmaceutical on average in OECD countries in 2016, and more than half the spending in five countries: Australia, Denmark, Iceland, Latvia, and Poland.[6] Out-of-pocket payments for pharmaceuticals include both cost-sharing requirements for medicines that are not financed by third-party payers as well as for the costs of medicines (prescribed or not), not included in the range of benefits covered. The respective shares of these two components of household payments vary widely across countries, depending on the market share of non-covered medicines and on levels of co-payments for covered medicines.

Figure 1.7. Expenditure on retail pharmaceuticals[1] by type of financing, 2015 (or nearest year



Note: 1. Includes medical non-durables. For Australia and Japan, data are for 2015 - In the United States, compulsory and voluntary private health insurance cannot be distinguished. Data on Mexico does not include public spending.
Source: OECD (2018), *OECD Health Statistics* (database), http://dx.doi.org/10.1787/health-data-en.

The coverage of *prescribed medicines* is on average better than the coverage of total retail pharmaceutical spending (which includes OTC medicines and medical non-durables). The Australian government, for example, finances 76% of the expenditure for prescribed medicines, while social health insurance in Poland covers almost 70%. Hungary, Latvia and Norway are the countries with the highest share of household financing of prescribed medicines, above 45% (see Annex Table 1.A.1).

Most OECD countries regulate pharmaceutical prices directly or indirectly through coverage determinations

Most OECD countries also regulate the prices of medicines directly or indirectly (through coverage determinations), at least in some market segments (OECD, 2008; Panteli et al., 2016). They generally use a mix of instruments, among which international benchmarking and health technology assessment (HTA) are commonly used.

Almost all OECD countries use international benchmarking, at least for some market segments

With the exception of Australia, Sweden, the United Kingdom, and the United States, all OECD countries use international benchmarking as one tool to regulate prices, at least in some market segments. For example, Canada references prices paid in seven OECD countries to regulate the price of patented medicines; France refers to prices paid in four European countries to regulate the prices of novel drugs reimbursed in outpatient care. International benchmarking can be used as supportive information in price negotiations (e.g. Germany, Spain) or as the main criterion (e.g. Canada, France). It can be used for new products only or for price revisions over time. The basket of countries considered varies across countries, from 3 for New Zealand to 28 for some EU countries. The method to compute the benchmark price also varies (see Table 1.1 and Vogler et al., 2015; Rémuzat et al., 2017).

Table 1.1. Use of international benchmarking in OECD countries

	Australia	Austria	Belgium	Canada	Chile	Czech Republic	Denmark	Estonia	Finland	France	Germany	Greece	Hungary	Iceland	Ireland	Israel	Italy	Japan	Korea	Luxembourg	Mexico	Netherlands	New Zealand	Norway	Poland	Portugal	Slovak Republic	Slovenia	Spain	Sweden	Switzerland	Turkey	United Kingdom	United States	other
Australia[1]																																			
Austria[2]			■			■	■	■	■	■	■	■	■		■		■			■		■			■	■	■	■	■	■			■		x
Belgium[2]		■				■	■	■	■	■	■	■	■		■		■			■		■			■	■	■	■	■	■			■		x
Canada										■	■						■													■	■		■	■	
Czech Republic[2]			■				■		■	■		■	■		■		■					■			■	■			■	■			■		x
Denmark		■	■						■		■				■							■		■						■			■		
Estonia																											■								x
Finland[2]		■	■			■	■	■		■	■	■	■	■	■		■			■		■		■	■	■	■	■	■	■			■		x
France											■						■												■				■		
Germany		■	■			■	■		■	■		■			■		■					■				■	■		■	■			■		
Greece[2]		■	■			■	■	■	■	■	■		■		■		■			■		■			■	■	■	■	■	■			■		x
Hungary[2]		■	■			■	■	■	■	■	■	■		■	■		■			■		■		■	■	■	■	■	■	■	■		■		x
Iceland							■		■															■						■					
Ireland		■	■			■	■		■	■	■											■							■				■		
Italy[2]		■	■			■	■	■	■	■		■	■	■	■							■		■	■	■	■	■	■	■			■		x
Japan										■	■																						■	■	
Korea										■	■						■	■													■		■	■	
Luxembourg[3]																																			
Mexico[4]																																			
Netherlands			■							■	■																						■		
New Zealand	■			■																													■		
Norway		■	■				■		■		■				■							■							■				■		
Poland[2]		■	■			■	■	■	■	■	■	■	■	■	■		■			■		■		■		■	■	■	■	■	■		■		x
Portugal										■																		■	■						
Slovak Republic[2]		■	■			■	■	■	■	■	■	■	■		■		■			■		■			■	■		■	■	■			■		x
Slovenia		■								■	■																								
Spain[2]		■	■					■	■	■	■	■			■		■			■		■				■	■	■							x
Sweden																																			
Switzerland		■	■				■		■	■	■											■											■		
Turkey										■		■					■									■			■						
United Kingdom																																			
United States																																			

Note: 1 – Australia may check the published prices in other countries fora small number of medicines, but countries benchmarked are not predefined. 2 – Countries referring to other EU countries. 2. Luxembourg refers to the country of origin of the product. 4. Mexico refers to prices in the six countries where the medicine has the highest sales.
Source: Vogler et al. (2015) and authors' compilation for other OECD countries.

International benchmarking is perceived as a policy that is relatively easy to implement, especially for countries with low capacity for health technology assessment. However, it also has a number of drawbacks, as it does not necessary reflect country-specific value of new products; it is increasingly blurred by confidential agreements; and it is a barrier to tiered pricing[7] (Vogler et al., 2015).

OECD countries increasingly use health technology assessment to inform decisions on coverage and prices

Many countries use health technology assessment to inform coverage or pricing decisions for medicines. Some of them mainly rely on clinical evaluation while others consider economic aspects to make coverage decisions. Some countries assess all new patented products (e.g. Germany[8]) or all products applying for coverage (e.g. Australia, France), while others only assess medicines with high costs and/or uncertain effectiveness (e.g. England) (Auraaen et al., 2016). Differences in methods and criteria notwithstanding, two simplified archetypes of evaluation for the purpose of reimbursement or pricing have been identified (Paris and Belloni, 2013; Panteli et al., 2016):

- Economic evaluation at the price set by the manufacturer to determine whether the medicine will be reimbursed at this price; or
- Clinical evaluation, where the assessment of the incremental benefit of the medicine in question is the basis on which to negotiate a reimbursement price.

The first approach applies, for example, in Sweden, Norway, the Netherlands, Australia, Canada and Korea. The second is used in France, Italy, and Germany.

The idea behind these processes is that improved health benefits over existing competitors deserve a price premium or, said differently, that public payers are ready to pay additional costs for additional benefits. In principle, the use of the cost-effectiveness criteria requires the definition of threshold for the incremental cost-effectiveness ratio (ICER) beyond which new products would not be covered (Culyer, 2016). However, payers or evaluation bodies have been reluctant to establish ICER thresholds (Auraaen et al., 2016), notably because defining such a threshold is not straightforward.[9] Where such thresholds have been determined, they have often been altered or not applied consistently, for instance for severe or terminal illnesses and rare diseases (Polton, 2015; Schuller, Hollak and Biegstraaten, 2015). In addition, even in countries using economic evaluation to inform coverage decisions, cost-effectiveness is often not the only criterion taken into account in decision-making (Auraaen et al., 2016).

Pressure to accept higher price per unit of health gain has been growing

Over time, public payers have been pushed to accept higher prices for a given level of health benefit (e.g. for a QALY). In England for instance, cost-effectiveness thresholds initially recommended by the National Institute for Health and Care Excellence (NICE) were increased for treatments for patients with short life expectancy when there is sufficient evidence that the treatment offers an extension to life (as, for example, for terminal cancer patients). Treatments for rare diseases were also accepted with incremental cost-effectiveness ratios higher than pre-defined thresholds (Timmins, Rawlins and Appleby, 2016). The government also established the NHS Cancer Drug Fund (CDF) in 2010, with an initial annual budget of approximately GBP 50 million to give cancer patients access to drugs not routinely covered by the National Health Service

(NHS) (NHS England, 2016). This scheme funds cancer drugs not recommended by NICE on grounds of insufficient cost-effectiveness as well as drugs not yet evaluated by NICE to accelerate access (Palnoch, 2016). A study estimated that the existence of the CDF resulted in considerable opportunity costs within NHS England, which can be measured in terms of forgone population health. Making reference to the NICE cost-effectiveness threshold of GBP 20 000 per QALY, the study estimated a net loss of 8 808 QALYs per annum (Leigh and Granby, 2016). Annual expenditure of the CDF had increased to approximately GBP 400 million by 2015, which led to the delisting of some drugs covered by the fund, the establishment of new criteria for funding and a mandate for NICE to appraise all new cancer drugs as well as the introduction of managed entry agreements with manufacturers (NHS England, 2016; Palnoch, 2016).

Similarly, the Australian government maintains the Life Saving Drugs Program (LSDP) through which patients can obtain funding from an annual budget for expensive drugs for very rare and life-threatening conditions that do not meet the cost-effectiveness criterion for reimbursement under the public Pharmaceutical Benefits Scheme (PBS) (Paris and Belloni, 2014). In September 2016, eight indications and corresponding medicines were listed in the LSDP (Australian Government Department of Health, 2016). Although overall expenditure for LSDP remains relatively small, it grew at an average annual rate of approximately 13% between 2010 and 2014 (Harvey and de Boer, 2015).

Research on stakeholders' role in the decision-making process and anecdotal evidence from approval of high-cost drugs suggest that pressure from the general public, industry and special interest groups representing patients or physicians exert influence on decisions (Vuorenkoski, Toiviainen and Hemminki, 2003; Ozierański, McKee and King, 2012; Aggarwal, Ginsburg and Fojo, 2014; Campillo-Artero, Garcia-Armesto and Bernal-Delgado, 2016). While stakeholders' participation in assessment and decision-making processes is being implemented in several countries, studies show that patients sometimes over-estimate the potential of new treatments and that mass-media may not contribute to a well-informed public debate (Weeks et al., 2012; Robertson et al., 2013; Mack et al., 2015).

Some evidence indicates that, when asked in surveys, the general public may give priority to treatment for rare diseases or to treatments for which no alternatives are available, but results from different studies are contradictory (Mentzakis, Stefanowska and Hurley, 2011; Aggarwal, Ginsburg and Fojo, 2014; Drummond and Towse, 2014). To encourage the development of treatments for small patient populations that might otherwise be neglected, legislation in many countries grants special status to orphan[10] drugs, including an acceptance of lower levels of evidence, and higher prices for benefits comparable to those delivered by treatments for more prevalent conditions.

Even when orphan drugs do not meet country-specific criteria for reimbursement, it is politically difficult to deny funding. In the Netherlands, for instance, pharmaceuticals to treat Pompe and Fabry disease were initially covered for a limited period in 2009, with conditions for further evidence development (CED). Treatment with these medicines cost EUR 200 000 to 700 000 per patient and year. The Dutch Healthcare Insurance Board subsequently suggested discontinuation of coverage on grounds of poor cost-effectiveness, but reimbursement was maintained following publication of the proposal in the media (van den Brink, 2014). Several countries exempt orphan drugs from regular assessments (OECD, 2017c). In Korea for instance, products are exempted from economic evaluation in the following situations: 1) the condition is severe and life-threatening, such as certain cancers and rare diseases, and no alternative intervention

exists; 2) it is difficult to generate evidence because of a paucity of patients; 3) the drug is listed in at least three out of seven countries (France, Germany, Italy, Japan, Switzerland, the United Kingdom, and the United States).

All these exceptions may well be justified by societal preferences, but they create some frustration among decision-makers, price negotiators and budget holders who, as a result, do not always have well-established rules to set a limit on prices claimed by companies, nor to determine which benefits should be displaced in other parts of the health system to fund these new treatments under budget constraints. Finally, in some circumstances, patients get access to medicines though judicial procedures invoking their right to health (see Box 1.3).

Box 1.3. When patients gain access to treatment through court decisions

In some countries, public payers have been required to grant access to medicines not covered by statutory benefit package following court decisions in favour of patients claiming access on the basis of their legal rights to health. Although rights to health are enshrined in constitutional legislation in many Latin American countries, Colombia and Brazil are often cited as examples where such rights have led to poor allocation of public funds (Vargas-Peláez et al., 2014). In Colombia, for example, the 1991 Constitution allowed for enforcement of the right to health in judicial claims by individual patients for reimbursement of specific treatments, including pharmaceuticals. In a 1995 decision that set a precedent for further litigation and was subsequently adopted as a general rule by the National Social Security Health Board, the Constitutional Court ruled that medications not covered by the statutory benefits basket must be provided using public funds to gravely ill or terminal patients even if the condition is not curable (Lamprea, 2014). The number of claims increased dramatically in the early 2000s. Favourable court decisions and increasing prices following price deregulation in 2006 led to an increase in expenditure of the national FOSYGA (Fondo de Solidaridad y Garantía) fund (which is required to honour court decisions for reimbursement of non-covered treatments to health insurers) from USD 160 million to more than USD 1 billion between 2006 and 2010, 87% of which was spent on reimbursement of excluded pharmaceuticals (Lamprea, 2014; Gaviria, 2016). Price regulation was reintroduced for some drugs in 2013 and subsequently expanded, in an attempt by a new government to regain control over costs.

US pharmaceutical policy relies on competition to achieve efficiency

In the United States, the population is covered for health care costs through several schemes, which all contribute to the financing of pharmaceutical expenditure. In 2016, more than two thirds (67.5%[11]) of US residents were covered by private health insurance; 16.7% by Medicare, the government programme for the elderly and disabled (see Box 1.4); 19.4% by Medicaid, the joint Federal-State programme for low-income individuals and families; and 4.6% by programs dedicated to military forces. About 8.8% of the population was uninsured (Barnett and Berchick, 2017). In 2016, 43.4% of expenditure for prescription drugs sold in retail outlets was financed private health insurance; 29% by Medicare; 10.2% by Medicaid; 3.1% by other health insurance programs; and 13.7% by households themselves[12] (CMS, 2018).

The US pharmaceutical market is complex (National Academies of Sciences, Engineering and Medicine, 2018), more than those of many OECD countries. A number of private

companies serving as managed care organisations, pharmacy benefit managers (PBMs), drug distributors, and pharmacies, play a role in benefit design (which drug is covered and under which conditions) and in the purchasing and distribution of pharmaceuticals. PBMs serve as third-party administrators of pharmacy benefits for private and public plans.[13] They administer benefits such as formulary design and electronic prescribing as a commercial service. After a pharmacy and therapeutics (P&T) committee review regarding clinical utility and cost-effectiveness, PBMs can negotiate with manufacturers, on behalf of insurance plans, based on the status of utilisation management in their formulary. The three largest benefit managers increased their share of the total commercial prescription volume from 42% in 2005 to 66-68% in 2015 (Aitken et al., 2016; Sood et al., 2017).

PBMs aggregate purchasing power to negotiate lower prices for prescription drugs from manufacturers and discounts from pharmacies, with many also providing direct mail-order pharmacy services to further lower costs. With these tools, payers can obtain significant discounts or rebates[14] from manufacturers in therapeutic areas where competition exists. Recent estimates suggest that rebates can amount up to 60% when brand competition is high and that average off-invoice discounts and rebates amount to nearly 30% in the United States (see Box 1.4).

The system, however, shows a number a limitations (National Academies of Sciences, Engineering and Medicine, 2018). Most PBMs do not disclose the prices they pay to retail pharmacies or their rebates from a drug manufacturer, although contracts may guarantee a health plan a specific percentage of that rebate. While purchasers of health insurance can benefit from these confidential rebates through premium reductions, patients purchasing the medicines do not directly benefit from them and may face high-cost-sharing requirements. This has led to a controversial practice whereby pharmaceutical companies help patients get access to costly medicines through co-pay assistance or coupons, which offset some of their costs. This practice can distort incentives used in benefit design. A 2013 analysis noted that 62% of coupons were for drugs with lower-cost therapeutic alternatives available (Ross and Kesselheim, 2013) and thus encouraged the use of high-cost medicines. The association of Pharmacy Benefit Managers (PBMs) estimates that couponing practices could raise 10-year prescription drug costs by USD 32 billion (Visante, 2011). More recently, there has been controversy with some PBM providers regarding fiduciary, transparency, and disclosure practices (National Academies of Sciences Engineering and Medicine, 2018). Particular features of Medicare drug coverage also limit the opportunities to exploit competition (see Box 1.4). For instance, the obligation to cover all drugs in six protected classes in Medicare Part D plans prevents insurers and PBMs to negotiate rebates in exchange for formulary listing.

In order to have their covered outpatient drugs paid for by Medicaid, manufacturers must agree to provide rebates to State and Federal Medicaid programs of an amount such that Medicaid does not pay more for brand name drugs than the lowest or “best price” that the manufacturer negotiates with others within the United States during a rebate period.[15] Providing these rebates to Medicaid is also a requirement for receiving payments under Medicare Part B.

Box 1.4. Coverage of prescription drugs by Medicare in the United States

Medicare covers pharmaceuticals through several programs, including Medicare Part B and Part D

Medicare Part B covers specialty drugs that are administered by a provider in a physician office or hospital outpatient setting. Medicines covered by this programme are overseen either by CMS nationally or by 1 of 12 local contractors. CMS cannot generally use cost information in benefit basket design, instead relying solely on the criteria "reasonable and necessary". There have been attempts to control drug costs, notably by reimbursing certain drugs at the level of the "least costly alternative" (LCA) from 1995 to 2010, but CMS discontinued the use of the LCA after a court ruled that it was contrary to the law that requires reimbursement at 106 percent of a drug's average sales price (ASP) (US Court of Appeals- District of Columbia Circuit, 2009). This removed the ability to incentivise use of the most cost-effective alternative, and further efforts have sought legislative authority for policies such as LCA (Levinson, 2012).

Medicare Part D was introduced in 2006 to provide coverage of outpatient medicines for Medicare beneficiaries. It is a voluntary programme, administered by private insurance providers. In 2016, about 43.2 million people were enrolled in Medicare Part D (13.8% of the population). Providers use the same tools to manage their Medicare Part D and private plans, but for Part D they carry some additional obligations. The authorising legislation for Medicare Part D specified a standard benefit design for plans to follow, but most offer alternative benefit designs including multi-tier formularies. All Part D plans, regardless of their benefit design, must cover "all or substantially all" products in six "protected classes": immunosuppressants, anti-depressants, anti-psychotics, anti-convulsants, anti-retrovirals, and anti-neoplastic drugs (Bach, 2009; Frank, 2012; CMS, 2016). Part D plans may still place products from protected classes on high cost-sharing tiers and employ utilisation management tools, but the constraints imposed by law on the selection of drugs limits opportunities to promote competition.

Insurers can also offer Medicare Advantage Prescription Drug (MA-PD) plans that offer both medical and pharmacy drug coverage as part of managed care, but the majority of Medicare beneficiaries receive medical and drug coverage from different sources, resulting in potential access issues in therapeutic areas with both self- and physician-administered approved products.

Policy makers face a number of challenges in pharmaceutical markets

Against the background presented in the previous sections, a number of challenges have emerged in pharmaceutical markets which are dominating policy debate. These challenges are linked to trends taking place in pharmaceutical markets:

- List prices of new medicines have been increasing at a high pace over time. This is true for launch prices, especially in some therapeutic areas, but also for the prices of existing on-patent drugs, at least in the United States.
- Increasing prices of new medicines particularly in oncology and orphan drugs are not always justified by commensurate increases in benefits for patients. All these trends have raised concern about the value and the sustainability of pharmaceutical spending.

- The high prices of treatment for highly prevalent diseases have raised concerns about budget impact.
- The prices of some off-patent medicines, in a *de facto* monopoly position, have gone up rapidly.
- Pharmaceutical treatments with high costs are not always available to patients who need them, because of those costs, but also other reasons.

The prices of new medicines have been increasing at a high pace

Pharmaceutical prices have recently received a lot of attention from policy makers, media, the general public and clinicians (Abboud et al., 2013; Tefferi et al., 2015; Council of the European Union, 2016). Concerns over increasing prices are not new. An analysis of media over the past 30 years identified several crises in the past (Leopold, Chambers and Wagner, 2016). In the late 1980s, media coverage on high drug prices focused on the novel AIDS treatment zidovudine (AZT), which cost USD 10 000 (USD 21 322) per patient per year in 2014. In the 2000s, media coverage spiked following the launch of new cancer medicines such as bevacizumab (Avastin®) for metastatic colon cancer and trastuzumab (Herceptin®) for breast cancer, with price tags of USD 100 000 (USD 126 450 in 2014 dollars) per treatment course (Leopold, Chambers and Wagner, 2016). Early in 2014 policy debates were dominated by the launch of sofosbuvir, a new and transformative treatment for hepatitis C, with an initial list price per treatment course of USD 84 000.

Authoritative information on prices and prices trends is scarce. The growing disconnection between list prices and actual prices that are paid by payers due to the use of confidential rebates makes analyses of price trends or price comparisons difficult. Furthermore, price indexes are only available in a few countries (see Box 1.5). However, a number of trends can be identified, described below.

Box 1.5. Price comparisons and analyses of price trends are increasingly difficult

The disconnect between list prices and actual prices paid has been increasing

Public reports and research studies most often rely on "list prices", which are the only prices available to researchers and citizens. Actual prices paid by health insurers, providers or governments may be lower thanks to off-invoice discounts and rebates.

In high income countries, discounts and rebates vary widely across products and across countries, from below 10% to more than 60% (Crédit Suisse, 2016; QuintilesIMS Institute, 2016a; Sawhney, Gordian and Behnke, 2016; Morgan, Vogler and Wagner, 2017). In 11 high-income countries/payers[1] surveyed in 2016, discounts and rebates were most frequently in a 20-30% range (Morgan, Vogler and Wagner, 2017). An analysis of 25 companies operating in the United States in 2015 estimated that rebates accounted for 37% of gross sales and that four companies had rebates higher than 49% (Crédit Suisse, 2016). In 2016, Quintiles IMS estimates that average off-invoice discounts and rebates amount to nearly 30% in the United States, 17% in Europe and are lower in the rest of world[2] (QuintilesIMS Institute, 2016).

Evidence suggests that confidential agreements on prices are becoming more frequent (Morgan, Vogler and Wagner, 2017) and that list prices are increasingly disconnected from actual prices paid. In the Unites States, for instance, discounts and rebates increased

from about 18% to 28% of total spending on brand-name drugs between 2010 and 2014 (Aitken et al., 2016). As a percentage of gross Medicaid drug expenditures, rebates increased dramatically from 17.6% in 2003 to 47.6% in 2013. Rebates in the Medicare programme have grown from 8.6% of total costs of brand-name and generic drugs in 2006 to 12.9 in 2013. As a result, while the compounded annual real growth rate of invoice prices in the period 2005–14 was 6.4%, the rate for net prices was only 5.4%—with most of the difference occurring after 2009 (ibid.). Off-invoice discounts and rebates in the United States typically apply to medicines competing in a therapeutic area where they can be negotiated in exchange of a "preferred" status in health plans' formularies.

In other OECD countries, health care payers (mainly governments and compulsory health insurance schemes) are also increasingly negotiating rebates on list prices through managed entry agreements (see Chapter 3). Managed entry agreements are more likely to affect newly launched medicines, with or without competitors for a short period after market entry.

Pharmaceutical spending as reported in the System of Health Accounts and OECD statistics is net of discounts and rebates.

International price comparisons and analyses of price trends are difficult

Confidential agreements essentially allow manufacturers to charge different prices to purchasers with different price sensitivity (price discrimination), within national markets (typically in the United States) or between countries with national payers or negotiators. Tiered pricing is generally considered as desirable in a global market (Danzon and Towse, 2003; OECD, 2008). The disconnection between list prices and actual prices, however, has a number of drawbacks. One of them is that analyses of price trends or price comparisons have become very difficult.

Price indices reported in national statistics reflect the evolution of prices of existing treatments. These changes are measured by comparing prices in year t and t-1 for an identical basket of medicines present in both years, holding volumes constant. Only a handful of countries regularly publish specific pharmaceutical price indices. A comparison of price trends in Finland, France and the United States using such indexes showed that between 2002 and 2012, prices have been declining in both European countries every single year, while prices in the United States have been increasing by 3% on average (Belloni, Morgan and Paris, 2016).

1. Australia, Austria, Canada, England, Germany, New Zealand, Norway, Scotland, Sweden, the Netherlands, and the United States (Department of Veterans Affairs).
2. Estimates from Morgan et al. are based on a survey of public payers while estimates from Quintiles IMS are based on IMS data on volumes and transaction ("off-invoice") prices, adjusted using sales reported in SEC filing for specific products to establish "net prices".

New medicines, especially in some therapeutic areas, are launched at high prices

Many medicines now have annual costs per patient exceeding USD 100 000. In the United States, the association of health insurers published a list of 150 drugs with annual average wholesale price higher than USD 10 000 in 2016. For about half of the indications treated with these drugs, annual costs exceeds USD 100 000 per year. Several treatments for rare genetic disorders cost USD 500 000 to USD 800 000 annually (AHIP, 2016). Although these prices are list prices and only relate to the US market – where

prices of patented medicines are typically higher than in other markets -- they give an indication that the prices of new treatments are getting higher.

In the United States, the monthly treatment costs of oncology medicines at launch have been increasing steadily since 2000, with an increase in the median price per patient per month from some USD 5 000 to more than USD 10 000 in 2015, adjusted for inflation. New treatments for chronic myeloid leukaemia (CML) were recently launched at prices ranging from USD 118 000 to USD 138 000 per year (Abboud et al., 2013). In 2017, a new cell-therapy was introduced for young adult and paediatric acute lymphoblastic leukaemia, at a list price of USD 475 000 per treatment, with an outcome-based agreement by which the company will charge for the drug when it achieves clinical response within 30 days (Kaltenboeck and Bach, 2017). Many of these high cost medicines target small populations, which moderates their impact on total pharmaceutical expenditures.

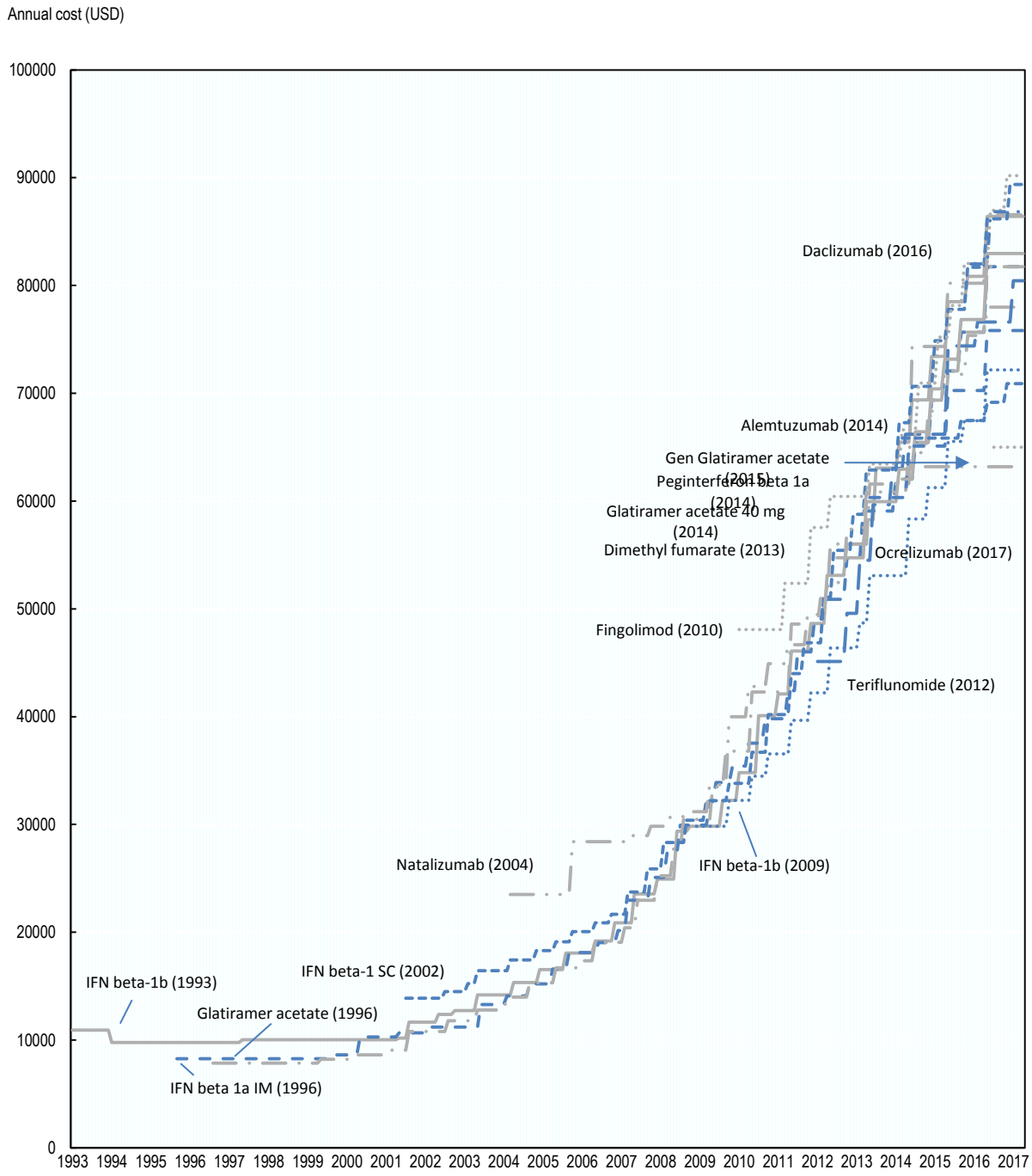
Increases in launch prices are also observed in treatments for multiple sclerosis. In the United States again, a study on nine disease modifying therapies approved between 1993 and 2013 showed that the annual cost of therapy at launch time increased from USD 8 300 for the cheapest drug introduced before 1996 to USD 58 000 for the drug approved in 2013 (a 7-fold increase in list prices at launch). Price increases in other countries might be more limited: the analysis of 2013 list prices observed for the same products in two countries showed that annual costs of the latest introduced therapy was twice that of the first introduced in Australia (USD 22 000 against 11 000) and in the United Kingdom (USD 29 711 against 12 018) (Hartung et al., 2015). Figure 1.8 presents an update of this study up to 2017 for the United States.

Orphan drugs are sometimes launched at high prices. A study of 74 medicines approved by the EMA between 2002 and 2014 for 63 indications, showed that 18% of them had annual treatment costs higher than GBP 100 000 in the United Kingdom; 58% had costs between GBP 10 000 and GBP 100 000 per year; and the remaining 24% had annual costs below GBP 10 000 (Onakpoya et al., 2015). Another study looked at 335 drugs[16] with at least one orphan indication[17] available in the United States in 2016. It showed that annual treatment costs ranged from less than USD 6 000 to more than USD 500 000. Among them, 8.4% had annual costs exceeding USD 200 000 per patient, accounting for 5.7% of sales for orphan indications; 15.8% had an annual cost between USD 100 000 and 200 000 and represented 27.6% of orphan drug/indications sales (QuintilesIMS Institute, 2017b).

In the United States, list prices of existing on-patent medicines are increasing rapidly in some therapeutic areas

The list prices of existing on-patent medicines in certain therapeutic areas are increasing, especially in the United States. Such trends are generally not observed in other countries where regulation prohibits or limits price increases for existing medicines.

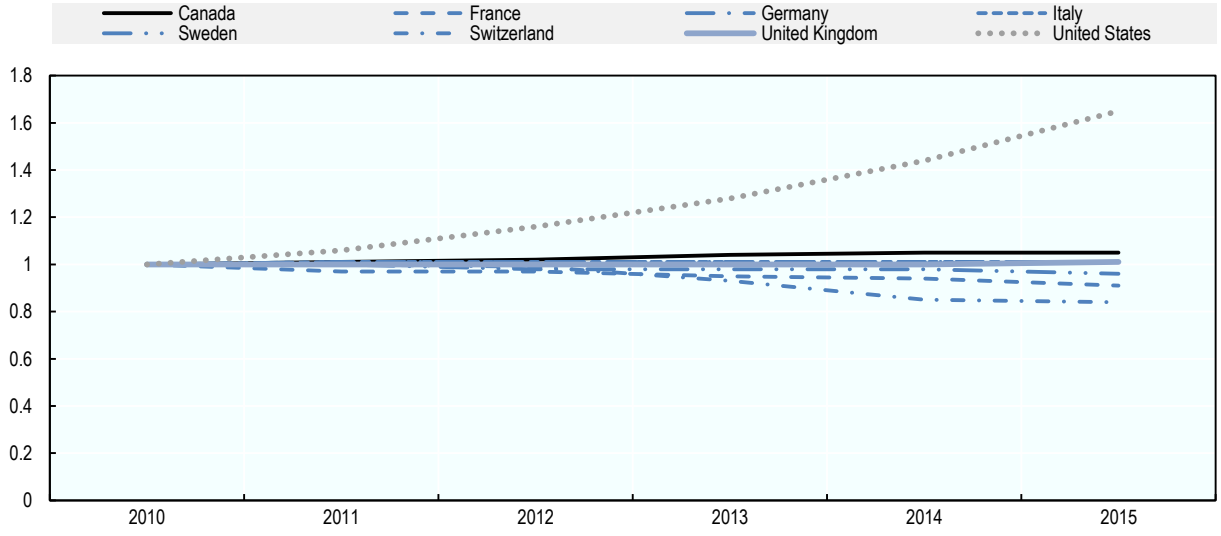
Figure 1.8. Trends in disease modifying therapy (DMT) pricing in the United States from 1993 to 2017



Note: Prices are estimated from WAC (wholesale acquisition cost) for a year of therapy. Alemtuzumab estimate is based on an average of doses for first and second year. IFN = Interferon; SC = subcutaneous.
Source: Hartung, 2017.

The Canadian Patented Medicine Prices Review Board recently compared the price increases from 2011 to 2015 of biological disease-modifying anti-rheumatic drugs (DMARDs) in several countries (see Figure 1.9). Over this period, the list prices[18] of biologic DMARDs increased by 65% in the United States and by 5% in Canada. By contrast, several countries, including Switzerland, France and Sweden, had marked price reductions over the same time period (PMPRB, 2016). Hartung (2017) showed that the list prices of disease modifying therapy drugs (DMT) for multiple sclerosis have increased over time after market launch in the United States, with an annual average price increase of 35% for two of the first drugs launched (see Figure 1.8). Part of the increase is offset by subsequent rebates for some purchasers, but these are unknown. Sharp increases in the list prices of insulin have also been reported in the United States. For seven common insulins, prices rose by 93% to 325% between 2010 and 2015 (The Alliance of Community Health Plans, 2015). From data submitted to the OECD in the course of this project and other sources, such price increases have not been observed in Australia or the Netherlands, for instance.

Figure 1.9. Trends in list prices for biological disease modifying anti-rheumatic drugs in Canada, France, Germany, Italy, Switzerland, United Kingdom and United States, 2011-15



Note: All prices are "list prices" as reported in the original MIDAS™ Database, 2011 to 2015, IMS AG, for hospital and outpatient markets.
Source: PMPRB, 2016.

In current debates in the United States, PBMs are often blamed for high and increasing list prices, due to the rebates they negotiate (Walker, 2016). In response to these allegations, the association representing PBMs commissioned an analysis of trends in list and net prices for the 200 top selling brand self-administered drugs[19] between 2011 and 2016. This study showed no correlation between increases in list prices and the percentage rebates consented over this period (Visante, 2017).

Increasing prices of new medicines particularly in oncology and orphan drugs have raised concerns about the sustainability and value of pharmaceutical spending

Projections of future trends do not permit the drawing of firm conclusions about future impact on cost at aggregate level and therefore on financial sustainability. Nevertheless, concerns have grown about the value of pharmaceutical spending in certain therapeutic categories.

Pharmaceutical spending is expected to increase in the next five years but financial sustainability may not be the main issue

Since the economic crisis, pharmaceutical spending has grown at a slower pace than spending in other parts of the health systems in many OECD countries. According to IMS estimates, global pharmaceutical spending is expected to grow by 4 to 7% per year between 2016 and 2021 (reduced to 3 to 6% when confidential rebates and discounts are taken into account), a slow-down by comparison to growth in 2014 and 2015. Growth will be driven by treatments in oncology (+9 to 12%), for diabetes (+8 to 11%) and for autoimmune diseases (11 to 14%) but on the other side, curbed by loss of market exclusivity of a number of products. Growth is expected to be higher in the United States, Korea and Canada than in many large European markets (QuintilesIMS Institute, 2016).

Trends in spending in oncology and treatments for rare diseases (some of which are rare cancers) have been identified as particularly worrying, due to the combination of high treatment costs; the multiplication of new medicines in these areas, offering new treatment opportunities; and a rich pipeline of potential new drugs. However, the impact this will have on future cost dynamics remain difficult to predict:

- Oncology medicines account for a significant share of pharmaceutical spending, ranging from 10.2% to 15.9% of pharmaceutical spending in G7 countries in 2015 (IMS Health, 2017), and their share in health expenditure is likely to increase over time. The share of health spending allocated to all types of oncology treatments might also be increasing though evidence is scarce and not always consistent. For two countries, data are available over a decade. In Germany, the share of cancer care related expenditure in total spending for health increased from 7% to 8.4% between 2004 and 2013, while in the Netherlands, it increased from 5% to 7.7% between 2003 and 2013 (Eurostat, 2016). That said, a report from the Office of Health Economics and the Swedish Institute for Health Economics published in 2016 noted that such a level of expenditure was relatively low given that cancer accounts for a large share of the burden of disease (Jönsson et al., 2016b). Future growth in global spending for oncology medicines until 2021 was estimated by IMS in two reports published in 2016 and 2017. While the first report anticipated an average annual growth during this period of 9-12%, the second report anticipated an average annual growth at 6-9% until 2021 (QuintilesIMS Institute, 2016, 2017a). These figures show that uncertainties about approvals and take-up of new medicines and about their prices make predictions quite difficult.
- Orphan medicines account for a smaller share of total spending. In the United States, pharmaceutical sales for orphan indications[20] account for 7.9% of total drug spending (QuintilesIMS Institute, 2017b). In European countries, this share is a little lower but increasing. In the Netherlands, between 2006 and 2012, the number of orphan drugs increased from 11 to 43, the number of patients

treated from about 2 200 to about 9 800 and associated spending from EUR 61.2 to 260.2 million. The proportion in total pharmaceutical spending quadrupled in 6 years, from 1.1% to 4.2% (Kanters, Steenhoek and Hakkaart, 2014). Another study assessed that spending for orphan medicines accounted for 2.1% of pharmaceutical spending in Sweden and 3.1% in France in 2012 and predicted that these shares could increase to 4.1% and 4.9% respectively in 2020 (Hutchings et al., 2014). A sensitivity analysis however, with different assumptions on the number of medicines approved, trends in launch prices and the impact of loss of market exclusivity, led to estimates of 9% and 11% respectively in 2020 (ibid.).

Although future spending dynamics remain difficult to predict, the most important question will be to assess whether increased spending in these two areas comes with commensurate increases in value for patients and societies.

Box 1.6. Sustainability of health spending

As on average three-quarters of health spending is financed publicly in OECD countries, sustainability is often viewed through the lens of fiscal sustainability, which is defined as "the ability of a government to maintain public finances at a credible and serviceable position over the long term" (OECD, 2015b). Fiscal sustainability does not preclude increases in government spending on health. Societies often express a willingness to contribute more for health care than other areas of government spending, reflecting the value placed on health. Such an increase, however, has to be considered in relation to other domains of government interventions, as well as to the willingness of the population to pay higher taxes or other contributions for health care.

Within public health spending, many governments set budgets by line item, such as pharmaceuticals or hospital care. Such "silo budgeting" often leads policy makers and analysts to narrowly focus on individual sectors, such as hospital care or pharmaceutical care. Any change in pharmaceutical spending, however, be it an increase, should not be considered in a vacuum. As shown in the first section of this chapter, spending more in pharmaceutical treatments sometimes offsets spending in other parts of the health system. Without well-informed predictions on trends in prevalence, upcoming new treatments and their potential impact, and on patent expiries and opportunities for increased competition, it is difficult to determine a desirable level for future pharmaceutical spending.

High prices are not always correlated with measurable health improvements

In some market segments, typically oncology and medicines used to treat rare diseases, high prices are not always correlated with measurable health improvement. As early as 2004, a study on medicines used in colorectal cancer showed that new treatments had significantly improved outcomes for patients with metastatic disease, nearly doubling the median survival time from 12 to 21 months, but had also increased costs 340-fold in 40 years (Schrag, 2004).[21] More recently, a study looking at oncology medicines approved between 1995 and 2013 in the United States found that the average survival benefit was a little less than six months. Over the same period, the list price paid for an additional year of life increased in real terms from USD 54 100 in 1995 to USD 139 100 in 2005 and USD 207 000 in 2013. These costs do not include the costs of other medicines or treatments used in combination nor the costs of dealing with adverse effects

(Howard et al., 2015). Drawing on a sample of 63 oncology medicines approved since the mid 1990s, a replication of this study in the French context showed that growth in the average launch prices of oncology medicines had given rise to increasing costs per life year gained, from EUR 20 700 in 1996 to EUR 175 968 in 2016.[22] This represents an eight fold increase or compound annual growth of 11%, consistent with the growth observed in unpublished net confidential prices (CNAMTS, 2017).

Bae and Mullins (2014) compared incremental costs par QALY of oncology and non-oncology pharmaceutical treatments in a sample of studies published between 2003 and 2013 and adopting the perspective of a US payer. The average ICER for oncology medicines was about USD 138 600 (vs USD 50 000 for other products). ICERs were above USD 50 000 in 55% of cases and above USD 100 000 in 30%.. Even if prices in other countries are often lower than in the United States, new oncology medicines often do not meet ICER thresholds in use.[23] In England, for instance, the proportion of oncology medicines not recommended by NICE has increased over time. While this proportion was of 31% for the whole period 2000-2016, it was 51% for indications approved by the EMA since 2007, in spite of an increase in the ICER threshold for these treatments during the period (Polton, 2015).

The issue of increasing prices for small improvements in health is also prevalent for orphan medicines (some of which are oncology treatments). A study looked at the level of evidence available for 74 approved drugs (2 of which have been withdrawn after approval) approved by the EMA for 63 orphan conditions, between 2002 and 2014. Of the 74 drugs, 5 (6.8%) were granted conditional approval, while 15 (20%) were granted approval under "exceptional" circumstances. Based on the GRADE criteria,[24] the overall quality of evidence could be rated as moderate in 54 (73.0%) drugs, low in 16 (21.6%) and very low in 4 (5.4%). While 85% of these drugs showed significant clinical effects, serious adverse events were reported in 86.5% of them. The annual cost in the United Kingdom ranged from GBP 726 to GBP 378 000, with a median cost of GBP 31 012.While the study could not systematically compare the association between costs and benefits of all drugs because of differences in outcome measurements, it noted that the five drugs approved for pulmonary hypertension had comparable benefits but very different price levels (a 1:2 ratio for the two more recent approvals) and found similar results for drugs approved in cancer. Within indications, the study showed an impact of the date of approval on prices (Onakpoya et al., 2015). A systematic review of economic evaluations of ultra-orphan medicines showed high levels of uncertainty in effectiveness leading to wide ranges in ICERs, ranging from EUR 351 622 to EUR 3 282 252 per QALY for Fabry disease, from EUR 153 405 to EUR 1 043 868 per QALY for Pompe disease, and from EUR 43 532 to EUR 432 540 for Gaucher disease (Schuller, Hollak and Biegstraaten, 2015).

Many observers, experts and stakeholders suggest that observable health improvements (in length and quality of life) may not be the only parameters that payers and societies value when defining their willingness to pay. They advocate for a wider framework and/or for the use of multi-criteria decision analysis to better take into account all dimensions valued by patients and societies, especially for orphan and oncology medicines (Angelis and Kanavos, 2016; Carrera and IJzerman, 2016; Eurordis, 2017). The disconnection between prices paid and health improvements, however, raises questions about the efficiency of pharmaceutical spending. A New Zealand study which analysed population health gains foregone from unfunded cancer medicines found that funding more new cancer medicines in order to achieve numerical parity with Australia or other countries would not result in substantive health improvement and would cost

significantly more. The authors suggested that selective funding of new medicines that demonstrate clear clinical benefit and that are cost-effective and affordable would be a sensible approach to deliver the best health outcomes for all New Zealanders (Evans et al., 2016). The disconnect between prices paid and measurable health benefits also raises questions in terms of signals being sent to industry for the development of new treatments.

Countries may be ill-prepared for the arrival of new treatment for highly prevalent diseases

The launch of a breakthrough treatment of hepatitis C in 2013 created a shock in many countries. Gilead's direct antiviral agents (DAAs) sofosbuvir entered the US market in 2013 at a list price of USD 84000. Prices were lower in other markets, as a result of the tiered-pricing strategy defined by Gilead, linking the price of its medicine to income level and prevalence of the disease in different countries. The therapeutic value of the new treatment was immediately recognised and it was found cost-effective, even at its high price. Payers, however, had not anticipated this launch and felt overwhelmed by the budget impact of treating the whole affected population at that price. For countries with the highest prevalence, it was considered unaffordable (Iyengar et al., 2016). In several OECD countries, payers initially limited access to the latest hepatitis C treatments to the most severely affected patients (CNAMTS, 2016), creating frustration for patients and clinicians.

Many payers negotiated lower prices and confidential discounts leading to reduced net prices (IMS Institute for Healthcare Informatics, 2016a), but prices really began to decrease when competition kicked in. Between August 2013 and August 2017, five new single-component DAAs and six new fixed-dose combinations received their first worldwide regulatory approval (Unitaid and WHO, 2017). Competition helped reducing prices and the last competitor entered the US market in 2017 with a list price of USD 26 400 per treatment course (before discounts), a monthly price 30% to 60% lower than that of competitors (Sagonowsky, 2017). The most recent negotiations in OECD countries where prices are regulated also achieved lower prices and expanded population coverage (see Box 1.7).

If public payers had better anticipated *first* the arrival of the sofosbuvir and *second*, the arrival of competitors, they might have responded differently. First, they could have planned and justified a prioritisation of treatment of the most severely affected patients and populations with high risks, in order to spread the costs over several years. In some countries, such an approach would have been anyway justified by the system's capacity to initiate treatments. They would have also benefited from the impact of competition on prices for a deployment of DAAs for the whole affected population.

This exceptional case also shows that the "willingness to pay" for a new product treating a highly prevalent disease does not only depend on its intrinsic value (or cost-effectiveness), but also on the total bill. Since production costs are relatively low, volumes are an important element of the company's returns on investments and caps on spending may well be acceptable for the company if volumes are high.

Box 1.7. Coverage and pricing of hepatitis treatments - examples

In **France**, the committee in charge of price regulation negotiated prices and confidential arrangements, while the Parliament enacted spending caps and *ex post* rebates (CEPS, 2016).

- From September 2013 (prior to the marketing authorisation obtained in 2014 from EMA), Sovaldi® (sofosbuvir) was available in France through a temporary authorisation for use (financed by health insurance, at the price set by the manufacturer). The Transparency Commission issued a positive recommendation for coverage in June 2014 for a restricted population and the Economic Committee for Health Products (CEPS) negotiated a price, informed by an economic evaluation undertaken by the Haute Autorité de Santé (HAS). Sovaldi® was included in the positive list in November 2014.
- Prior to its inclusion in the positive list, Sovaldi was accessible to patients for a standard price of treatment, set by Gilead at EUR 56 000, fully covered by health insurance. In addition, the CEPS negotiated an agreement with *ex post* rebates linked to volumes of sales and performance of the product observed in a large cohort of patients. The net price was substantially lower than the list price.
- Two other DAAs, Daklinza® (daclatasvir) from Bristol-Myers Squibb and Olysio® (simeprevir) from Janssen were included in the positive list in May 2015, with list prices of EUR 46,000 per treatment course with managed entry agreements (MEAs) similar to those of Solvaldi. In August 2015, the listing of two other products from Abbvie, Exviera® and Viekirax®, used in association allowed a further price reduction.
- In addition, two provisions were included in the Social Security Finance Acts of 2014 and 2015: 1) the restitution by Gilead of the difference between the price set by the CEPS and price used by the company before listing, multiplied by the volume of sales, for the whole period prior to listing; and 2) the implementation of an expenditure ceiling on DAAs for 2014 and 2015 (respectively EUR 450 million and EUR 700 million), beyond which companies had to pay rebates. Rebates paid by individual companies can be defined through individual agreements or computed using the default rule set by law. *Ex post* rebates for DAAs amounted to EUR 21.4 million for the two years 2014 and 2015.

In May 2016, the French Minister of Health announced the expansion of treatment to all infected patients. The pricing committee negotiated again, first with MSD and then with Gilead, to further lower prices. From April 2017, the cost of a treatment with Sovaldi has been lower than EUR 28 700. All treatments are fully reimbursed by health insurance (Ministère des affaires sociales et de la santé, 2017).

In **Australia, DAAs for hepatitis C have been reimbursed since early 2016** (more than 18 months after the approval of the first entrant) without any restrictions in terms of population. This broad access for Australians with hepatitis C arises from the close interplay between the role of health technology assessment (HTA) and the role of the payer.

- First, the statutory HTA expert advisory committee advising government (the Pharmaceutical Benefits Advisory Committee or PBAC) paid close attention to the appraisal of cost-effectiveness. For example, the PBAC's assessment of sofosbuvir published in March 2015 set a broad context in order to provide its advice to the Minister for Health; noted the gains in clinical effectiveness and safety and the shorter duration of the new treatment regimens; and justified the use of a (lower than usual)

ICER/QALY threshold of AUD 15 000 as the basis for back-calculating a cost per course per patient and thus a price across the proposed regimens (PBAC, 2015). PBAC assessments for other DAAs also influenced the negotiations between the Australian government and sponsor companies.

- Second, the government adopted a clear approach to price and expenditure negotiations across the competing sponsors of hepatitis C medicines. Finalisation of these negotiations was backed by formal Deeds of Agreement comprising special (confidential) pricing arrangements and (financial) risk sharing arrangements.
- According to public statements, the Australian government committed over AUD 1bn in funding to an HCV treatment programme over a five-year period for an estimated treatment population of 62 000 (Unitaid and WHO, 2017). A key objective of the scheme was to achieve budget certainty through an annual budget cap above which manufacturers would be required to rebate treatment costs. The programme subsidises unrestricted access for patients regardless of route of transmission or disease stage. In addition, GPs are allowed to prescribe DAAs (Australian Government Department of Health, 2017).
- While PBAC's assessments produced an initial estimate of 6 600 patients in year one of the programme, an estimated 32 400 individuals initiated DAA treatment in 2016 (from March to December), or 14% of the people living with chronic HCV infection in Australia (Kirby Institute, 2017).

In countries outside the OECD, new DAAs and fixed-dose combinations have been made available at lower prices through multiple mechanisms including voluntary licenses granted by companies marketing these products and the production of generic products where patent protection does not exist (Unitaid and WHO, 2017). For example:

- In May 2014, Egypt, the country with the highest HCV prevalence, concluded an agreement with Gilead to purchase a 12 weeks' course of sofosbuvir for USD 900. Gilead has since extended this price to 101 low- and middle-income countries included in its voluntary licences, and subsequently set the price of sofosbuvir/ledipasvir for these countries at USD 1 200 for 12 weeks. In September 2016, Gilead reduced its prices to USD 750 for 12 weeks of sofosbuvir and USD 900 for 12 weeks of treatment with either sofosbuvir/ledipasvir or sofosbuvir/velpatasvir. Four additional countries (Armenia, Georgia, Moldova and Ukraine) are now eligible to procure at these prices. Other countries like Argentina or Brazil are not eligible and pay substantially higher prices (more than USD 6 000 for sofosbuvir).
- In September 2014, Gilead signed voluntary licences for sofosbuvir and ledipasvir with a number of major generic producers in India. These companies have the right to manufacture generic versions of sofosbuvir and ledipasvir, and supply them to the 101 countries included in the licence. In January 2015, these licences were amended to include velpatasvir. The voluntary licence does not include middle-income countries such as Brazil and China.
- Generic prices of sofosbuvir and sofosbuvir/ledipasvir fell well below "access price" levels set by Gilead and prices as low as USD 66 for a 12-week course of treatment for sofosbuvir and USD 191 for sofosbuvir/ledipasvir in India in 2016-2017 (Unitaid and WHO, 2017).

The prices of some existing off-patent medicines have increased rapidly

A few cases of sharp price increases in off-patent drugs have received substantial media attention recently. For instance, Mylan came under public scrutiny in August 2016 after reports that since acquiring rights to EpiPen in 2007, the company had implemented a series of gradual price increases in the United States, inflating the price of the drug from USD 56.64 to USD 317.82, a 461% increase. In 2015, Turing Pharmaceuticals increased the price of its HIV medicine Daraprim by 5 000%. The price of the drug was raised from USD 13.50 to USD 750 overnight (Pollack, 2015).

Increases in off-patent medicines are not only a US phenomenon. From 2005 to 2015, the prices of 10 generic drugs increased by 1 000% or more in the United Kingdom. The pain medication and antidepressant doxepin saw the biggest rise. In 2005, its list price was GBP 2.36 (USD 2.89). By 2015, the price had increased to GBP 124.56, a change of more than 5 000%. The prices of six other generic drugs have increased by at least 2 000% over the same period. In response to a query launched with the Pharmaceutical Pricing and Reimbursement Information (PPRI) network, Austria reported a price increase of 2 584% for a sodium chloride infusion solution, as well as price increases of more than 100% for about 50 medicines since 2012, of which 16 were for medicines covered by social health insurance (OECD, 2017e).

An exhaustive search of all cases of price increases brought to competition or anti-trust authorities and reported in the PaRR database between 1 January 1 2007 and 28 February 2017 was undertaken as part of this project.[25] Twenty cases were reported in the United States, two in the United Kingdom and one in Italy, all filed between 2013 and 2017, for price increases ranging from +80% to 8 281%. On 15 May 2017, the European Commission initiated formal anti-trust proceedings against Aspen for a suspected breach of EU rules prohibiting abuse of market dominance (European Commission, 2017).

Price increases among off-patent drugs have only occurred for a small number of products and are unlikely to significantly increase health spending. In Canada, for instance, prices of single-source non-patented drugs[26] have increased on average by 18% between 2010 and 2016 but the budget impact remains limited: these drugs represented only 2.5% of total expenditure of public drug plans in Canada (PMPRB, 2017). In the United Kingdom, however, after a decade in which the annual change in the average price of generics ranged from -17% to 5.1%, in 2015 the figure shot up to 14.4% (RAPS, 2016). In the United States, a study showed that one in five generics marketed for the whole 2010-15 period experienced extraordinary price increases (higher than 100%), which moderated the price erosion of "established" generics (GAO, 2016).

The common element in all these international cases of price hikes in off-patent medicines is that the providers have a monopoly on the supply of the medicine in question. There is, in fact, significant market concentration in the generics market. A recent study of trends in US generic markets between 2004 and 2016 showed that 40% of generic molecules were supplied by a single manufacturer; another 40% are supplied by more than four manufacturers; the remaining 20% molecules being supplied by two or three manufacturers. The number of generic manufacturers has been decreasing recently and generic prices have risen faster than inflation, especially in markets with few competitors (Berndt, Conti and Murphy, 2017). Recently, new measures have been introduced to facilitate more efficient generic drug review by the FDA, with the objective of enhancing competition and thereby lowering prices (FDA, 2018).

Innovative medicines are not always available to patients who need them, either because of cost - or for other reasons

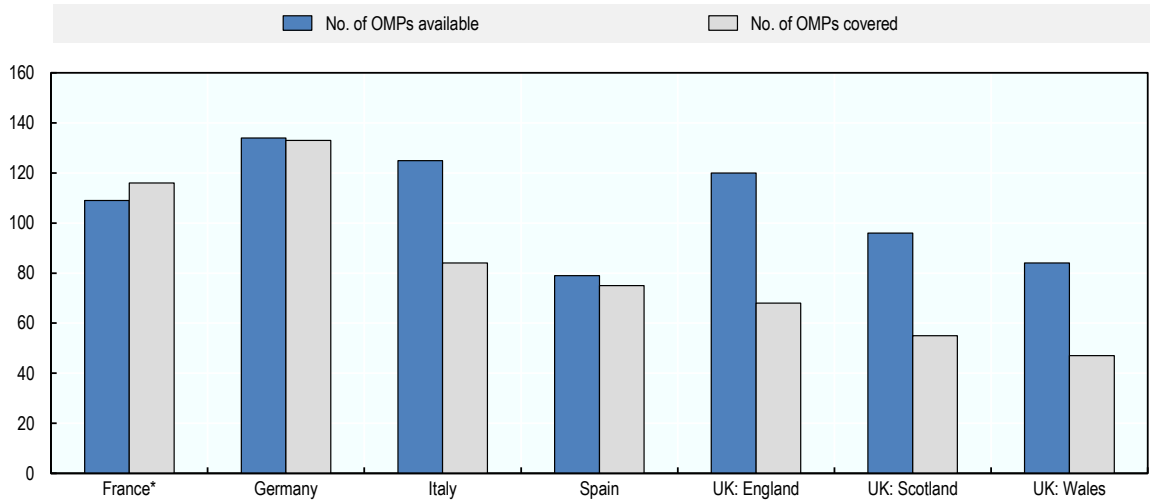
Several studies have shown that innovative medicines are not always available to patients who need them. High prices are not the only cause of poor access (see Box 1.8 for a discussion of access). Sequential launch strategies, delays imposed by health technology assessment and price negotiations, and characteristics of health systems (e.g. low capacity or inefficiencies) can also delay or impede access to treatment.

One study compared the availability and coverage of 45 oncology drug indications approved in the United States between 1 January 2009, and 31 December 2013 in the United States, Canada, Australia, and the United Kingdom. The US Medicare programme covered all indications in June 2014. Of 30 indications already approved by the European Medicines Agency, 87% were covered in the United Kingdom. In Canada, 54% of the 24 indications approved were recommended by the Committee in charge of assessing oncology drugs to inform coverage decisions (which public plans remain free to follow or not). In Australia, 46% of the 24 indications approved were publicly covered (Zhang, Chantel Hueser and Hernandez, 2017).

A study of the European Society for Medical Oncology (ESMO) evaluated the formulary availability of licensed anti-neoplastic medicines in 49 European countries; patient out-of-pocket costs for the medications and their *actual* availability for patients with valid prescriptions. It showed that oncology treatments are more often available and covered in Western European countries than in Eastern European countries, where many drugs are either not available or only available at full cost to patients. Most of the medicines included in the 2015 updated version of the WHO Model List of Essential Medicines, however, were available with no out-of-pocket cost to patients, even in Eastern European countries, and were reported as being always or usually available. Problems impeding actual availability were reported in some Eastern European countries, including Hungary, Latvia, Slovenia, and the Slovak Republic (Cherny et al., 2016).

A recent study assessed the availability and accessibility[27] of all orphan medical products (OMPs) approved by the EMA to mid-2016 in several EU countries (Zamora et al., 2017). Since the introduction of the orphan drug legislation in Europe, 143 orphan drugs have obtained a marketing authorisation according to the centralised procedure (for 145 indications). Of these, nearly 40% (56) were products used in oncology. This report shows that availability varies from a low of 55% in Spain to 97% in Germany, and access (i.e. coverage) from 33% in Wales to 93% in Germany (see Figure 1.10). However, these factors do not guarantee patients will be treated with these medicines, and information on diffusion and uptake – together with information on prevalence – would be useful to complement these data. Marketing authorisation, coverage and price are not the only potential barriers in access to care for patients with rare diseases. Delayed diagnoses, limited access to resources, and absence of specific therapies often preclude patients from receiving proper, timely care (Dharssi et al., 2017). In the United States, a recent study of the coverage of 138 orphan medicines marketed between 2000 and 2016 by 20 leading commercial payers revealed that 80% of orphan medicines are covered by at least 75% of payers and one third are covered by all payers. About 44% of these medicines are in formularies' tier 4, with the highest levels of cost-sharing. The authors also noted an increase over time in the number of coverage denials, in patient cost-sharing, and in use of prior authorisation and quantity limits (Cohen and Awatin, 2017).

Figure 1.10. Availability and coverage of 143 orphan medical products (OMPs) approved centrally by the EMA in five EU countries between 2000 and May 2016



Note: * In France, innovative medicines responding to high unmet needs may be available to patients before marketing authorisation through "temporary authorisation for use", fully covered by health insurance.
Source: Zamora et al., 2017.

Box 1.8. Accessibility and affordability of medicines

For health care in general, access can be defined as the ability to obtain health care services based on medical need and irrespective of factors that are not related to need, such as physical location, socio-economic status, or income and ability to pay (Oliver and Mossialos, 2004). For medicines more specifically, this requires that they are marketed in a country, affordable (no financial barriers for patients or for the health system) and that they are physically accessible at a reasonable inconvenience or cost. For purposes of monitoring achievement of the Millennium Development Goals, the United Nations Development Group defined access as "having medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour's walk of the population" (UNDP, 2003).

In addition to general availability through marketing of a medicine in a country, the existence and magnitude of financial access barriers can serve as one measure of access because the full prices of health services paid to providers or manufacturers of medicines are usually beyond the financial means of all but the wealthiest patients in need of treatment. Therefore, indicators of access include the coverage of medicines by publicly funded health care or insurance schemes, levels of public spending or medicine prices.

Medicine prices determine affordability not only from the point of view of individual patients but also for publicly funded health care systems. If prices of medicines are very high, they may be excluded from public coverage or restricted to only the most severe cases. The latter has been a problem in resource constrained settings for some time but more recently also in high-income countries. It is difficult to define affordability in general because it is an inherently normative concept dependent on local constraints or preferences (Niëns and Brouwer, 2013). Some practical definitions have been developed with reference to incomes, wages or wealth in the population or levels of expenditure that would lead to impoverishment (ibid.).

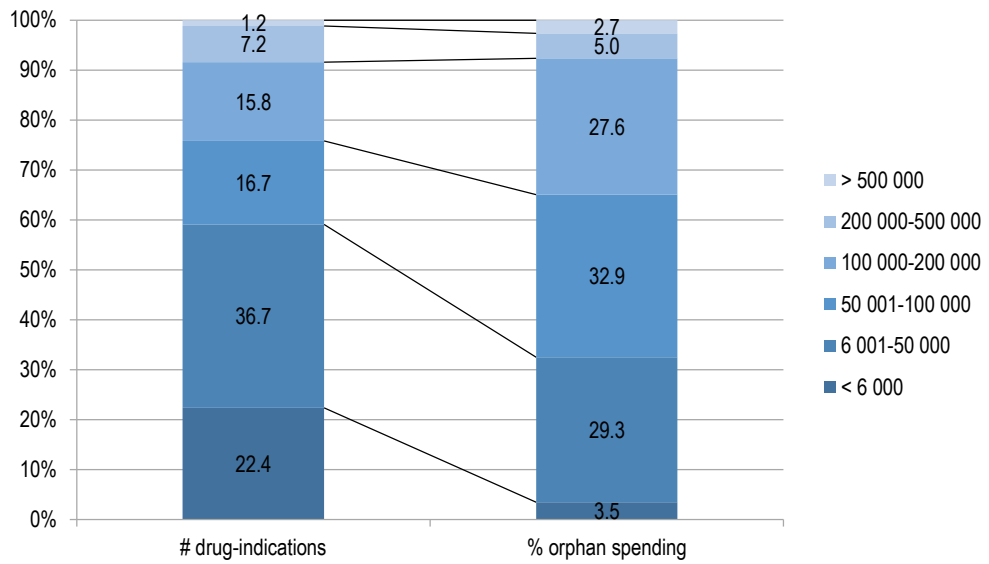
Incentives for the development of orphan medicines may not always be closely aligned with their intended policy goals

Between 5 000 and 8 000 rare diseases have been identified to date. Many of them are degenerative and life-threatening, 80% have a genetic origin, and half have a childhood onset, causing about one-third of child deaths before one year of age (López-Bastida et al., 2016). Since the population affected by each of disease is small, commercial incentives to develop medicines for patients with rare diseases were seen as inadequate. To encourage the development of such treatments, several countries (United States, European Union, Australia and Japan) have introduced specific "orphan" drug policies. While eligibility criteria and incentives differ across countries, they have undoubtedly helped foster the development of drugs for orphan conditions (Giannuzzi et al., 2017). A number of trends, both in science and in pharmaceutical markets, however, have raised questions about the ability of existing policy frameworks to support the objective of encouraging the development of therapies that would otherwise be considered commercially unattractive.

First, a few orphan drugs have reached the market at high prices in the past decade. A recent report by Quintiles IMS shows that in 2016 approximately one quarter of orphan medicines in the United States had annual costs of more than USD 100 000, accounting for 35% of all sales for orphan indications (see Figure 1.11). The report shows that medicines for conditions with very low prevalence are likely to command higher prices, but does not provide any information on price trends, even though the sample of products spans 33 years of approvals. In 2014 in the United Kingdom, 18% of orphan medicines had annual treatment costs higher than GBP 100 000 (about USD 130 000) (Onakpoya et al., 2015).

Second, if companies obtain orphan indications for which they charge high prices, they may subsequently develop non-orphan indications for which they are able to maintain this price. This strategy, however, can only be used in the United States, where a brand-name medicine can be sold for both orphan and non-orphan indications. Of 449 orphan drugs approved by the FDA between 1983 and 2016, 98 (22%) have both orphan and non-orphan indications, among which 34 obtained an orphan indication first and 10 orphan and non-orphan indications simultaneously (QuintilesIMS Institute, 2017b). In Europe, medicines used in the treatment of orphan and non-orphan indications must be marketed with different brand names and are likely to be priced differently.

Figure 1.11. Distribution of 335 drug-indications according to their list price and their shares in total sales for orphan indications in the United States in 2016



Source: QuintilesIMS Institute, 2017b.

Third, incentives for the development of orphan medicines are being provided even for drugs with revenues exceeding USD 1 billion. Côté et al. (2012) showed that 43 brand-name medicines with at least one orphan indication had annual global sales of exceeding this figure in 2008. Among them, 18 products only had orphan indications. A more recent study observed that a number of top selling drugs had one or more orphan designations: in 2015, seven out of the ten top-selling drugs worldwide had orphan indications, with global sales ranging from USD 5.2 billion to USD 14.1 billion (Daniel et al., 2016). In interpreting these figures, however, several points need to be taken into account:

- First, this problem mainly seems to concern US-specific incentives for orphan drugs. EU orphan drug legislation is very different and the number of approvals of orphan indications is much lower. Between 2001 (first year of implementation of the EU legislation) and 2015, 339 orphan drugs were approved by the FDA and only 117 by the EMA (OECD, 2017b).
- Second, two cases should be highlighted. In some cases, so-called blockbuster medicines have both orphan and non-orphan indications. For Humira®, for instance, the company developed six orphan indications, four of which have been approved, but orphan indications account for less than 4% of the product's sales in the United States (QuintilesIMS Institute, 2017b). The question is then: would the company have developed these indications without the specific 50% tax-credit on R&D spending and extended exclusivity for these indications? In other cases, these blockbusters only have orphan indications. This was the case for 18 products among 43 blockbusters with orphan indications identified in 2008 (Côté and Keating, 2012). For example imatinib (Gleevec®) first obtained FDA orphan designation and marketing approval as a breakthrough treatment for patients with CML in 2001. Subsequently, it obtained a further eight orphan indications through 2014,[28] and had global sales of USD 4.65 billion in 2015 - just prior to generic entry in the United States (Pharmaceutical-Technology, 2016).

- With the development of precision medicines and targeted therapies, many oncology products may be proposed for a large number of indications with small populations. PD-1 inhibitors have such profiles. Nivolumab for instance (Opdivo®), first approved in melanoma and lung cancer, has been tested in more than 50 trials - as a monotherapy or in combination with other therapies - for multiple tumour types while pembrolizumab (Keytruda®) has been tested in 85 clinical trials for 30 tumour types (Gibney, 2017). Nivolumab has FDA orphan drug designations (as monotherapy or in combination) in 14 indications and pembrolizumab has 11.[29] With high unit prices, Keytruda® and Opdivo® achieved respectively USD 3.8 billion and USD 4.9 billion in global sales in 2017, 60% of which were in the United States (Bristol-Myers Squibb Company, 2018; Merck & Co. Inc., 2018). In such cases, the question is whether current incentives are sufficient for these companies to develop as many indications as possible.

Finally, a few new orphan products are "repurposed" medicines, previously prescribed off-label to patients at low prices and launched with an approval for an orphan indication at a high price (see Box 1.9). While it is necessary to compensate developers for the costs of generating data to demonstrate the safety and efficacy of a product in a new indication, appropriate policies may be needed to ensure that patients with orphan diseases can continue to access these drugs.

Box 1.9. Examples of repurposing at high cost to patients and payers

Murphy et al. provide a few examples where orphan drug legislation in the United States did not improve patient access (Murphy, Puwanant and Griggs, 2012):

- Tetrabenazine was approved as orphan drug in 2008 for treatment of chorea associated with Huntington's disease. This medicine has been used for decades in the United Kingdom and many other countries in this indication. Prior to FDA approval, patients could try to import the product from abroad with a prescription from their doctor, based on FDA's Personal Importation Policy, but had to pay the full cost themselves. In 2012, the cost per month for the initial dose of 25mg/day was estimated at USD 2 055 in the United States, while the same dose was available in the United Kingdom for approximately USD 43.

- Adrenocorticotropic hormone (ACTH, corticoptropin) has been used as a first-line treatment for infantile spasms in many countries - including the United States - since the 1950s, albeit without FDA approval for this indication. In 2007, the price for one vial increased from USD 1 650 to USD 23 000, when the company applying for the orphan drug indication adopted an "orphan-style pricing model". In October 2010, the FDA approved the product for the treatment of infantile spasms in children under two years, a very small target population estimated at 800 children per year. The cost per vial in the United Kingdom was still under USD 523 in 2012. The manufacturer subsequently obtained other indications, including multiple sclerosis, for which it originally kept the same price in the United States. The current US list price is approximately USD 39 000 (Hartung et al., 2018). As a high-priced drug, it is likely to be placed on a higher or specialty tier in insurance formularies and associated with a significant co-payment or co-insurance amount, and/or subject to prior authorization. While the manufacturer provides a co-pay programme, assistance is limited. Finally, the exceptionally high cost of the drug to third-party payers is likely to influence treatment choices and to have flow-on effects for the magnitude of premiums and deductibles (Drash, 2018).

Incentives for the development of orphan drugs have to be sustained. Although the number of therapies available to patients with rare diseases has increased overtime, it is important to stress that treatments are available for less than 5% of the 6 000-8 000 rare diseases. More efforts are also needed to make sure that available therapies are available in different countries. A recent study showed that 64 orphan drugs approved either in the United States or in the European Union were not approved in the other region, with or without an orphan drug designation/status (Giannuzzi et al., 2017). The question raised in this section is whether incentives are still well targeted to encourage the development of medicines that would not occur in the absence of these policies.

Notes

1. Overall cancer survival gains are higher than survival gains by individual cancer sites because it includes other types of cancers.
2. Pharmaceutical spending, as reported in the System of Health Accounts and OECD statistics, is net of discounts and rebates.
3. Although Quintiles IMS refers to "spending", the Institute publishes estimates based on sales from wholesalers to their customers, including pharmacies and hospitals. These sales are in general reported at the invoice prices wholesalers charge to their customers. In some countries, these prices are exclusive of discounts and rebates paid to governments, private insurers or the specific purchasers, while in others, such discounts and rebates do not occur [see (QuintilesIMS Institute, 2016b); p.12). In this report, to avoid any confusion with OECD data on "pharmaceutical spending", which includes all distribution margins and VAT where relevant but excludes discounts or rebates, data from QuintilesIMS, now IQVIA, are referred to as "pharmaceutical sales". These, however, do not coincide with industry's revenues, which are lower, due to discounts and rebates that are not accounted for.
4. See Note 2.
5. The period of observation predates the introduction of the new legislation in Germany, in 2011, which may have changed how markets function.
6. Data on Mexico do not include public spending and are thus not comparable.
7. Tiered Pricing is a means of supplying products at different price points in different markets. In this context if refers to different prices in different countries.
8. All new patented medicines introduced in the German market are subject to the evaluation and price negotiation process, except those with annual expenditure for statutory health insurance (SHI) below EUR 1 million. For orphan drugs, additional therapeutic benefit is assumed by virtue of marketing authorisation without reference to an appropriate comparator in Germany for as long as annual SHI expenditure for the drug remains below EUR 50 million.
9. At the time of the an OECD survey launched in 2014-2015, only five countries including Hungary, the Republic of Korea, Poland, the Slovak Republic and the United Kingdom, had published an ICER threshold range; 2 to 3 times GDP per capita in Hungary, GDP per capita in the Republic of Korea (may vary by disease), 3 times GDP per capita in Poland, EUR 18 000 to 26 500 in the Slovak Republic and GBP 20 000 to 30 000 in the United Kingdom.
10. Orphan drugs refer to medicines developed for rare conditions. Countries use different thresholds to consider if a disease is rare: "rare conditions" are those that affect less than

200 000 people in the United States (or about 1 in 1 500 people), less than 1 in 2 000 people in the European Union and less than 1 in 2500 people in Japan.

11. The estimates of population covered by type of coverage are not mutually exclusive; people can be covered by more than one type of health insurance during the year (Barnett and Berchick, 2017).

12. These percentages differ from those presented in Figure 1.8 because the latter takes into account OTC drugs and medical non-durables.

13. PBMs administer drug benefits for commercial health plans, self-insured employer plans, Medicare Part D plans, the Federal Employees Health Benefits Program, and state government employee plans.

14. Discounts refer to price reductions while rebates refer to funds returned to the payer after the transaction.

15 . The unit rebate is the highest of (1) the Average Manufacturer Price (AMP) minus Best Price or (2) 23.1% of AMP. The AMP is defined as the average price paid to the manufacturer by wholesalers and retail pharmacies that purchase the drug directly from the manufacturer.

16. This is a sub-sample of the 449 medicines approved in the United States with at least one orphan indications, which were still marketed in 2016 and for which price information was available.

17. In the United States, a brand-name medicine can have both orphan and non-orphan indications. In Europe, a same product has to be marketed with a different brand-name for non-orphan indications.

18. Prices reported in this report are list prices, estimated from the MIDAS database, in retail and hospital market sectors. They do not account for potential confidential rebates.

19. This analysis covers the US non-Medicaid markets for these self-administered products.

20. This share only takes into account spending for orphan indications for drugs which have both orphan and non-orphan indications.

21. During the same period (1960-2002), the general inflation in the United States was +504.4% (a 6-fold increase) (https://data.bls.gov/cgi-bin/cpicalc.pl).

22. Prices presented in current Euros in the original study have been adjusted for inflation using the Consumer price index published by INSEE.

23. Many countries do not publish cost-effectiveness thresholds (Auraaen et al., 2016).

24. Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria,18 which assesses the five domains: study design; consistency of evidence; directness of the evidence; precision; and reporting biases

25. The Policy and Regulatory Report (PaRR) competition database is a subscription-only proprietary tool that tracks competition developments from almost 200 agencies worldwide. The parameters for this search were pharmaceutical cases initiated between 1 January 2007 and 28 February 2017 in OECD member countries. The review of cases focused on instances of sudden price increases of patented or generic pharmaceuticals. Cases concerning frivolous patent lawsuits, so-called product hopping, pay-for-delay agreements, or other barriers to market entry of generics were not included. A companion document will be made available on the OECD website and is available upon request.

26. These are off-patent products that are only available from a single manufacturer.

27. Where "availability" is defined as the ability to prescribe the medicine and "access" is defined as full or partial coverage by a public payer.

28. For more information, see https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm (accessed 2 July 2018).

29. See previous note.

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Annex 1.A. Supplementary table

Annex Table 1.A.1. Expenditure on prescribed medicines by financing schemes, OECD countries, 2016

	Government schemes	Compulsory contributory health insurance schemes	Voluntary health care payment schemes	Household out-of-pocket payments
Australia*	75.9	..	1.0	23.2
Austria	..	88.1	0.3	11.6
Belgium	..	78.4	0.2	21.3
Canada	38.7	3.9	35.7	21.7
Czech Republic	..	75.6	..	24.4
Denmark	62.6	..	8.4	29.0
Estonia	0.2	65.5	0.4	33.8
Finland	..	66.1	0.5	33.4
Germany	5.1	88.7	0.4	5.7
Hungary	1.9	47.4	4.1	46.7
Iceland	63.3	..	2.8	33.9
Japan*	9.2	75.7	1.1	13.9
Korea	7.8	58.3	1.1	32.8
Latvia	51.6	..	0.2	48.3
Luxembourg	..	80.1	8.0	11.9
Mexico	..	..	4.0	96.0
Norway	..	54.1	..	45.9
Poland	1.5	68.3	0.4	29.8
Slovak Republic	..	71.3	..	28.7
Slovenia	..	64.1	34.3	1.6
Spain	84.7	4.3	..	11.0
Sweden	72.1	..	..	27.9
Switzerland	2.4	64.1	2.5	31.0
United States**	13.6		72.7	13.7

Note: * 2015; ** In the United States, payments from private health insurance cannot be split between compulsory and voluntary PHI.
Source: OECD (2018), *OECD Health Statistics* (database), http://dx.doi.org/10.1787/health-data-en.

Chapter 2. Discovering and selling medicines

This chapter describes the biopharmaceutical industry, beginning with an examination of its role and significance in the national economies of OECD countries in terms of employment, economic output, trade and research and development (R&D) expenditure. It then takes a closer look at the process of pharmaceutical R&D, outlining the main phases of the development of new medicines and their attendant risks; examining the contributions to R&D of the public and private sectors; comparing R&D intensity in the pharmaceutical industry with that of other industries; and considering R&D expenditure and activity in the context of health needs. Finally, the chapter describes trends in the industry, observing that while R&D productivity has declined over time and is increasingly focused on the development of medicines for small patient populations, the industry remains highly profitable.

The statistical data for Israel are supplied by and under the responsibility of the relevant Israeli authorities. The use of such data by the OECD is without prejudice to the status of the Golan Heights, East Jerusalem and Israeli settlements in the West Bank under the terms of international law.

Introduction

This chapter discusses the structure of the pharmaceutical and biotech industry, and addresses questions such as: What are the relative contributions of the public and private sectors to pharmaceutical R&D? How much is spent on R&D? What are the risks and uncertainties associated with the development of a new medicine? What are the returns for investors? The chapter also emphasises the significance of the pharmaceutical sector in OECD country economies. The main results can be summarised as follows:

- The pharmaceutical industry plays a significant role in some OECD country economies, in terms of employment, gross value added, R&D activities and trade balance. The United States is home to by far the largest pharmaceutical industry in absolute terms, but relative to the size of their national economies the industry plays a greater role in Denmark, Ireland, Slovenia and Switzerland.
- Both private investors and governments finance pharmaceutical R&D and both bear the risk of failed R&D projects. Public and private contributions to R&D are complementary, with governments mainly financing basic research and private firms focusing on translational research and product development.
- Product development is risky and costly. The probability of gaining marketing approval for a drug entering in phase I clinical trials has been estimated at 14% on average, but ranges from 3% to 45%, depending on the therapeutic area, type of drug, the indication and the approval process. The clinical development of a new drug typically takes eight years.
- The productivity of pharmaceutical R&D, measured as the amount spent per approved medicine, has declined over time – as it also has in other industries that rely on R&D for productivity gains, such as information technology and agricultural production.
- Nevertheless, the pharmaceutical industry has made, on average, consistent *economic profit* in recent decades and has remained more profitable than many other R&D-intensive industries. Increasing drug prices and growing markets could be possible explanations of why profitability has remained stable even where the cost of R&D has increased.
- Return on investment is concentrated in a small number of products.
- The *effective* duration of market exclusivity[1] for novel medicines (before entry of a competing generic or biosimilar product) has declined slightly since 1995 to 12-13 years in 2015. Competition from follow-on patented products can occur earlier in the product life-cycle.
- Scientific progress has steered R&D efforts increasingly towards the development of medicines targeting small populations ("targeted" and orphan medicines).

The pharmaceutical industry plays a significant role in some OECD economies

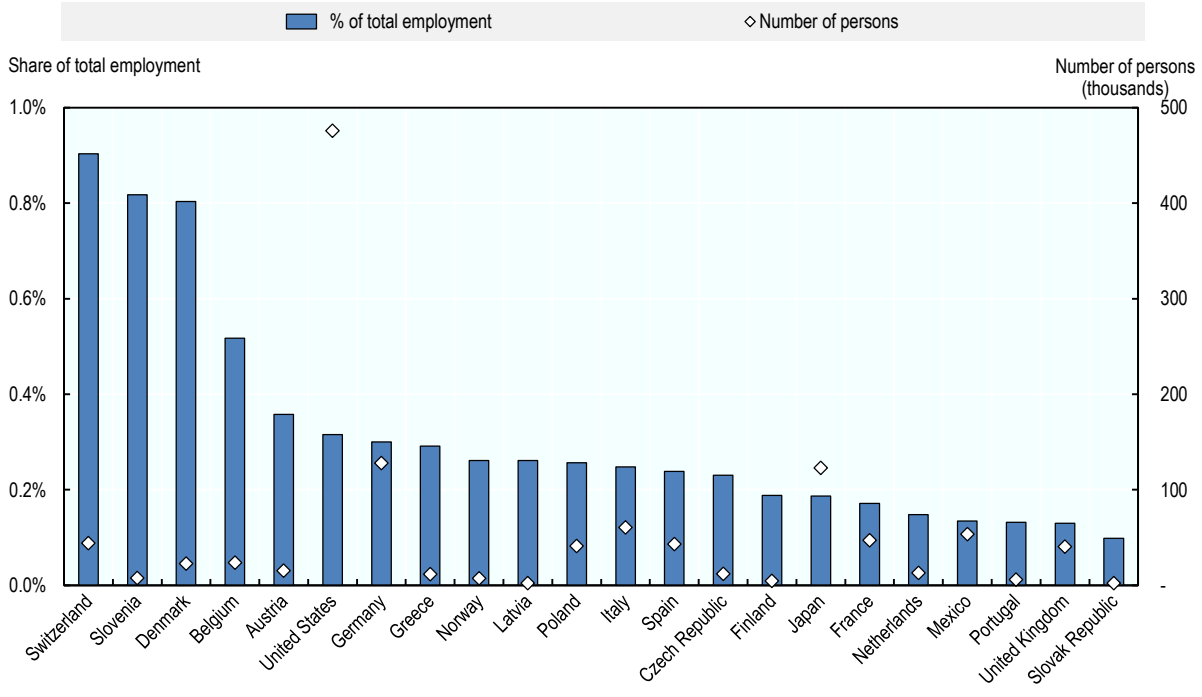
The pharmaceutical industry represents a sizeable share of the economies of some OECD countries. While the pharmaceutical industry is present in all OECD countries, its economic activity (i.e. location of corporate headquarters, R&D or manufacturing) is concentrated in a small number of countries. The United States is home to by far the largest pharmaceutical industry in absolute terms, but relative to the size of their national

economies the industry plays a greater role in Denmark, Ireland, Slovenia and Switzerland. For policy makers, retaining a strong presence of the pharmaceutical industry in a country can be an explicit goal of industrial and economic policy. This section provides a brief overview of the contribution of the pharmaceutical industry to the economies of OECD countries, in terms of employment, value added, R&D spending and trade.

The pharmaceutical industry employs more than 1.2 million people in OECD countries

Across 22 OECD countries for which data are available, the pharmaceutical manufacturing industry directly employed approximately 1.2 million people in 2015.[2,3] This represents only a fraction of total employment related to medicines, and does not include persons whose activities may be related to pharmaceutical R&D or distribution classified in other general categories, such as "scientific research and development" or "wholesale and retail trade." No internationally comparable data are available according to broader definitions of the industry similar to data published by the Pharmaceutical Research and Manufacturers of America (PhRMA) concerning the United States. In small countries with large pharmaceutical industries, such as Switzerland, Slovenia and Denmark, persons engaged in the pharmaceutical manufacturing industry represent approximately 0.8% to 0.9% of total employment. In the United States, with around 480 000 people in the sector,[4] the pharmaceutical industry represents 0.3% of total employment (Figure 2.1).

Figure 2.1. Persons engaged in the pharmaceutical industry, 2015 or 2014



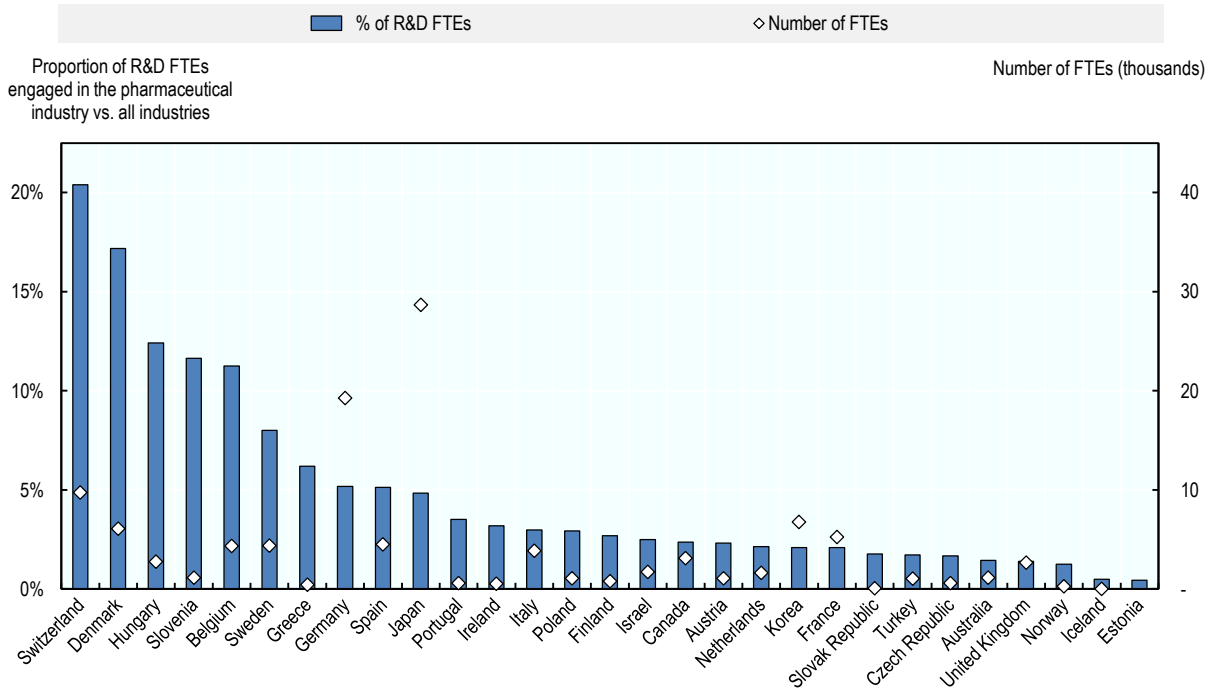
Source: OECD Structural Analysis (STAN) database (OECD, 2017g).

A significant proportion of jobs in the industry relate to R&D, which requires highly developed skills. Recent data on the share of R&D personnel in total employment in the

pharmaceutical industry are only available for nine OECD countries.[5] Among these countries, the share of full-time equivalents (FTEs) working in R&D is highest in Switzerland (26%), followed by the Netherlands (14%) and France (12%). With almost 10 000 FTEs in R&D, Switzerland also employs the highest absolute number of R&D personnel among these countries.

In some small countries with large pharmaceutical sectors, the pharmaceutical industry employs a large proportion of the total R&D workforce in the country (Figure 2.2). In Switzerland, more than 20% of all FTEs engaged in R&D work in the pharmaceutical industry, the highest proportion among OECD countries for which data are available. Denmark has the second highest share (17%), followed by Hungary and Slovenia (12% each). In absolute terms, the largest pharmaceutical R&D workforce is likely to be found in the United States. According to data from the Business R&D and Innovation Survey (BRDIS), 117 000 persons were employed in pharmaceutical R&D by businesses in 2013 in the United States, which represents 8% of all R&D-related employment by businesses. But these data are not directly comparable to data available from other OECD countries. Large R&D workforces are also found in Japan and Germany, where approximately 29 000 and 20 000 R&D FTEs are employed in the pharmaceutical industry respectively.

Figure 2.2. Full-time equivalents (FTEs) engaged in R&D in the pharmaceutical industry, 2015 or most recent year available



Note: 2011 data for Sweden, 2012 for Switzerland; all other countries 2015, 2014 or 2013.
Source: OECD Structural Analysis (STAN) database (OECD, 2017g).

The industry contributes to the economic output of OECD countries

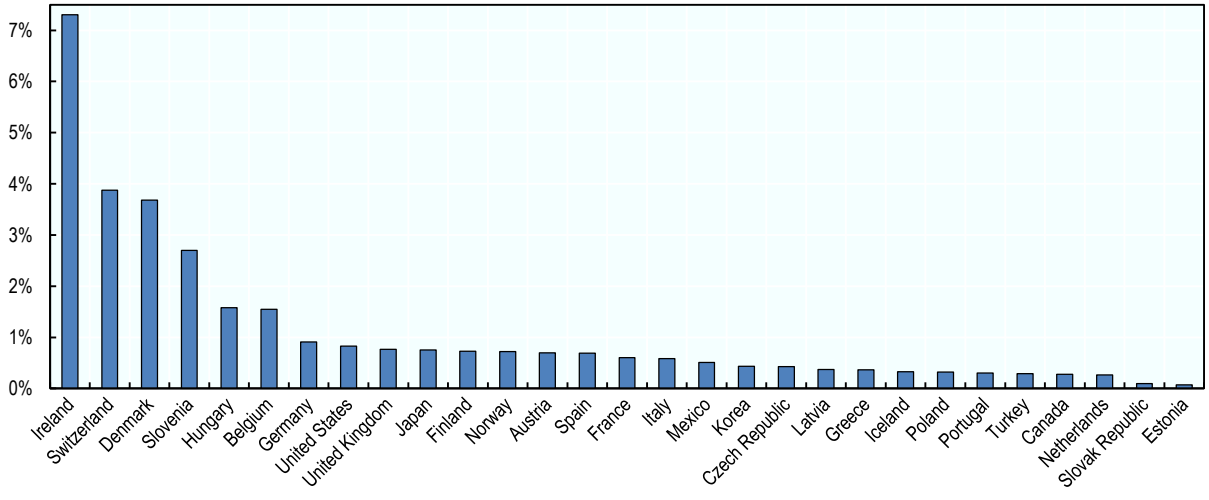
The relative contribution of the pharmaceutical industry to each national economy is highest in a number of small OECD member countries that host production facilities or corporate headquarters (Figure 2.3). Gross value added (GVA) by the pharmaceutical

industry as a percentage of total GVA in the economy is highest in Ireland (7.3%), followed by Switzerland (3.9%) and Denmark (3.7%). In Ireland, where 37% of total GVA in the economy is generated by the manufacturing sector,[6] the pharmaceutical industry is comparable in size to the Finance and Insurance and Information and Communication sectors, which account for just under 7% and 9% of total GVA respectively. Denmark and Switzerland have smaller manufacturing sectors (18% and 15% respectively). In Denmark, the pharmaceutical industry contributes somewhat less than the finance and insurance and the information and communication sectors (6% and 5% respectively), while in Switzerland, its contribution is similar to that of the information and communication sector (4%) but lower than that of the finance and insurance sector (10%) (OECD, 2017i).

The pharmaceutical sector is a relatively small contributor to total GVA in the largest economies. For example, pharmaceuticals accounted for only 0.8% of total GVA in Germany, Japan and the United States. In all of these countries, this is significantly less than the finance and insurance or information and communication sectors, which account for 5% each of total GVA in Germany and Japan, and 6% in the United States. The entire manufacturing sectors in these four countries range from 12% of GVA in the United States economy to 23% in Germany (OECD, 2017i).

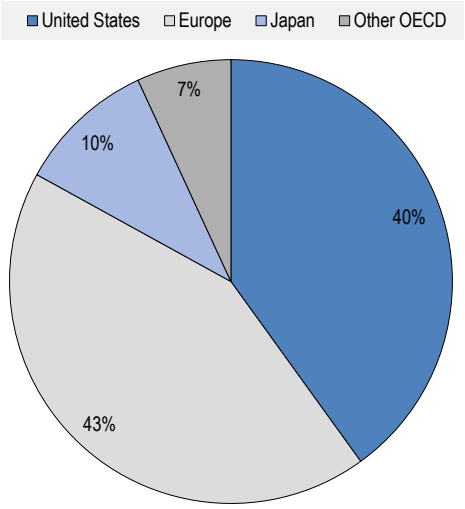
A small number of countries contribute a large share of the total GVA generated by the pharmaceutical industry across all OECD countries (Figure 2.4). The United States alone accounted for approximately 40% of total pharmaceutical GVA across all OECD countries for which data are available for 2015 (or a recent year since 2012). Japan contributed 10% and European OECD countries collectively accounted for 43% of GVA, with the highest shares contributed by Germany (8%), Switzerland, the United Kingdom (5% each) and Ireland (4%). The remaining 7% of GVA was generated in other non-European OECD countries.

Figure 2.3. Gross value added by the pharmaceutical industry as a percentage of total gross value added in national economies



Note: Based on data for 2015 or the nearest year available between 2012 and 2014.
Source: OECD System of National Accounts (SNA) and Structural Analysis (STAN) databases (OECD, 2017a, 2017g).

Figure 2.4. Gross value added in the pharmaceutical industry by OECD country or region

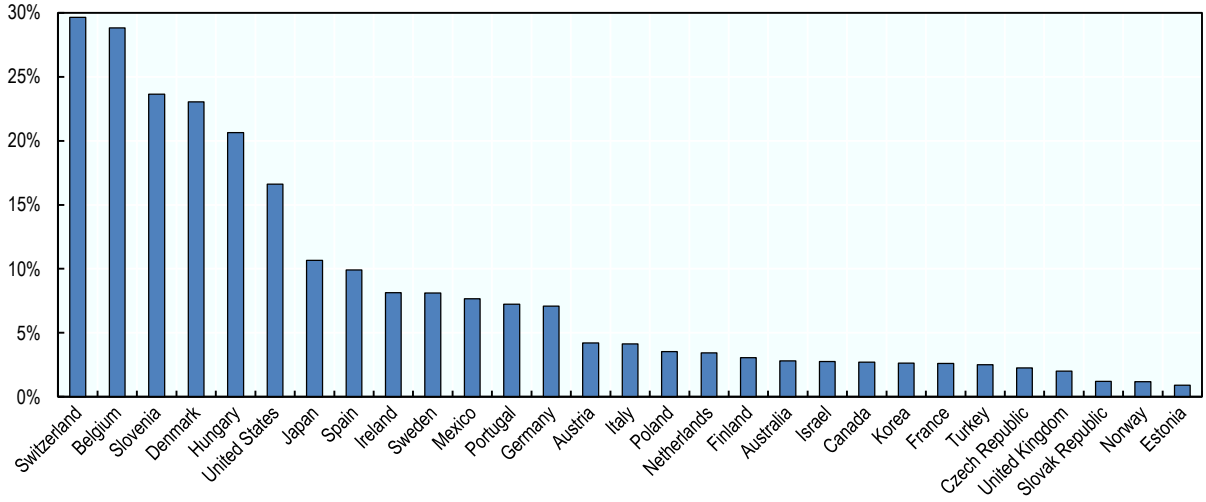


Note: Based on data for 2015 or the nearest year available between 2012 and 2014. Total does not include Australia, Chile, Israel, Luxembourg, New Zealand and Sweden.
Source: OECD System of National Accounts (SNA) and Structural Analysis (STAN) databases (OECD, 2017a, 2017g).

OECD countries host most of the world's biomedical R&D activities

Most biomedical R&D activity, including pharmaceutical R&D, takes place in OECD countries (Chakma et al., 2014). The pharmaceutical industry spent approximately USD 100 billion on R&D in 2014 across OECD countries (OECD, 2017f). More than half the spending in OECD countries occurs in the United States, where the pharmaceutical industry spent more than USD 56 billion (0.3% of GDP). Industry spent USD 26 billion (0.1% of GDP) in Europe and USD 15 billion (0.3% of GDP) in Japan. As a share of GDP, industry spending is highest in Switzerland (0.6%), Belgium (0.6%) and Slovenia (0.4%). In some small countries with large pharmaceutical sectors, pharmaceutical industry expenditure on R&D[7] also represents a large share of total business enterprise expenditure on R&D (BERD) (Figure 2.5). For example, the pharmaceutical industry accounts for 30% and 29% of total BERD in Switzerland and Belgium respectively, and for 24% and 23% of BERD in Slovenia and Denmark. However, the share of total BERD represented by the pharmaceutical industry is also significant in larger countries such as the United States (17%) and Japan (11%).

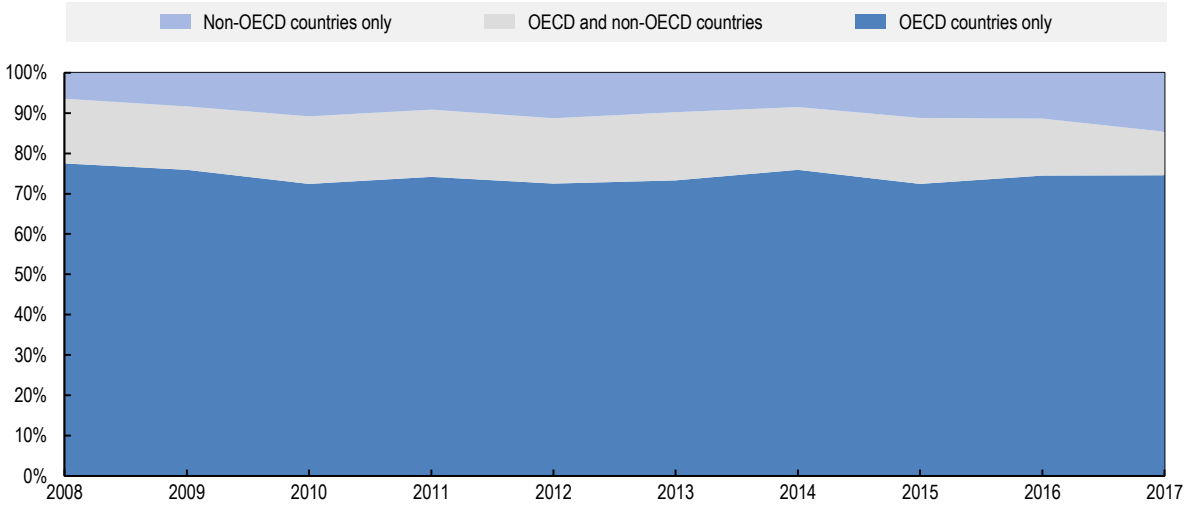
Figure 2.5. R&D expenditure in the pharmaceutical industry as a percentage of total business enterprise expenditure on R&D (BERD), 2015 or latest year available



Source: OECD Research and Development Statistics database (OECD, 2017f).

More than three-quarters of all registered clinical trials worldwide (not specific to medicines) take place in OECD countries. With increasing geographical scope of trials and varying regional or national registration requirements, it is not straightforward to obtain exhaustive information on clinical trial activity across all OECD countries. The WHO maintains the International Clinical Trials Registry Platform (ICTRP) that collates data from 17 regional or national registers, including those in the European Union, Japan and the United States. Of more than 500 000 studies registered in the ICTRP as at end of July 2017, 77% were undertaken in OECD countries. About 20% of all registered clinical trials were conducted in the United States, followed by Japan (6%), the United Kingdom and Germany (5% each). However, this includes a wide range of clinical studies, including RCTs, observational studies and trials of healthcare interventions other than medicines, such as procedures, devices, delivery system changes, and behavioural and lifestyle interventions. ICTRP does not provide a breakdown by healthcare intervention or study sponsor that would allow for isolation of industry-sponsored trials for drug development in the total. The vast majority (approximately 90%) of patients recruited for industry-sponsored trials registered with the US National Institutes of Health (NIH) come from OECD countries (see Figure 2.6 and Annex 2.A for further details).

Figure 2.6. Clinical studies of drugs or biologics registered with the United States NIH with industry as lead sponsor, share by recruitment country, 2008 to 2017



Note: These figures likely overstate the importance of OECD countries because only registration of trials of drugs and biologics subject to FDA regulation is compulsory; 55% of trials registered with the NIH recruit patients in the United States and other countries, and 34% in the United States only, which is a significantly higher share than the 20% of the studies conducted in the United States according to the WHO International Clinical Trials Registry Platform (ICTRP).
Source: US NIH, 2017a.

One-third of OECD countries are net exporters of pharmaceuticals

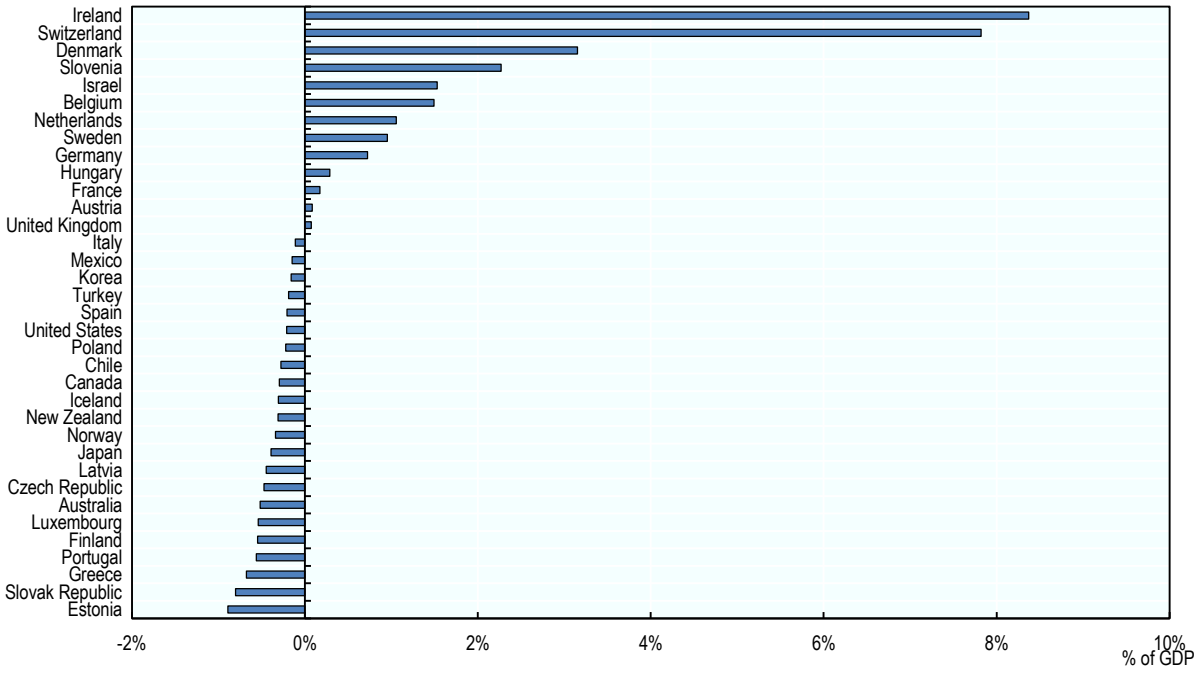
In 2015, Switzerland, Germany and Ireland were the biggest net exporters of pharmaceuticals, with trade surpluses of USD 41 billion, 28 billion and 27 billion respectively (OECD, 2017g). With net imports of USD 38 billion, the United States had by far the largest pharmaceutical trade deficit (ibid.). Japan and Australia had the next highest net imports, amounting to USD 20 billion and USD 6 billion respectively (ibid). Net pharmaceutical exports represented more than 8% of GDP in Ireland in 2015, approximately 8% in Switzerland and 3% in Denmark, but less than 1% in Germany (Figure 2.7). Net imports represented 0.5% of GDP in Australia, 0.4% in Japan and 0.2% in the United States (Figure 2.7).

Exports and imports of medicines most often take place between companies manufacturing medicines and their licensees, distributors or affiliates. However, price differentials between countries provide an incentive for arbitrage and can prompt trade by wholesalers or other entities in the supply chain. The resale of goods between countries and placement on the market outside the formal channels authorised by the product manufacturer is often referred to as *parallel trade* (OECD, 2008). In the United States, trade across national borders outside manufacturers' channels is referred to as *cross-border trade* (ibid.), and is generally prohibited except for personal consumption. By contrast, parallel trade in medicines by intermediaries is legal in the European Union, where the single market aims to ensure there are no unnecessary barriers to the free trade of goods between member states. The proportion of parallel imports in outpatient pharmaceutical markets varies considerably across European Union countries. According to estimates reported by the European Federation of Pharmaceutical Industries and Associations in 2016, parallel imports accounted for nearly 25% of the retail market in

Denmark and 12% in Sweden. In Germany and the United Kingdom, the two largest markets for which estimates are available, parallel imports accounted for 9% of the market. In contrast, in Austria, Belgium or Poland, the share of parallel imports was between 1% and 2% (EFPIA, 2016).

In the United States, cross-border imports of drugs for personal use by patients have generated a lot of debate (Fralick, Avorn and Kesselheim, 2017). While the US Food, Drug, and Cosmetic Act currently prohibits such imports, the Food and Drug Administration (FDA) has generally not enforced this prohibition when patients import products for their personal use (ibid.). A survey conducted in November 2016 found that 8% of United States households had bought prescription drugs from Canada or other countries outside the United States in order to obtain them at lower prices (KFF, 2016).

Figure 2.7. Trade balance in pharmaceuticals, 2015



Source: OECD Structural Analysis (STAN) database (OECD, 2017g).

The process of pharmaceutical R&D is complex

Pharmaceutical R&D is a complex ecosystem of activities involving public and private stakeholders. While unpredictable advances in basic science are a key driver of progress, business opportunities for private investors are also important (Nicholson, 2012; Lo and Naraharisetti, 2014). R&D relies heavily on private investment and as alternative investment opportunities compete for capital, the returns expected by private investors increase with the anticipated risk. With low production costs, returns on investment in medicines depend in part on the costs of R&D, the associated probability of successful marketing approval (or risk of failure), and the value of expected sales (volume x price). In making choices about R&D projects, firms seek to maximise future revenues, considering both the potential volume of sales of a successfully approved new

product, as well as the prices that the product can command in various markets. As in all other sectors that rely on private capital, pharmaceutical firms have an incentive to charge prices that maximise revenue. The challenge is therefore apparent: in harnessing the private sector for investment in R&D, policy seeks to strike a balance between prices that encourage that investment and the development of effective treatments that address unmet needs, as well as to allocate health care budgets as efficiently as possible. If the budget impact of novel treatments is too great, both public and private payers may be unable to afford them.

The following subsections discuss the process of R&D and its inherent risks, the contributions of the public sector and the industry to R&D, dynamics in the pharmaceutical market, and how these affect the business model of the industry.

Pharmaceutical R&D is a long and risk-prone process

Pharmaceutical R&D can be broken down into three stages: basic research, translational research, and clinical development (Milken Institute and Faster Cures, 2012; Chakravarthy et al., 2016). Clinical development generally comprises three phases of clinical trials. Phase 1 trials test the safety and tolerability (dosage) of drugs in small numbers of healthy volunteers (20 to 100) and last several months. Phase 2 trials observe efficacy and side effects in patients with the disease/condition targeted. They usually recruit up to a few hundred people with the disease and last from several months to two years. Phase 3 trials aim to assess efficacy and monitor adverse reactions to a drug vs a placebo or an existing treatment. They involve a larger sample of patients (from 300 to 3 000) and may last one to three years, depending on the disease/condition (Hobbs and McCarthy, 2009; FDA, 2017b).[8] Some R&D continues post marketing approval, also referred to as phase 4, through trials to meet post-market regulatory requirements, test new dosage strengths, regimens or new formulations (Hobbs and McCarthy, 2009; Chakravarthy et al., 2016).

Effective R&D relies on a fundamental understanding of the disease, which is generated by basic research. This basic knowledge may often be relevant to a broad range of fields and therapeutic areas, and requires translational research for effective application in product development. Knowledge generated from basic research cannot in itself be easily appropriated in commercial products, making it unattractive to for-profit private investment. On the other hand, translational research and product development are both more amenable to intellectual property protection, and thus offer greater financial incentives for private investors. Translational research has been identified as the most risky stage or "valley of death" (Milken Institute and Faster Cures, 2012). However, knowledge generation is not a unidirectional process, and these stages are complementary: basic research can be guided by knowledge generated in translational research and product development.

Investments in pharmaceutical R&D are inherently risk prone. Progress is subject to significant uncertainty and often dependent on intrinsically unpredictable breakthrough discoveries, which can then trigger a wave of follow-on discoveries. Similar to other sectors, pharmaceutical innovation is therefore mainly incremental, and breakthroughs are rare. The experience thus far with treatments for Alzheimer's disease, for example, shows that even significant investments do not guarantee progress towards effective treatments (Cummings, Morstorf and Zhong, 2014; Cummings et al., 2017).

The probability that a drug entering clinical trials is successful in gaining marketing authorisation is low. In a sample of 15 102 investigational drugs that entered phase 1 of

industry-sponsored clinical trials between 2000 and 2015, 14% received market approval after a median time of eight years of clinical development (Wong, Siah and Lo, 2018). The probability of successful transition to the subsequent development phase was highest in phase 1 and lowest in phase 2 (see Table 2.1). Based on other and smaller samples of products and different methodologies, various prior studies have estimated success rates between phase 1 and marketing approval to lie between 7% and 26% (Mestre-Ferrandiz, Sussex and Towse, 2012). Success rates vary by disease, indication, patient stratification, and regulatory path (Hay et al., 2014; Wong, Siah and Lo, 2018). Prior studies agree that success rates are below average in oncology, for example, but higher for infectious diseases, including vaccines. Wong, Siah and Lo (2018) estimated that success rates range from 3% in oncology, with a median development time of 13 years, to 33% for infectious disease vaccines, with a median development time of 6 years. Success rates have been estimated to be higher than the average for lead indications[9] than for other indications in most disease areas, though not for infectious disease vaccines (Hay et al., 2014; Wong, Siah and Lo, 2018). Wong, Siah and Lo (2018) estimated that the success rate for lead indications was 22% across all diseases and 11% in oncology. Conflicting results have been found for drugs with orphan designation. Hay et al. (2014) estimated significantly higher success rates for orphan drugs (33% for all orphans including oncology, 45% for non-oncology orphans) while Wong, Siah and Lo (2018) found lower success rates (6% and 1%). It is unclear what is driving the differences in results between studies. Reasons could include different estimation methods and the effects of missing data,[10] or that the study by Hay et al. (2014) is based on data only from the United States, while Wong, Siah and Lo (2018) use an international dataset. Inaccuracies can also stem from the classification of trials as some drugs are not designated as orphan until late-stage development phases. Furthermore, Wong, Siah and Lo (2018) found that the use of biomarkers for patient selection is associated with higher success rates. Hay et al. (2014) also found that in the United States products that benefit from FDA special protocol assessment had higher success rates (ibid.).[11]

Estimates of success rates in clinical development do not take into account successes and failures that may occur throughout the R&D that precedes clinical testing. One study estimated the rate of successful transition from pre-clinical R&D into clinical development at 35% after more than five years on average (Mestre-Ferrandiz, Sussex and Towse, 2012). Overall, successful R&D of a new medicine therefore takes an average of 10 to 15 years (Mestre-Ferrandiz, Sussex and Towse, 2012; Chakravarthy et al., 2016) but can be significantly shorter or longer for individual compounds.

Table 2.1. Success rates in clinical development phases for investigational drugs that entered clinical trials between 2002 and 2007

Development phase	Probability of transition to the subsequent phase	Probability of eventual marketing approval
Phase 1	66%	14%
Phase 2	58%	35%
Phase 3	59%	59%

Source: Wong, Siah and Lo, 2018.

Given the low overall probability of marketing approval, there is a strong argument in favour of duplication in R&D, similar to other industries in which the success of any given project is uncertain. In this context, an analysis of the optimal number of "parallel paths" cautiously suggested that there was not enough duplication in R&D of large pharmaceutical companies in 2009 and 2010, even from the perspective of a single profit-

maximising firm (Comanor and Scherer, 2013). Another study suggested, however, that there was redundancy in the R&D priorities of large pharmaceutical companies, with the majority of molecules in development for the treatment of cancer by these companies having "overlapping" mechanisms of action (Fojo, Mailankody and Lo, 2014).

The public and private sectors finance innovation

Global expenditure on health-related R&D amounted to USD 240 billion in 2009, which is the latest estimate available. In high-income countries, 60% of these investments came from the business sector, 30% from governments and 10% from other sources, including private not-for-profit organisations or universities (Røttingen et al., 2013). Some 90% of the global total expenditure was incurred in OECD countries. However, expenditure in some emerging economies, notably China, has been growing significantly since 2000 (Chakma et al., 2014).

OECD governments spend 0.1% of their GDP on average in health-related R&D

Government funding focuses on basic research, through direct research grants, subsidies and publicly-funded universities. In 2014, governments of OECD countries budgeted about USD 51 billion on health-related R&D, representing about 0.1% of their collective GDP (OECD, 2017f).[12] Health-related R&D budgets refer to funding aimed at protecting, promoting and restoring human health, including all aspects of medical and social care, not necessarily pharmaceutical R&D. Isolating pharmaceutical-related R&D expenditure can be difficult, especially in basic research that seeks to improve health-related knowledge, and cannot be associated with the development of specific products. However, this figure also understates total government support, since it excludes funding for higher education or publicly-owned corporations and tax incentive schemes. General university funding allocated to health accounted for another 0.05 to 0.2% of GDP in countries for which such data are available.[13]

The United States government budgeted approximately USD 33 billion or 0.2% of its GDP on health-related research in 2014, which is the highest spending among OECD member countries, both in absolute terms and relative to GDP (OECD, 2017f). Government R&D budgets in the United States include the National Institutes of Health (NIH), with a budget of approximately USD 29 billion in 2014, of which some 54% were allocated to basic research (down from 59% in 2000) and 46% to applied research (NSF, 2017a). Meanwhile, the higher education sector in the United States allocated USD 37 billion to research and development in life sciences and related fields, of which 56% were allocated to medical sciences (NSF, 2017b). Expenditure by higher education includes funding by the institutions themselves, as well as funding from government, businesses and non-profit organisations.

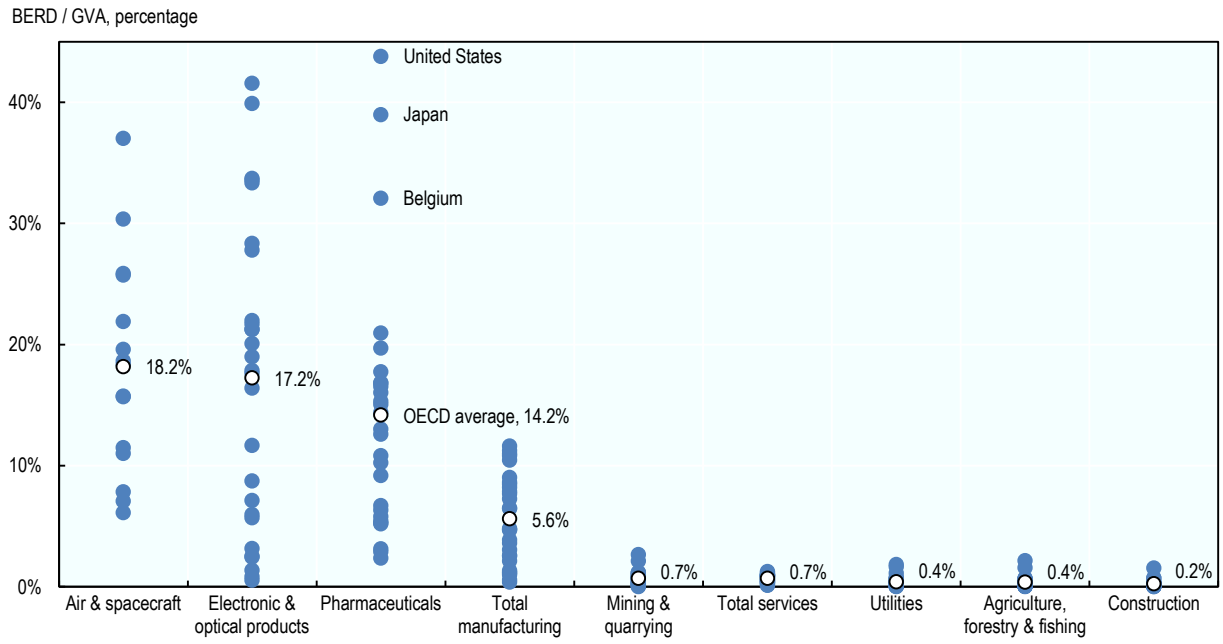
Business enterprises spend 0.2% of GDP on pharmaceutical R&D on average across OECD countries

Expenditure by the business enterprise sector on pharmaceutical R&D amounted to USD 100 billion across OECD countries in 2014, representing roughly 0.2% of GDP (OECD, 2017f).[14] R&D conducted in the business enterprise sector in the United States contributed nearly USD 57 billion to this total, which represents 0.3% of its GDP (ibid.). This includes all R&D performed by businesses in the United States regardless of the source of funding.[15] According to a survey by the National Science Foundation (NSF), in 2013 approximately 12% of pharmaceutical R&D expenditure by businesses

was not funded by the businesses themselves (NSF, 2016b). Relative to GDP, business expenditure in pharmaceutical R&D is highest in Switzerland and Belgium (0.6%), Slovenia (0.5%) and Denmark (0.4%). In these countries, pharmaceutical R&D represents between 23% and 34% of total business enterprise expenditure on R&D.

The pharmaceutical industry is among the sectors with the highest R&D-intensity in OECD countries. On average across OECD countries, R&D expenditure by the pharmaceutical sector represents approximately 14% of gross value added (GVA), compared to 18% in the air and spacecraft industry and 17% in electronic and optical products (Figure 2.8).

Figure 2.8. R&D intensity by industry: business enterprise R&D expenditure (BERD) as a proportion of gross value added (GVA), 2014 or nearest year



Note: Industries are based on the United Nations International Standard Industrial Classification of All Economic Activities (ISIC). The air and spacecraft, electronic and optical products and pharmaceutical industries are sub-categories of total manufacturing. All other industries are totals at the same level as total manufacturing.
Source: OECD Health at a Glance 2017 (OECD, 2017b).

Within the business sector, different types of firms engage in pharmaceutical R&D, and technologies are often licensed between different businesses and institutions, or acquired during the R&D process. Originators of new technologies are found across the spectrum of private and public institutions, and among different size firms. Scientists or institutions that first discover compounds and may initially rely on public or private funding, often patent their inventions or create business spin-offs from research institutions, and intellectual property rights are then licensed or acquired. Among all new chemical entities (NCEs) launched in the United States between 1996 and 2015, 74% were launched by a company other than the patentee (QuintilesIMS Institute, 2017). Among a sample of 94 marketing authorisation applications for new actives substances (NAS) that received a positive opinion from the European Medicines Agency (EMA) between

2010 and 2012, 55 products (58%) were transferred between different categories of originator entities (Lincker et al., 2014). R&D also relies on small and mid-cap firms, backed by venture and private equity capital, which play a particularly important role in the translational research stage (Milken Institute and Faster Cures, 2012; Nicholson, 2012). Venture capitalists may target high investment returns on their portfolios but also accept a high degree of risk (Nicholson, 2012; Garber et al., 2014).

Large and publicly traded firms are able to diversify risk, can reinvest cash flow from existing products into R&D, and have lower capital costs (Nicholson, 2012), allowing them to raise funds for large-scale clinical trials more easily. However, they are also sensitive to stock price fluctuations and shorter-term performance targets, which can make them more risk averse than firms backed by venture or other forms of private capital (Milken Institute and Faster Cures, 2012; Fagnan et al., 2013; Lo and Naraharisetti, 2014). While large pharmaceutical firms are active in all stages of R&D, they play a larger role in acquiring technology in the translational or clinical stages of R&D (Mayhew, 2010), funding clinical trials required for marketing approval, and commercialising approved technologies. In the sample of 94 marketing authorisation applications with EMA between 2010 and 2012, the largest number of transfers (41 products, 44% of all transfers) were from small and medium-sized enterprises (SMEs) or academic/public institutions to large or intermediate-sized companies (Lincker et al., 2014). Large companies held marketing authorisation for 63% of the products in the sample while they were the originators of 30% (ibid.).

Some 65% of R&D expenditure by firms operating in the United States is related to product development. The share of R&D expenditure spent on product development increased from 45% in 1992 to 69% in 2004 before decreasing slightly by 2013, while the share of basic research declined from 17% in 1992 to 8% in 2004 and then increased again to 12% in 2013 (NSF, 1998, 2009, 2016b). The share of applied research continued to decrease from and 39% in 1992 to 23% in 2004 and 22% in 2013 (ibid.).

R&D efforts are correlated with health needs with some notable exceptions

Some studies have shown that the intensity of health-related and pharmaceutical R&D activity and R&D output by disease area is correlated with health need, but this correlation is not perfect and there may be disproportionate concentrations of private or public R&D in some areas, while unmet need remains in others (Catalá-López et al., 2010; Atal et al., 2015; Barrenho, Miraldo and Smith, 2017). Other studies have found that medical research is mainly driven by the market size for treatments, defined as a combination of local health need in a country and its income, but not the global burden of disease, because less research is conducted in diseases with a high burden in low-income countries (Evans, Shim and Ioannidis, 2014).

Mismatches between disease burden and private R&D are inevitable and result from both financial incentives and scientific opportunities (Barrenho, Miraldo and Smith, 2017). Private investors have no economic incentives to allocate R&D resources to areas where market prospects are poor or expected return on investment is low.[16] On the other hand, some areas might provide attractive market prospects but innovation may be particularly challenging given the state of scientific knowledge. An example of the latter is dementia and Alzheimer's disease; while the ageing population of OECD countries and limited therapeutic value of currently available medicines leave need unmet and large market potential untapped, the struggle to understand the underlying pathological processes and predisposing factors has led to a number of late-stage failures.

A perfect alignment between pharmaceutical R&D and unmet health need should not necessarily be the target for policy, as some diseases may be more amenable to non-pharmacological treatments or interventions (Barrenho, Miraldo and Smith, 2017). Furthermore, in some areas, high disease burden does not only result from a lack of availability of pharmaceutical treatments, but also from lifestyle choices, low treatment rates, environmental and social determinants, and issues of health system performance and access.

Nevertheless, some prior studies have investigated the alignment between health need and R&D, with need defined in terms of disease burden (measured in disability-adjusted life years – DALYs) and R&D in terms of activity or output measures, such as the number of clinical trials or new drug approvals. These studies did not consider products in pre-clinical development. An analysis of 115 000 RCTs found that globally, a disproportionately high number of trials investigate malignant neoplasms or mental and behavioural diseases, while common infectious diseases and neonatal disorders are under-researched relative to their disease burden (Atal et al., 2018). However, this analysis did not disaggregate R&D effort between medicines and other interventions. It also showed that R&D is more aligned with disease burden in high-income countries, while the R&D shortfall in common infectious diseases and neonatal disorders is driven by low RCT activity and high disease burdens in countries in South Asia and Sub-Saharan Africa (ibid.). An earlier study of the correspondence between the number of new drug approvals in the European Union between 1995 and 2009 and burden of disease found that, despite a clear positive correlation overall, innovation was over-represented in infectious and parasitic diseases, blood and endocrine disorders, diabetes and genitourinary diseases (Catalá-López et al., 2010). Another study of global new drug approvals and burden of disease in 1990 and 2010 found that these were relatively well-aligned with global disease burden, but that there was some disproportionate concentration in diseases with high burdens and large markets, such as cardiovascular, circulatory and musculoskeletal diseases or neoplasms (Barrenho, Miraldo and Smith, 2017). Examples of where R&D activity and output are currently poor relative to disease burden or public health need include, but are not limited to:

- Antibiotics: Poor market prospects have hindered private investments in the development of new antibiotics to fight anti-microbial resistance (AMR), which is now a global threat. International efforts aim to provide alternative incentives to reward companies for new treatments (OECD, 2016a).
- Mental and behavioural disorders: a study found relatively few new approvals in some diseases with a high, such as dysthymia, anxiety or unipolar depressive disorders (Barrenho, Miraldo and Smith, 2017).
- Neonatal disorders: a study found relatively few new approvals in neonatal encephalopathy (Barrenho, Miraldo and Smith, 2017).
- A group of heterogeneous diseases defined according to the lack of R&D activity, referred to as *neglected diseases*. In a broad group of 35 neglected diseases,[17] affecting large populations with limited ability to pay and accounting for more than 8% of disability-adjusted life years (DALYs) lost and 6% of all deaths globally (IHME, 2015), only USD 3.4 billion were invested in public and private R&D in 2014, of which 68% was for HIV/AIDS, malaria and tuberculosis (Policy Cures, 2015). Among a more narrow group of 18 neglected tropical diseases (NTDs),[18] a study found disproportionately low levels of R&D in the highest burden NTDs that predominantly affect developing countries, and that R&D was

biased towards diseases with low burden and low market sizes, such as dengue and Chagas disease, relative to diseases with high burden (Barrenho, Miraldo and Smith, 2017).

Governments and other stakeholders have been exploring new innovation models, regulatory and reimbursement reforms, and strengthened stakeholder collaboration for areas such as dementia and diseases that have been recognised as neglected (OECD, 2017c). Specific legislation to increase financial incentives, through mechanisms such as extended market exclusivity, reduced regulatory fees or tax credits, and subsidies for clinical trial costs, are in place in the European Union and the United States (Hall and Carlson, 2014). Alternative models have often taken the form of partnerships between industry and the public sector or NGOs (Moran, 2005), particularly for diseases where the lack of R&D has been attributed to limited market potential. Of the USD 3.4 billion invested in R&D in neglected diseases in 2014, the public sector contributed 64%, the philanthropic sector 20%, and industry the remaining 16% (Policy Cures, 2015). Development of 67% of 151 high-priority, low-incentive products in 2015 was undertaken through partnership between industry and non-industry entities (Access to Medicine Foundation, 2016). Six manufacturers accounted for development of around three quarters of these products. Chapter 3 further discusses models of public and private partnerships to address unmet needs.

Business models in the pharmaceutical industry are changing

R&D costs have been increasing and R&D productivity – as measured by new drug approvals per amount of R&D spending - has been declining, as in other sectors. Return on investment stems from a small number of products achieving commercial success. Scientific progress is increasingly steering R&D efforts toward the development of medicines targeting small populations and likely to command high unit prices. On average, the pharmaceutical industry has provided stable *economic profits* to investors in the past decade, suggesting that profits were higher than needed to compensate investors for risk.

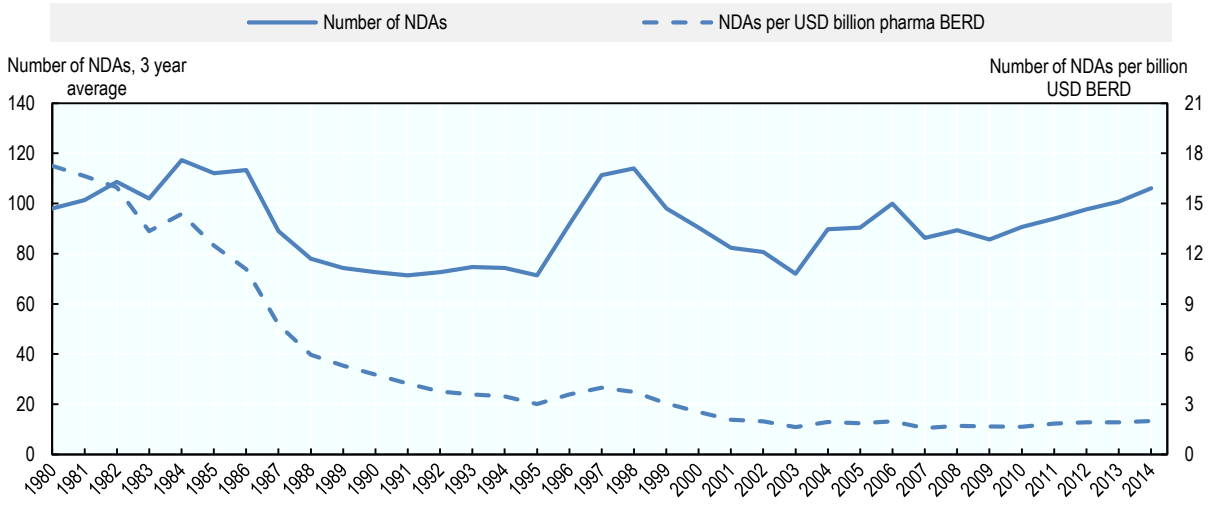
As in other sectors, the productivity of R&D has declined

By several measures, the productivity of R&D in the pharmaceutical industry has declined in recent decades. Measures of productivity comprise measures of input, such as financial or human resources, and measures of output, which would ideally be expressed in terms of health gains delivered by new treatments. With the latter being difficult to capture, however, proxy measures such as the number of new drug approvals or patents are often used. In the United States, for example, the number of new drug approvals (NDAs)[19] for every billion USD of inflation-adjusted R&D expenditure by the industry has declined from more than 17 in 1980 to 2 in 2002 and has been largely flat through 2014 (Figure 2.9). However this is a rather simplistic measure because it compares approvals in a given year to R&D expenditure in the same year, despite (as described above) more than ten years of R&D being required on average for successful approval of a given new drug, and thus approvals in a given period are dependent on expenditure made earlier.

SSR Health (2016) analysed the R&D productivity by R&D spending of the 22 largest publicly listed pharmaceutical firms in the United States, in terms of innovative output and returns to investors. The analysis of innovative output uses as its output measures the number of patents granted in a given year, adjusted for the accumulation of citations of

these patents in subsequent patents as an indicator of the "quality" of the initial patent, and inflation-adjusted R&D expenditure in the same year, for the years 1990 through 2014. The analysis of economic returns accounts for the lag between R&D expenditure and revenue by computing, for the years 1969 through 2014, net income returns after cost of capital in a given year on R&D expenditure incurred ten years earlier. Both analyses also found a consistent trend of declining productivity of R&D expenditure in the period from 1990 to 2014 (SSR Health, 2016).

Figure 2.9. Annual new drug approvals (NDAs) and number of NDAs per billion USD pharmaceutical business expenditure on R&D (BERD) in the United States, inflation-adjusted



Source: OECD, 2017b.

Declining R&D productivity may be related to several interrelated factors. The phenomenon is not specific to pharmaceuticals or healthcare technology but is also found in other sectors, such as computer science and agricultural production (Bloom et al., 2017). The decline has, for example, been attributed to the opportunistic nature of R&D. This implies that ideas that are "easy" to find are exploited first and, as the stock of knowledge increases, new ideas become harder to find and output can only be sustained or increased by large increases in research effort that offset declining productivity (ibid.). In pharmaceuticals, this is apparent in an ever-increasing *back catalogue* of effective drugs and a shift towards more complex conditions that has increased the complexity of clinical trials and failure rates (Scannell et al., 2012; Deloitte Centre for Health Solutions, 2016; SSR Health, 2016). More stringent requirements to gain marketing authorisation have also been hypothesised to have increased the costs of clinical trials (Scannell et al., 2012; SSR Health, 2016).

On the other hand, declines in productivity are also driven by rising R&D costs, which can be both a cause and an effect of increasing drug prices. Profit-maximising firms make investment decisions based on expected future revenue so that expectations of higher prices can make increasingly expensive R&D projects financially viable. High levels of investment in R&D can in turn justify high prices. The increasing licensing and acquisition activity that has been observed in pharmaceutical R&D in the past (Mayhew, 2010; Comanor and Scherer, 2013) can also contribute to this dynamic. Firms that acquire

technology in the R&D process pay premiums over R&D costs, which are also based on anticipated future revenue. Acquisition costs have to be recouped through subsequent revenue.

The pharmaceutical industry remains profitable

On average, and by comparison with other industries, the pharmaceutical industry has provided high and stable returns in the past decade. Increasing drug prices or growing markets are possible explanations of why profitability remains stable even as the cost of R&D increases and R&D productivity declines or remains flat. Figure 2.10 provides estimates of the difference between the rate of return and the cost of capital in the R&D-based pharmaceutical industry, based on a sample of 87 publicly-traded pharmaceutical firms, and of 6 996 firms across all other sectors of the economy. Since 2007, the R&D-based pharmaceutical industry has consistently made economic profits and has been more profitable than some other R&D-intensive industries, such as aerospace and defence, information technology (IT) hardware, or other healthcare technology. Estimates in Figure 2.10 are averages across all firms in each sector, weighted for the capital invested in each firm. The methodology is discussed in further detail in Box 2.1. Firms generate economic profit when their return on assets (RoA) exceeds their cost of capital (CoK), or the return investors demand for the risk of investing in the firm. Because the analysis is at the firm level, the market's assessment of the risk of investing in these firms is taken into account. This analysis of the profitability of the pharmaceutical industry is confirmed using a different method of estimating the cost of capital used by Koijen, Philipson and Uhlig (2016). This showed that the returns on firms engaged in medical equipment and pharmaceutical products were substantially higher –respectively 6.4% and 5.4% per annum- than the estimated returns required based on risk, as predicted by standard empirical asset pricing models, such as the capital asset pricing model and the Fama-French model. Economic profits can be a result of a number of market imperfections. They can be an indication of a lack of competition and market power of producers as a result of entry barriers or of unusual risks to investors that are not appropriately captured in CoK estimates; further analysis would be required to identify the reasons for economic profits in the R&D-based pharmaceutical industry.

Box 2.1. Rates of return less cost of capital as indicator of profitability

The difference between the rate of return in the sector and its cost of capital (CoK) is used as an indicator to compare the profitability of the pharmaceutical sector with other sectors of private investment. In an efficient capital market, CoK increases with the risk of an investment because investors demand higher compensation for investing in firms with more uncertain returns. Therefore, subtracting CoK from the rate of return accounts for differences in the risk profiles of sectors.

Rates of return can be expressed in terms of return on assets (RoA) or return on equity (RoE). RoA is a measure of the overall economic profit (or loss) of firms beyond what is necessary to compensate all types of investors that finance their operations, including shareholders and creditors. RoE is a measure of profitability relevant for shareholders because it represents the return on owning equity in the firm after the cost of debt. In fully efficient product and financial markets, the difference between RoA and CoK would be equal to zero in the long run because economic profits would lead to new entrants to the sector and downward pressures on profit margins while losses would lead to firm exits

from the sector. For various reasons, this may not be the case in reality. For example, economic losses can be the result of prior overinvestment and excess capacity while government interventions, such as subsidies, can prevent firms exit. Conversely, economic profits can be a result of barriers to entry and an indication of excess margins.

The cost of capital (CoK) is determined by the cost of equity and the cost of debt. Cost of equity is usually higher than the cost of debt because shareholders are compensated after payment of interest to creditors and therefore bear more risk. Firms can increase RoE by increasing the proportion of debt financing, referred to as leverage. This also increases the level of risk to shareholders. Debt requires stable sources of cash flow for interest payments. As a result of the uncertainty inherent in drug development, pharmaceutical firms rely more heavily on equity than on debt financing so that CoK is close to CoE.

For analysis in this report, these measures are calculated based on the following definitions:

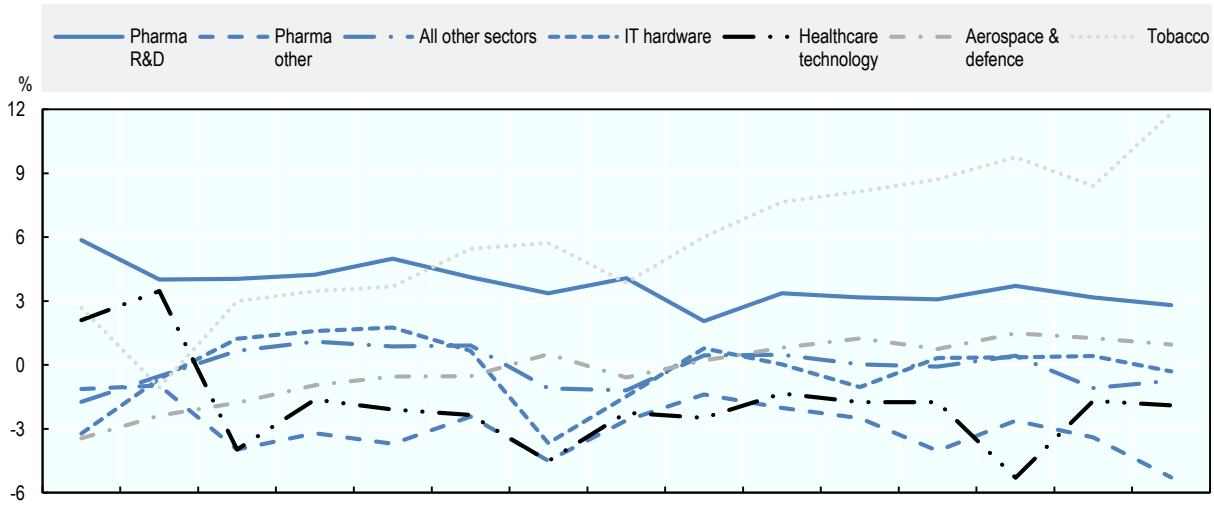
- Return on assets (RoA) is calculated as the ratio of net income to total assets, including assets financed from equity and debt.
- Cost of capital (CoK) is the average cost of equity and cost of debt weighted by the respective share of equity and debt in total assets.
- Cost of equity (CoE) is calculated as the sum of dividend yield, buyback yield and underlying trend in earnings per share growth.

In corporate finance and financial markets, CoE is often estimated using the single-factor capital asset pricing model (CAPM) or the multi-factor Fama-French model. The CAPM adds to the risk-free rate of return an incremental rate of return investors expect from investing in the equity market multiplied by an investment-specific factor that represents risk that cannot be eliminated through diversification. The Fama-French model is also based on risk but also accounts for firm size and book-to-market ratio. The method described above is an approximation of the CAPM.

Rates of return are ratios of income to assets. In the pharmaceutical industry, there is a long delay between R&D expenses and revenue. Current revenue is generated with products whose R&D was conducted in the past while current R&D cost is related to products that may generate revenue in the future. However, R&D costs are usually recognised as current expenditure and not capitalised. These accounting conventions can lead to divergence between financial statements and the true economic costs and returns of R&D for new products. This may lead to overstatement of current operating expenditure, and therefore understatement of income, and understatement of capital expenditure, and therefore understatement of assets.

Source: DiMasi, Grabowski and Hansen, 2016; Damodaran, 2017; OECD, 2017d, 2017e.

Figure 2.10. Difference between return on assets (RoA) and cost of capital (CoK) by industry in OECD countries, 2002 to 2016



Note: Classification based on the Global Industry Classification Standard (GICS), except the pharma sectors. Both pharma sectors in the figure are part of GICS industry sector *Pharmaceuticals and biotechnology*. *Pharma R&D* includes 87 pharmaceutical firms identified by the OECD as R&D-based; *Pharma other* includes all other firms in the GICS industry sector *Pharmaceuticals and biotechnology*.
Source: OECD analysis based on Bloomberg World Equity Index (BWEI).

A small number of new medicines account for a large share of industry revenue

Some studies suggest that, among all drugs that receive marketing authorisation, only a small subset achieve significant sales and that average sales per compound have declined in the recent past. In a sample of 466 novel active substances launched in the United States between 1991 and 2009, for example, 50% achieved life-time sales of less than USD 1.5 billion and approximately 10% had sales exceeding USD 10 billion (Berndt et al., 2015). Average life-time sales were lower for compounds launched between 2005 and 2009 than in the period 1991 through 2004 (ibid.). In a cohort of the top 12 - publicly-listed pharmaceutical manufacturers by R&D expenditure in 2008 and 2009,[20] the projected and risk-adjusted sales of all compounds in phase 3 trials have declined from USD 800 to USD 400 million between 2010 and 2016 (Deloitte Centre for Health Solutions, 2016). These studies also attempt to estimate the average profitability of the same compounds and also find a declining trend because, while sales are declining, R&D and other costs are not. However, costs in these lifetime net-present-value (NPV) calculations are based on broad assumptions and averages that are not product-specific, so that estimates of profitability are not reliable.[21] It is also unclear whether samples are representative of the industry and if the trends identified will continue in the longer run.[22]

The effective duration of market exclusivity[23] has declined slightly

New medicines are shielded from generic competition for a limited period through a combination of patent protection and other forms of exclusivity conferred by regulators. During this period, competition can only arise from the marketing of medicines developed for the same indication by other manufacturers.

The standard term of patent protection in OECD countries is 20 years from the date of filing, but because the time required to develop new products and conduct clinical trials

creates a lag of several years between filing of patent applications and product launch, the effective duration of patent protection is often significantly shorter. In most OECD countries, including the United States and countries that are members of the European Union, regulatory frameworks also provide for other forms of protection from competition, usually for a period of time beginning at the point of marketing authorisation. During this period, generics or biosimilars may not rely on the efficacy and safety data submitted in support of the approval of the originator (data exclusivity), or may not be granted marketing approval by the regulator. Market exclusivity differs across products and geographic areas. For example, in EU member countries, new active substances are given market exclusivity for 10 to 11 years (European Commission, 2015). In the United States, new chemical entities are granted 5 years (Kesselheim, Sinha and Avorn, 2017), new indications 3 years, new biologics 12 years, and orphan drugs 7 years. Different periods of exclusivity are also conferred on antibiotics and products for which paediatric trials have been undertaken at the direction of the FDA.

The *effective* duration of market exclusivity, i.e. the time from marketing authorisation of an originator to entry of the first competing generic or biosimilar product, has slightly declined over time. An analysis of effective market exclusivity of 288 new molecular entities (NMEs) that experienced initial generic entry between 1995 and 2014 in the United States found a slight decline from 13.5 to 12.9 years over that period (Grabowski, Long and Mortimer, 2014; Grabowski et al., 2016). The time from marketing authorisation of new active substances to *legal* "loss of exclusivity"[24] also declined somewhat in the United States, from approximately 14 years for products launched in 1996 to 12 years for products launched in 2015 (QuintilesIMS Institute, 2017). Future loss of exclusivity of the more recently launched products in this sample, however, is subject to some uncertainty since products can obtain extensions of market exclusivity for various reasons.[25]

The duration of market exclusivity can vary quite significantly between individual products. For instance, oncology drugs, products with annual sales of more than USD 1 billion, and first-in-class drugs had longer duration of effective market exclusivity (QuintilesIMS Institute, 2017), which can reflect a combination of different patenting strategies, expedited regulatory approvals, or differences in development lead times (Kesselheim, Sinha and Avorn, 2017; QuintilesIMS Institute, 2017).

During the period of market exclusivity, medicines may nonetheless face competition from other products approved for the same indication(s). The lag between launches of *first-in-class* and *me-too* products appears to have decreased.[26] The introduction of me-too drugs can deliver improvements over first-in-class products, expand the range of available therapies and lead to price competition. Recent empirical evidence of the impact of competition in on-patent markets is not available. An analysis of 94 drug classes in which a first-in-class compound and at least one follow-on product developed by another manufacturer were approved in the United States between 1960 and 2003, showed that the average time between approval of the first-in-class and the first follower declined from 3.5 years in the 1980s to 2.7 years in the 1990s. The average time between entry of the first and second follower declined from 2.8 to 2.2 years (DiMasi and Faden, 2011). A further decline was found for the period between 2000 and 2003, albeit based on a small sample (ibid.). However, the effects of oligopolistic competition on prices and volumes seem to vary across therapeutic classes and across countries (see Chapter 1).

New medicines often target small "niche" populations

Scientific opportunities and the development of precision medicine have pushed firms to focus increasingly on new medicines for small populations. Targeted medicines now account for one quarter of FDA approvals and for the majority of approvals in oncology (OECD, 2017c). About 31% of all new active substances launched in the United States between 1996 and 2015 had an orphan indication (QuintilesIMS Institute, 2017). Between 2000 and 2015 the number of new orphan designations in the United States and the European Union has increased steadily (OECD, 2017c). Worldwide, the share of orphan drugs in total sales of branded prescription drugs has increased from 6% in 2000 to over 16% in 2016, and has been projected to reach 21% by 2022 .

Notes

1. In this report, "market exclusivity" is an umbrella term used to refer to all forms of legal protection from competition by generic or biosimilar products. The nature of the protection arrangements and terminology differ across countries and regions.
2. Subject to data availability, using data for 2015 or 2014. No recent data were available for Australia, Canada, Chile, Estonia, Estonia, Hungary, Iceland, Ireland, Israel, Korea, Luxembourg, New Zealand, Sweden and Turkey.
3. OECD Structural Analysis (STAN) database, based on Annual National Accounts statistics submitted by national statistics institutes in reply to official OECD surveys. Reflects the number of persons engaged in activity "manufacture of basic pharmaceutical products and pharmaceutical preparations" per the United Nations International Standard Industrial Classification of All Economic Activities (ISIC Rev.4).
4. Estimates for the United States are based on the number of persons engaged in the broader activity "manufacture of chemical and pharmaceutical products" per Annual National Accounts statistics and the proportion of persons engaged in its sub-activity "manufacture of basic pharmaceutical products and pharmaceutical preparations", classified to North American Industry Classification System (NAICS) activity "pharmaceutical and medicine manufacturing" in the United States Census Annual Survey of Manufacturing (ASM). Pharmaceutical Research and Manufacturers of America (PhRMA) estimated that approximately 850,000 persons were directly employed in the pharmaceutical industry in 2014 when also accounting for persons whose activities may be related to pharmaceuticals but are classified in other general categories of NAICS, such as "scientific research and development" or "wholesale and retail trade" (PhRMA and TEConomy Partners, 2016).
5. Austria, Czech Republic, France, Italy, Netherlands, Norway, Portugal, Spain and Switzerland using data from between 2012 and 2014.
6. The total manufacturing sector includes the pharmaceutical sector.
7. The industry classification by the "main activity" of firms results in a number of firms being classified into the ISIC industry category "scientific R&D", which contains, for example, firms that provide R&D services to pharmaceutical firms but don't sell pharmaceutical products. Therefore, BERD by main activity may result in underestimating the total amount of R&D spending by industry in a given country. While the problem exists in all countries, it affects countries to different extends. BERD in Belgium, France and the United Kingdom might be significantly underestimated.
8. These are general definitions of the three phases of clinical trials that may not fully apply in all cases, for example when research ethics do not allow for testing drugs in healthy humans. Cancer drugs, for example, may have high toxicity and significant side effects

that can preclude testing in healthy subjects or in placebo-controlled trials (Hobbs and McCarthy, 2009).

9. The lead indication is the one that is advanced the farthest in the clinical development phase, among all indications for which a drug is in clinical trials, i.e. the indication for which the drug is developed first.

10. Earlier studies, including Hay et al. 2014, estimated an overall probability of success by first computing, in a separate sample for each phase, a probability of transition to the next phase as the proportion of observed phase transitions, and then multiplying successive transition probabilities. The study by Wong, Siah and Lo, 2018, on the other hand, modelled each individual drug development path (combination of drug and indication) to compute the proportion that make it through from phase 1 to approval. The latter is shown to be more accurate because it considers any path that ends in approval as a success, even if data on success or failure in a prior phase are missing.

11. Special protocol assessment (SPA) allows the FDA to review study protocols prior to the initiation of studies required for marketing authorisation and to provide input into the design of these studies to agree with study sponsors on scientific and regulatory requirements to be met (US Department of Health and Human Services, 2002).

12. Excluding Latvia, for which no data is available. Using data for 2014 or the nearest year available; 2011 data for Mexico; all other countries 2014 or 2013.

13. Data are available from Austria, France, Germany, the Netherlands, Spain or Sweden.

14. Excluding Luxembourg, for which no data is available. Using data for 2014 or the nearest year available; 2012 data for Switzerland; all other countries 2014 or 2013.

15. Business enterprise expenditure on R&D (BERD) covers R&D carried out by corporations, regardless of the origin of funding. BERD is recorded in the country where the R&D activity took place, not the country providing funding. National statistical agencies collect data primarily through surveys and according to the OECD Frascati Manual but there is some variation in national practices. “Pharmaceutical R&D” refers to BERD by businesses classified in the pharmaceutical industry. Firms can finance R&D from their own resources or receive external funding for R&D. External funding can include, for example, research grants or subsidies.

16. See (OECD, 2017h) for a detailed description of challenges and current policies to address this lack of private investments.

17. See (Policy Cures, 2015, p. 9)

18. African sleeping sickness, buruli ulcer, chagas disease, cysticercosis, dengue fever, dracunculiasis, echinococcosis, fascioliasis, leishmaniasis, lymphatic filariasis, leprosy, malaria, onchocerciasis, rabies, schistosomiasis, soil-transmitted helminths, trachoma, yaws.

19. This includes approval of new chemical entities (NCEs) and biologics as well as approval of new formulations or indications, to take into account all types of innovation. It does not include generics.

20. Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GSK, J&J, Merck, Novartis, Pfizer, Roche, Sanofi and Takeda.

21. Assumptions on R&D, production (costs of goods sold – COGS) and sales, general and administrative (SG&A) costs are based on published studies that estimate industry averages, using other samples of compounds and non-disclosed surveys of a subset of manufacturers. The study by (Berndt et al., 2015) assumes an unrealistically high effective tax rate of 30%, based on an estimate from the 1990s, to calculate after-tax costs.

22. The same study that followed the cohort of 12 manufacturers also found that, in an extension cohort of 4 other manufacturers (AbbVie, Biogen, Celgene and Gilead), projected and risk-adjusted sales increased from USD 800 million in 2013 to USD 1.1 billion in 2015, before declining again in 2016 to USD 800 billion (Deloitte Centre for Health Solutions, 2016).

23. See Note 1.

24. In this QuintilesIMS study, loss of exclusivity is defined as, "the latter of either patent expiry or other forms of exclusivity. These forms can include cases where a molecule holds extended exclusivity such as for paediatric indications, or when those molecules are for orphan diseases, or are a new chemical entity." (QuintilesIMS Institute, 2017, p. 27)

25. Medicines which are still protected from generic/biosimilar competition, may be approved for new indications (including paediatric, orphan) and further extend their legal period of exclusivity so that the actual date of loss of exclusivity may differ from the date estimated at the time of the analysis.

26. *First-in-class* drugs use a new and unique mechanism for treating a medical condition (FDA, 2017a), while followers that use the same mechanism are often referred to as *me-too* drugs.

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Annex 2.A. Public and private contributions to R&D – Sponsoring of clinical trials

To illustrate the contributions of various sectors to clinical research, this annex presents breakdowns and trends in the number of clinical drug development trials conducted in Europe and the United States by type of sponsoring entity.[1]

In the United States, 93 018 clinical trials involving a pharmaceutical product were registered with the US NIH between January 2008 and July 2017. The pharmaceutical industry was the lead sponsor of 43% of these trials, the remaining being sponsored by other types of organisations such as hospitals, universities and NGOs (OECD analysis based on US NIH, 2017a). Following a decline in the annual number of trials registered between 2008 and 2013 from approximately 8 700 to 7 700, the number had increased again to 8 800 in 2016 driven by an increase in trials with hospitals, universities, NGOs and others as lead sponsors. The share of trials with industry as lead sponsor has decreased from 57% in 2008 to 40% in 2016 (see Annex Figure 2.A.1).

Among the 79 143 drug and biologics trials that were registered with the NIH and for which information on the development phase was available,[2] industry was the lead sponsor of more than 60% of trials in phases 1 and 3. In phases 2 and 4, hospitals, universities, NGO and other organisations were lead sponsors of 54% and 76% of trials respectively, while the industry was lead sponsor of 42% and 23% of trials (Annex Figure 2.A.3). The highest number of trials (28%) was associated with phase 2, followed by phase 1 (26%), phase 3 (19%) and phase 4 (18%) (US NIH, 2017a). Seven percent of trials, spanned both, phases 1 and 2, and 3% phases 2 and 3 (ibid.).

In Europe, 48 867 clinical trials involving patients from the European Economic Area (EEA) were registered in the EudraCT database of the European Medicine Agency between 2004 and 2016, of which 61% had a commercial sponsor (see Annex Figure 2.A.2). The share of industry-sponsored and commercial trails has declined slightly in the past ten years, in both the United States and the EEA (Annex Figure 2.A.1 and Annex Figure 2.A.2). A brief discussion of data on clinical trials is provided in Annex Box 2.A.1.

Annex Box 2.A.1. Information on pharmaceutical-related clinical trials registered in OECD countries

Since 2007, all trials of drugs and biologics subject to Food and Drug Administration (FDA) regulation, except phase 1 investigations, have to be registered in the clinical trials register of the United States National Institutes of Health (US NIH, 2017b). In September 2016, the United States NIH issued a policy requiring the registration of all trials of FDA-regulated products that receive NIH funding. The register also includes a large number of studies that are not subject to registration requirements and for easy identification of drug-related trials and of the type of primary sponsors.

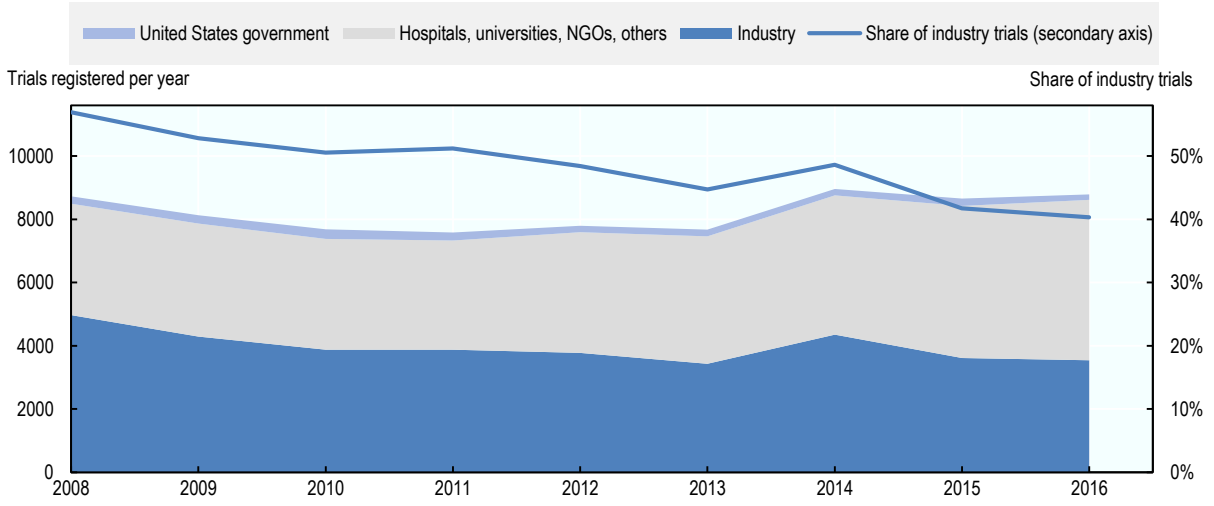
Between January 2008 and July 2017, 93 018 clinical trials involving a pharmaceutical product were registered with the US NIH and for 79 143 of them, information on the phase (1 to 4) is available). In 37 629 of these trials (48%) industry was the lead sponsor while in 39 304 (50%) a wide range of organisations, including hospitals, universities and NGOs, were the lead sponsor and in 2 210 (3%) the United States government was the lead sponsor. Following a decline in the annual number of trials registered between 2008 and 2013 from approximately 8 700 to 7 700, the number had increased again to 8 800 in 2016 driven by an increase in trials with hospitals, universities, NGOs and others as lead sponsors. The share of trials with industry as lead sponsor has decreased from 57% in 2008 to 40% in 2016 (Annex Figure 2.A.1).

Among the 37,629 industry-sponsored drug and biologics trials that were registered with the NIH between 2008 and July 2017, information on the countries in which patients were recruited were available for 32 973. Of these, 74% recruited patients in OECD countries only and 16% recruited patients in at least one OECD country but also in non-OECD countries. The share of trials recruiting patients in OECD countries only declined from 78% in 2008 to 75% in 2017 while the share of trials recruiting patients in OECD and non-OECD countries declined from 16% to 11%, so that the share of trials recruiting patients in non-OECD countries only increased from 6% in 2008 to 15% in 2017 (Figure 2.6).

The European Medicines Agency (EMA) provides information on all interventional clinical trials on medicines with recruitment sites located in countries of the European Economic Area (EEA) through the EudraCT database. The database categorises trials according to whether the sponsor is a commercial or a non-commercial entity. Between 2004 and 2016, a total of 48 867 trials were registered, of which 29 600 (61%) were commercial and 19 267 (39%) non-commercial. Following an increase in the annual number of trials registered between 2005 and 2007, driven by an increasing number of non-commercial trials, there has been a trend of declining registrations since 2007, with the share of commercial trials remaining at close to 60% (Annex Figure 2.A.2).

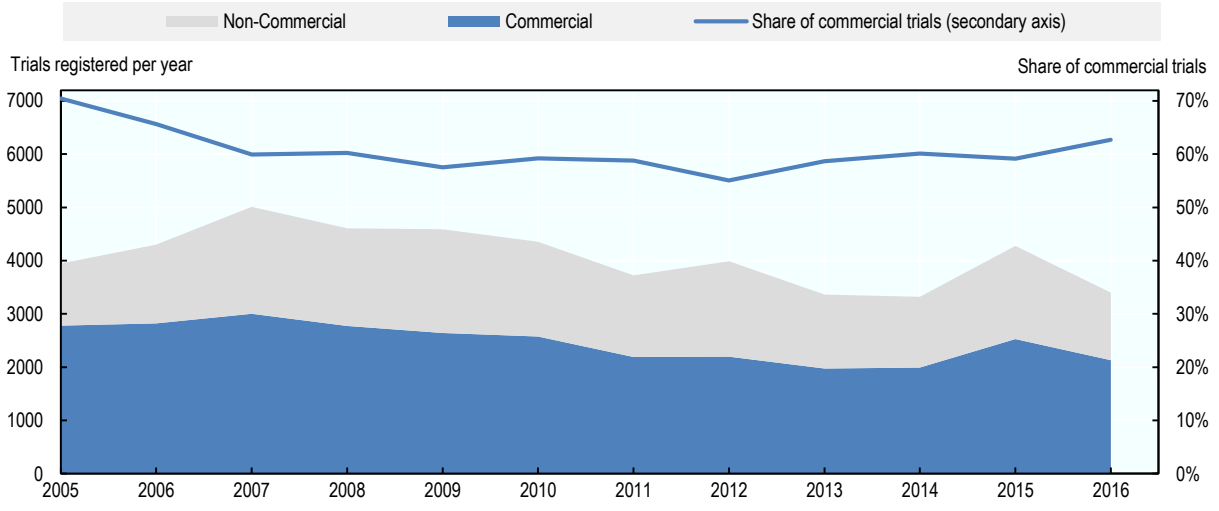
Source: EMA, 2017a, 2017b; US NIH, 2017a, 2017b.

Annex Figure 2.A.1. Number of clinical studies of drugs or biologics registered with the United States NIH, by lead sponsor type, 2008 to 2016



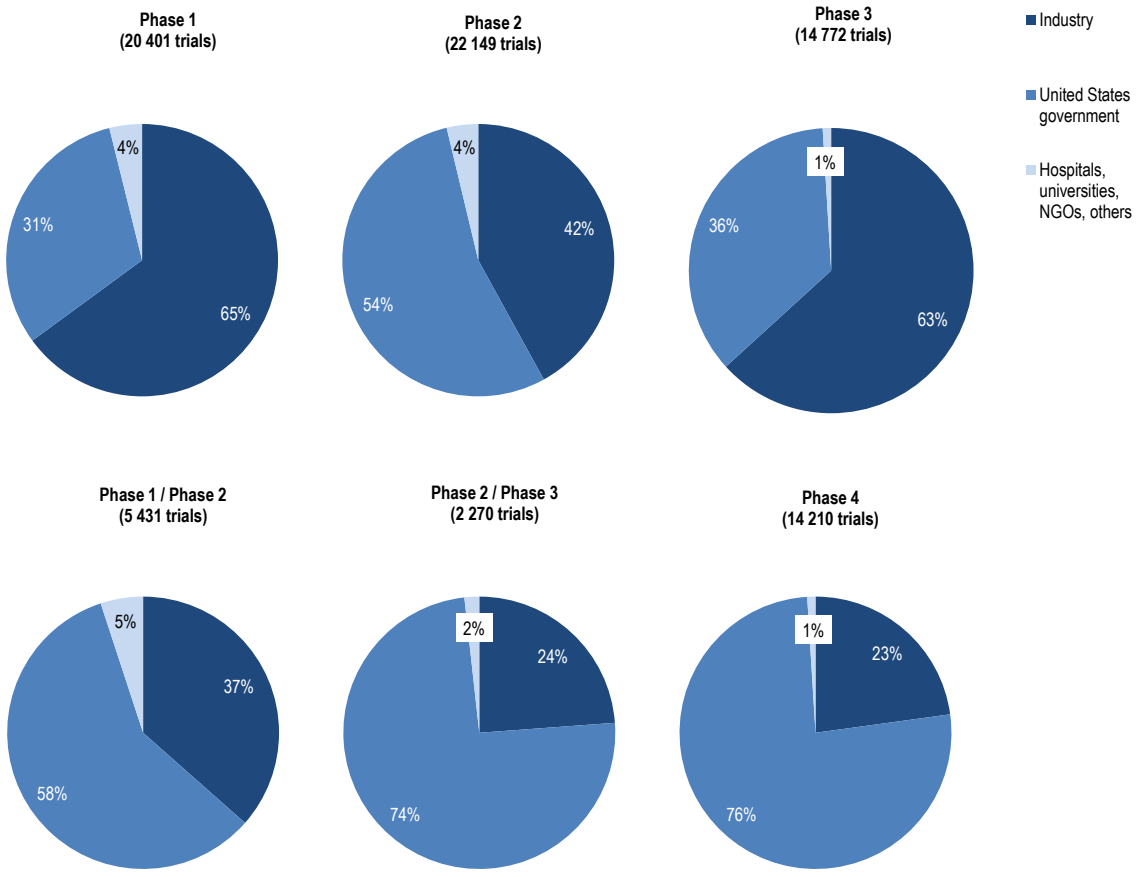
Source: OECD analysis based on (US NIH, 2017a).

Annex Figure 2.A.2. Number of clinical studies of medicines recruiting patients in countries of the EU and EEA, by sponsor status, 2004 to 2016



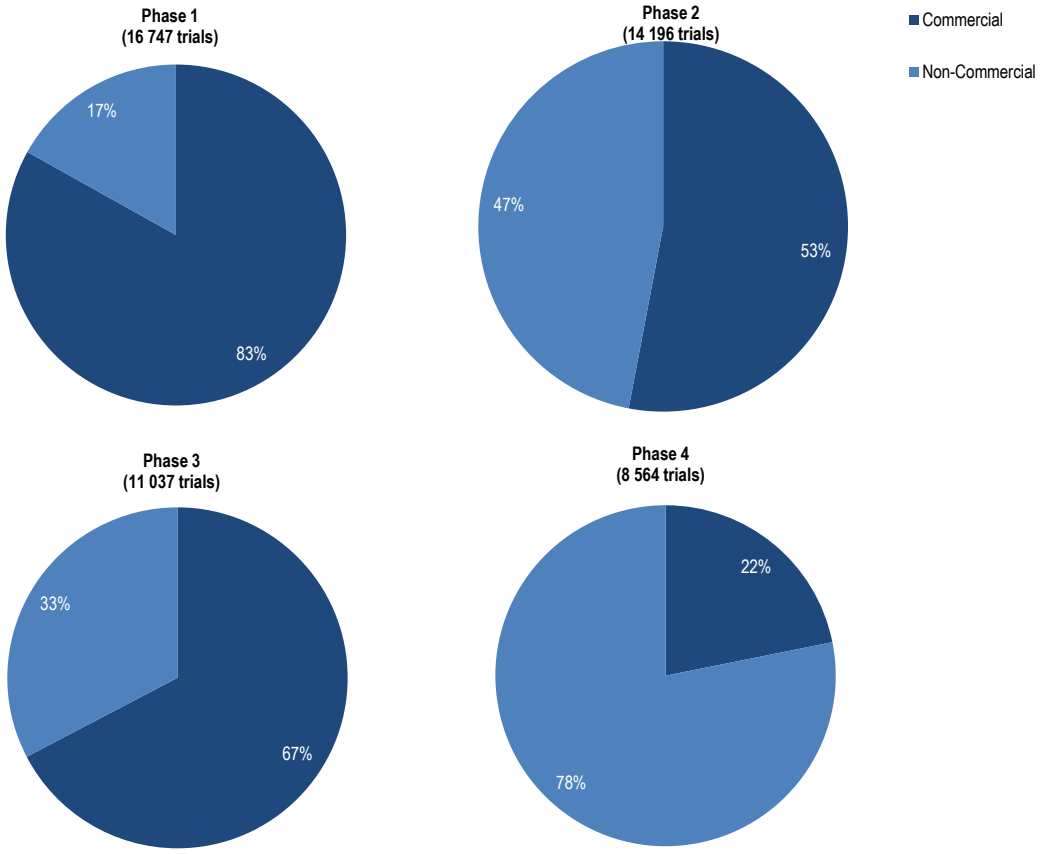
Source: OECD analysis based on (EMA, 2017b).

Annex Figure 2.A.3. Clinical studies of drugs or biologics registered with the United States NIH, by phase and lead sponsor type, 2008 to 2017 (79 143 trials in total)



Note: Registration of phase 1 trials is not mandatory in many cases, but in September 2016 the NIH issued a policy requiring the registration of all trials of FDA-regulated products that receive NIH funding.
Source: OECD analysis based on US NIH, 2017a.

Annex Figure 2.A.4. Number of clinical studies of medicines recruiting patients in countries of the EU and EEA registered in EudraCT, by phase and sponsor status, 2005 to 2016 (48 867 trials in total)



Source: OECD analysis based on EMA, 2017b.

A similar pattern in sponsorship as in the United States is apparent among trials of medicines with recruitment sites located in countries of the EEA. In phases 1 and 3, 83% and 67% of trials were commercial while the split was more balanced in phase 2, where 53% of trials were commercial. In phase 4, 78% of trials were non-commercial (Annex Figure 2.A.4). Among the 48,867 trials between 2005 and 2016, 33% were associated with phase 1, 28% with phase 2, 22% with phase 3 and 17% with phase 4 (EMA, 2017b). This suggests that R&D funded by industry plays a larger role in development phases where success rates are high (refer to Table 2.1).

Notes

1. *Sponsors* of clinical trials initiate and take responsibility of the trial. They may receive funding from other entities so and analysis of trials by sponsoring entity does not necessarily reflect the sources of funding.
2. No information on the development phase was available for 13 875 of the 93 018 drug and biologics trials registered.

Chapter 3. Policy options to address current challenges

This chapter proposes a range of policy options to address the challenges described in Chapter 1. It begins by describing the principles and objectives that guided the development of these options: increasing the value of pharmaceutical spending, ensuring access in countries with different levels of development, supporting a rules-based system, fostering competition, and promoting better communication and dialogue among stakeholders. It goes on to describe sixteen policy options falling into five broad categories: reducing R&D costs and accelerating market access; increasing spending efficiency; determining willingness to pay for new treatments or health benefits; developing push and pull incentives to encourage innovation in areas of high unmet need; and strengthening the information base used to support policy decision-making.

Introduction and guiding principles

The two first chapters of this report described current trends in pharmaceutical markets and the many challenges currently facing policy makers. In preparation of this draft report, the OECD Secretariat engaged in extensive consultations with a broad range of stakeholders and experts. They contributed to the identification of a number of policy options with the potential to address some of the challenges highlighted in the first two chapters of this publication.

This chapter explores these policy options. It considers their strengths, weaknesses and feasibility. Since OECD countries have adopted very different approaches to pharmaceutical policy, certain options are not relevant or would be unlikely to work in some countries. Some would require international co-operation, while others would require changes only at the national level. In all cases, the policy options examined are not recommendations to governments, but rather, possible actions for consideration within each specific country's national context and according to its priorities regarding the three objectives of providing access, ensuring spending efficiency, and fostering innovation.

The advantages and disadvantages of different options have been assessed using two broad criteria. First and foremost, the assessment is based on the available empirical evidence of effectiveness in achieving their stated objectives. In some cases, the evidence is substantial; for other options, however, there is little or no evidence of how effective they may be. In addition, when reviewing and assessing the potential of different policy options and the trade-offs among the three policy goals listed above, this report has been guided by five principles:

1. **Increasing the value of spending on medicines.** The overall objective is to ensure that maximum value is obtained from the expenditure made. This could lead to reduced (or curtailed) expenditure on low value items and/or increased expenditure on high value items; it may mean seeking to reduce prices (to ensure a desired level of cost effectiveness) or varying payment methods; or it may involve varying the ways in which certain products are deployed within the health care system. While payers may wish to reward innovation explicitly in order to encourage further, effective private investment in research and development (R&D), at the same time they may wish to send clear signals intended to guide investment toward the kinds of innovations that reflect *their* priorities.
2. **Ensuring access in countries at different levels of development.** The most effective way of ensuring that patients in countries at different levels of development can access innovative treatments is to apply differential (or tiered) pricing. Under this paradigm, wealthy countries pay more for medicines than poor countries and firms are able to earn sufficient profits in affluent countries to make further investments in R&D.
3. **Supporting a rules-based system.** The application by public payers of transparent criteria in determining willingness to pay for added health benefits would enable developers to know in advance what level of reward they may expect.
4. **Fostering competition in both on-patent** (between available treatments for the same indication) **and off-patent markets** (though the use of generic and biosimilar products) improves the efficiency of pharmaceutical spending. On-

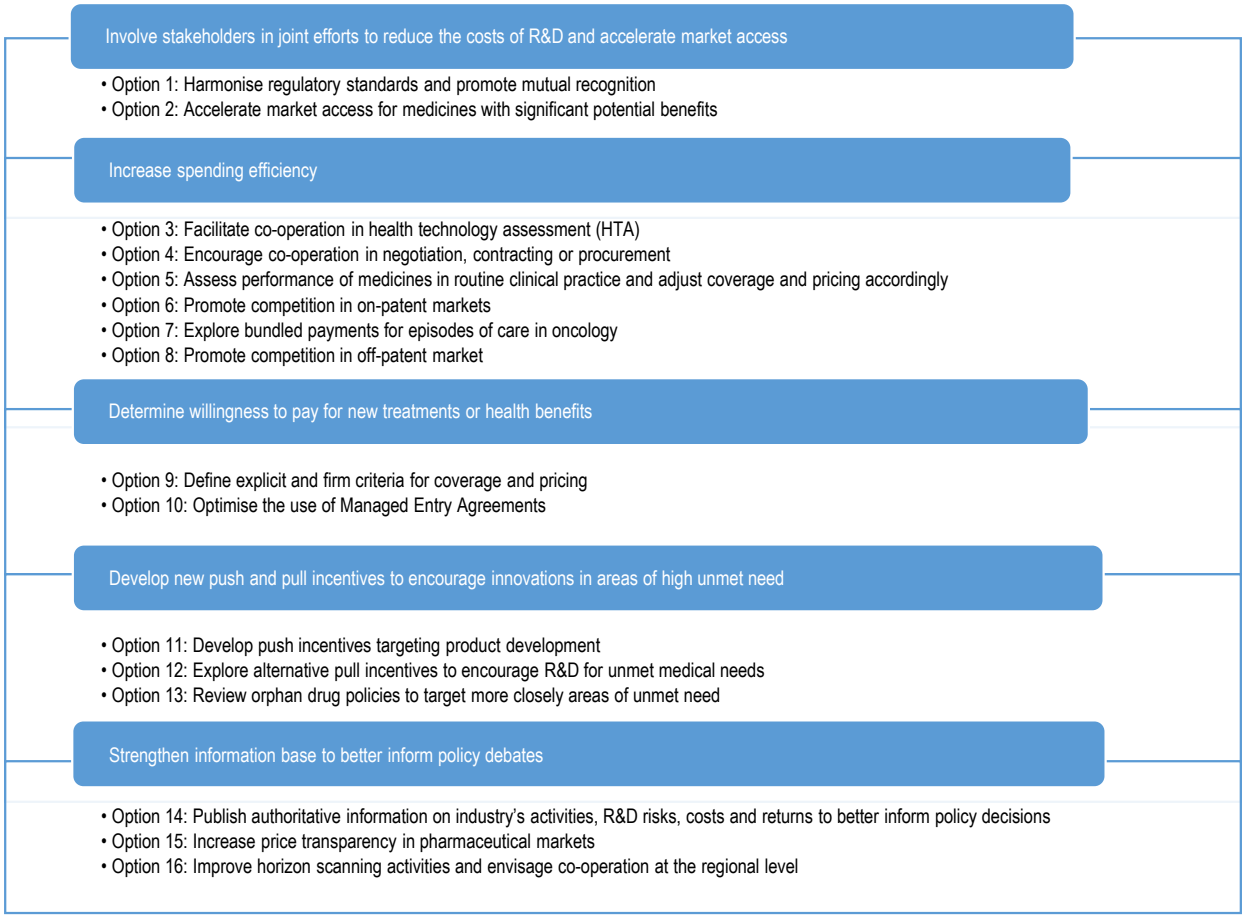
patent competition is not assured even where there are multiple therapies for the same indication, but can be fostered with appropriate procurement and payment policies.

5. **Promoting better communication and dialogue** to increase trust among stakeholders and improve alignment of industry R&D with societal priorities. Policy debates and decisions need to be informed by authoritative information on industry activities, R&D costs, and forthcoming products.

An overview of policy options

Policy options have been organised into five categories according to their main objective. These are shown in Figure 3.1.

Figure 3.1. An overview of policy options



Policy options considered in this report are described in detail in the third section of this chapter, together with their advantages, weaknesses and feasibility. Box 3.1 describes options that are not considered in the report, and explains the reasons why. Detailed descriptions of policy options also include definitions of technical terms where necessary, as well as bibliographic references supporting statements made in the paragraphs below. This section provides an overview of the policy options.

Box 3.1. Policy options which were not retained for consideration

Compulsory licensing. Compulsory licensing was rejected for inclusion in this report as a solution to balancing value for money and incentives to invest because its use reflects the failure of the pharmaceutical market to reach a price that all parties accept is appropriate, and this report focuses on how to ensure that this state of affairs does not occur in the future. A compulsory license granted to a generic manufacturer allows it to produce and sell a generic version of a patented medicine without the consent of the patent owner. International law allows for compulsory licenses in clearly defined circumstances, as long as certain procedures are followed and the patent owner is paid a royalty, leaving considerable leeway for governments in determining when to grant them. While compulsory licenses have been granted on a few specific occasions in OECD countries, wider use risks undermining the incentives that intellectual property protections create. Rather than debating whether the use of compulsory licensing might be justified, this report focuses on how an appropriate pricing policy framework might be agreed.

Rate of return regulation. Intellectual property rights give companies market power to maintain higher prices than they otherwise could, for a period of time, as an incentive to encourage greater than otherwise private investment in research and development. Consideration has been given to regulating the use of that market power, for example through regulation of the rate of return of firms in monopoly positions, or price capping. A system along these lines was put in place in the United Kingdom (the PPRS). This approach was, however, largely discredited in an assessment report by the UK Office of Fair Trading (OFT, 2007). Companies would, in effect, be paid for any costs they incurred, irrespective of how (in)efficient they had been. The OFT further noted that rate of return regulation amounts to paying companies for the amount of capital invested rather than for their output (i.e. benefits for patients) and may provide incentives for companies to over-invest in low-risk projects if the allowed rate of return is above the cost of capital. These reasons, along with practical problems in its implementation, led the OFT to recommend that other mechanisms be used to provide incentives for pharmaceutical innovation. It is therefore not considered further in this report.

Other policy options have been put forward by stakeholders, but have not been considered in depth in this report. For example, this is the case of the development of self-care and over-the-counter markets, which could relieve some pressure on public funding. This however, requires improvements in the health literacy of the population and is not considered practical in the short to medium term.

Involve stakeholders in joint efforts to reduce the costs of R&D and accelerate market access

Efforts could be made to reduce the overheads involved in complying with the evidentiary requirements of multiple regulators and HTA entities, for example through greater international co-ordination and harmonisation and even by way of joint or shared assessments. To achieve the objective of increased financial sustainability for payers, such measures would need to be accompanied by reductions in medicine prices and improvements in the value proposition.

Greater harmonisation of regulatory requirements for marketing approval is a means of reducing some development costs for companies and potentially accelerating market

entry, benefiting patients needing treatment while at the same time generating earlier revenue flows for companies. Harmonisation can also reduce effort and costs for individual regulatory agencies. Many regulatory agencies are already collaborating through international networks to harmonise documentation and assessment standards, and some have bilateral agreements to share information on assessments of specific products. Other national agencies (e.g. in Mexico) go further, relying to some extent on market approval granted by another trusted agency, or establishing mutual recognition procedures (e.g. European agencies for medicines that are not approved centrally). See Option 1.

Accelerated marketing authorisation can provide faster access to treatments for unmet medical needs and can reduce the costs of evidence generation prior to market access. However, it also increase uncertainty about the safety and efficacy of new treatments and impose greater risks on patients. Ensuring its use is limited to situations where there is genuine and substantial unmet need as well as stringent rules for compliance with post-market collection of evidence and appropriate patient information are key for this option to work for the benefit of patients, payer and companies. See Option 2.

Increase spending efficiency

Countries need to seek efficiency gains and tackle waste in all parts of their health systems, including the pharmaceutical sector where policies could improve the value of both innovative and existing medicines. This could be achieved through co-operation in health technology assessment (HTA), international collaboration in price negotiation or drug procurement, more frequent assessment of the performance of medicines in clinical practice, policies that promote competition in both on-patent and off-patent markets, and measures that encourage appropriate prescribing and rational use.

Co-operation in health technology assessment (HTA) offers the potential to reduce duplication of effort and related costs for both companies and HTA agencies (see Option 3). Some national HTA agencies are already involved in regional and international HTA co-operation initiatives. These vary from loose networks that share information on methods or completed assessments, to full integration of activities. Greater integration of HTA (or joint evaluation) can be envisaged for clinical assessments, but is much more problematic for economic assessments. Greater co-operation requires, however, that participating countries share similar standards of care (to ensure the appropriate choice of comparator). It also means that national agencies need to agree on methods and parameters for HTA, which might be among the most challenging barriers to co-operation on HTA. See Option 3.

Greater international **co-operation in price negotiations, contracting or procurement** could increase bargaining power of buyers, competition among sellers, and impose greater discipline in negotiation and pricing processes through improving the information available to buyers. Co-operation could also potentially reduce transaction costs for industry and payers. International co-operation could take the form of joint price negotiations - i.e. exchange of information or joint drafting of technical specifications, without tendering together, or fully integrated international joint procurement. All these options have their own merits and weaknesses. Their appropriateness depends on market characteristics (e.g. the level of competitiveness in a therapeutic area); on political will to cede sovereignty and independence in order to benefit from co-operation; and on the level of harmonisation that can be achieved between national regulations and processes to evaluate medicines and make pricing or purchasing decisions.

Co-operation in price negotiation or contracting is compatible with value-based pricing and may even be compatible with tiered pricing, as long as participating countries have similar income levels and willingness-to-pay, or if the contract includes provisions allowing companies to charge different prices in different countries.

Pooled tendering or contracting can lead to the award of a significant proportion of, or the total market for a medicine, or class of medicines, to a single supplier. This can reduce the choice of products available to physicians and patients, and can lead to higher market concentration or an eventual supplier monopoly. This in turn can not only create the potential for price increases in the longer run but can also jeopardise the security of supply through increased dependence on a small number of, or even a single supplier. These risks can be mitigated by appropriate tendering and contracting mechanisms that include strong supply guarantees, or strategies that do not result in sole-supplier arrangements. See Option 4.

Countries could also **use routinely collected data to assess the performance of medicines and adjust coverage conditions and prices** after market entry to better reflect effectiveness and cost effectiveness of medicines in routine clinical practice. With the current capacity of health care systems to analyse routine data, this is unlikely to be practical for all products, and may be unnecessary for many products for which cost-effectiveness has been well established. However, it could be applied selectively to those treatments whose performance is uncertain and for which budget impact is high (see Option 5). Routinely collected data could also be used to measure performance in some MEAs and thus reduce their administrative costs. This is an area where advances in other parts of the health system – e.g. the use of ICT, and accessing data for health system governance – are necessary for improving effectiveness in the pharmaceutical system. See Option 5.

As highlighted in Chapter 1, countries could **promote competition in on-patent markets**. However, sometimes particular market features prevent competition from working effectively. In particular, in countries with national "positive lists" and regulated prices, payers are not always in a position to harness price competition. By contrast, formulary management[1] and tendering are two options to foster price competition between products with similar indications and pharmacological profiles. **Competitive tendering by indication** could be used at the national level and follow a formal, transparent process to allocate the desired market shares to the lowest bidders, achieving an optimal trade-off between improving spending efficiency and maintaining a competitive market with more than one manufacturer in each market segment. See Option 6.

Bundled payments for episodes of care are another option to foster competition and increase the value of medical care. With appropriate quality standards, they could be used to incentivise providers to use the most cost-effective treatment for a given pathology and to negotiate procurement prices with companies. Such payments are being piloted in oncology in the United States, and preliminary evidence suggests that they offer an option for increasing the efficiency and quality of cancer care, as well as reducing the costs. With bundled payment mechanisms, monitoring quality and outcomes are important both to ensure patients do not receive sub-standard care and to link payments to value. See Option 7.

The first chapter of this report highlighted several challenges in off-patent markets: the fact that some countries do not fully exploit the potential of generics and biosimilars; the small number of competitors in some off-patent market segments; and as a consequence,

sporadic price surges for a limited number of off-patent products in *de facto* monopoly positions. The risks of shortages are not addressed in this report, but these are obviously a concern when there is only one supplier for a given molecule.

Countries could consider a range of policy options to **promote competition in off-patent markets**. They could work toward getting generics approved more quickly, mobilise a range of incentives to encourage uptake of generics and biosimilars, and improve procurement mechanisms (see Option 8). These policy options are likely to minimise the risks of sporadic and sharp price increases. In addition, OECD member countries could implement a system to allow purchasers to report sharp price increases so that these could prompt investigation by competent competition or anti-trust authorities. See Option 8.

Determine willingness to pay for new treatments or health benefits transparently

Most OECD countries regulate or constrain the prices of publicly-funded on-patent drugs indirectly, through coverage conditions. Methods and processes for decision-making have evolved and over time have generally become more transparent. However, the number of medicines with high prices entering the market has been increasing, notably in oncology and for rare diseases. In some cases these medicines greatly improve patients' health and quality of life, while in others the health benefits are more modest. Often these treatments do not meet pre-defined criteria for positive coverage and pricing decisions, which leads to case-by-case negotiations with unpredictable outcomes for all stakeholders. On a different note, the launch of new and very effective treatments for hepatitis C initially generated outcry and frustration because payers were not prepared for, and had not anticipated the launch of an extremely effective treatment for a disease of high prevalence. The combination of such a high price and high prevalence for a new product is rare. Nevertheless, this recent example demonstrated that existing models for determining societal willingness to pay, where they existed, were inadequate. The result was case-by-case negotiations.

Public payers could consider **re-defining criteria for coverage and pricing decisions** to anticipate more diverse scenarios, including circumstances in which effective treatments come to market for diseases with high prevalence. Decision rules may vary for a given medicine as a means of segmenting prices where cost effectiveness varies across different populations or indications, or where there is uncertainty about clinical and cost effectiveness in some indications. In some cases, the payer may initially commit the full price for the drug and require the manufacturer to refund all or part of the cost if the treatment does not work as anticipated, or the anticipated cost effectiveness is not achieved in practice. Information on how these agreements work is scant; as such, an important issue is that despite their widespread use the collective understanding of the performance of the medicines that are the subject of these agreements does not advance, as the results generally remain confidential. While the outcomes tracked via the implementation of such agreements cannot replace randomised control trials as a basis of effectiveness or value assessment, countries could **optimise the use of managed entry agreements (MEAs)** by addressing current limitations. See Option 10.

Develop new push and pull incentives to encourage innovation in areas with high unmet needs

Countries could consider the **development of push incentives for targeted product development**. The public sector already contributes substantially to pharmaceutical R&D

but the allocation of funds could be improved. Current examples of public contributions include funding of public and academic health research, tax credits for private R&D spending or public-private partnerships at various levels of the R&D process. Public funding of R&D could seek to target more effectively those therapeutic areas of high unmet need that are not adequately addressed by private investment. High priority needs could be assessed both at national and international level, as they may differ, and some funds could be pooled to be distributed among these priorities (e.g. for the development of antibiotics). When public funds are targeted towards the development of specific products, governments could partner with industry to develop access plans, as is already done in the development of treatments for neglected diseases. See Option 11.

A number of alternative pull incentives have been proposed in the past, for example to spur the development of treatments for neglected diseases, and such approaches are envisaged to foster the development of new antibiotics to combat antimicrobial resistance. Alternative pull incentives could target priority product profiles that might be agreed internationally and made conditional on the affordability of the resulting medicines. To achieve this, countries could **continue to explore alternative pull incentives to encourage R&D and obtain desired innovation for unmet medical needs**, such as prizes and similar innovation rewards, or advance market commitments (AMCs). See Option 12.

Countries could **review orphan drug policies to target more closely areas of unmet need**. Orphan drug policies have been introduced in several OECD countries to encourage the development of treatments for rare diseases for which market incentives are too weak. The number of medicines and indications available to treat rare diseases has been increasing over time, and while this is good for patients with rare diseases, orphan designations and related advantages are sometimes granted for narrow indications of products with other registered indications that generate "blockbuster" revenues. The development of precision medicine implies that indications will increasingly target small populations, making them potentially eligible to receive advantages arising from orphan drug policies. These advantages often come at a cost to taxpayers, through reduced or absent evaluation fees, tax credits, and extended market exclusivity in some countries. Current trends suggest that these costs will increase, without necessarily spurring development of the types of medicines for which orphan drug policies were intended. It may be useful to assess whether existing policies are delivering the right outcomes, and to assess alternative options. See Option 13.

Strengthen the information base to better inform policy debates

Public debates reveal a lack of trust in available information on the activities and performance of the pharmaceutical industry, and perceptions that it generates excess profits from its activities. **Publishing authoritative information on industry activities and performance**, including R&D spending and profitability, could be a first step towards fostering trust among stakeholders and better informing policy debates. Stakeholders could agree on a set of relevant indicators and relevant sources (original data collection vs use of existing databases). The OECD could contribute to this effort by relying on its multi-sectoral capacity, that is, by involving several directorates (e.g. the Directorate for Employment, Labour and Social Affairs – responsible for health – together with the Directorate for Financial Affairs and the Directorate for Science, Technology and Innovation). Such an undertaking would require an agreement on relevant indicators and data sources, and would provide an opportunity for open dialogue. See Option 14.

OECD member countries could also **increase price transparency** in pharmaceutical markets. Levels of price opacity are high and increasing. The disconnect between list prices and prices actually paid by purchasers has a number of drawbacks: high list prices serve as an anchor in price negotiations; they blur international benchmarking; therapeutic choices cannot rely on comparisons of costs and benefits; patients sharing the costs of treatments may not benefit from confidential discounts or rebates; analyses of price trends have become partly irrelevant; and companies may be criticised for high list prices that are never applied. The effects of full price transparency are uncertain and full transparency may not be a realistic goal, especially if tiered pricing is to be applied in markets that are not segregated, and if countries continue to use international benchmarking. Co-operation among stakeholders could, however, improve price transparency. See Option 16.

OECD countries could also **improve horizon scanning and promote co-operation at regional level** to better prepare for the market launch and diffusion of new medicines. For example, some countries were taken by surprise when Sovaldi® entered the market in 2013, and had not made provisions for funding and delivering the new treatment. This made discussions over the price more difficult than necessary. Although horizon scanning is already undertaken in some countries, with more or less formal and institutionalised processes, health system preparedness and anticipation of the impact of new technologies and innovative medicines could be improved in many of them. Some parts of horizon scanning would remain country-specific, such as epidemiology or forecasting economic impact, but given the globalised nature of pharmaceutical markets, the identification of forthcoming medicines and their potential impact on health and health care systems would certainly benefit from co-operation. This could potentially be more comprehensive and less costly for individual countries. Pharmaceutical companies would in turn benefit from countries' preparedness for more rapid adoption of the most effective technologies. See Option 16.

To conclude, a range of options is available to policy makers to create incentives for the industry to develop needed therapeutics, while providing patients with better access to products, improving the efficiency or value of pharmaceutical spending, and respecting the budgetary limitations of health systems. These can help to align the public interest more closely with that of the industry, and increase the aggregate value society obtains from spending on pharmaceuticals. Policy makers, however, need to find a balance between the objectives of ensuring patient access and financial sustainability, and allowing firms to earn sufficient return on their outlay to ensure continued investment in research and development of new products. This requires considering an overall policy package rather than picking and choosing among single measures to address only one policy goal or specific challenge.

A. Involve stakeholders in joint efforts to reduce the costs of R&D and accelerate market access

Option 1: Harmonise regulatory standards and promote mutual recognition

Summary

Co-operation among regulatory agencies could further accelerate patient access and potentially reduce costs of the later phases of R&D. Such co-operation could span the exchange of information on assessed products or harmonisation of evidence requirements, to reliance on assessments by other agencies to inform decision making.

Background

Regulatory agencies responsible for the approval of medicines have varying capacity and apply different methods, evidentiary requirements and judgements. All these differences lead to differences in both the duration and outcome of the drug evaluation process. The approval time for new active substances by leading regulatory agencies (in United States, Japan, the European Union, Switzerland, Canada and Australia) has declined and converged over the past decade. However, while the average of median approval times was about one year in 2016, the difference between the fastest and slowest agencies was still 180 days (Bujar, McAuslane and Liberti, 2016). Several studies show that the FDA approval process – at least for oncology drugs – is shorter than in other countries, partly the result of its various accelerated approval pathways (Roberts, Allen and Sigal, 2011; Samueland Verma, 2016).

In terms of process, one study of all approvals by FDA and EMA between January 1999 and May 2014 showed that FDA was more likely than its European counterpart to approve drugs without randomised-controlled trials (RCTs) (Hatswell, Baio and Freemantle, 2016). A qualitative study on decision-making in oncology drugs at the FDA and the EMA outlined a number of differences. First, the study reported that the two agencies valued endpoints differently; while EMA respondents (to the survey) tended to identify progression-free survival (PFS) as a clinical benefit per se, FDA respondents considered that this surrogate endpoint had to be confirmed by a benefit in overall survival. FDA appeared more inclined to approve drugs based on activity data and phase II single-arm trials. Among factors not directly linked to the type and level of evidence but deemed to influence decision-making, the study mentioned that FDA had more interactions with the industry, and was also less risk-adverse and more willing to hasten access to medicines than its European counterpart (Tafuri et al., 2014).

Outcomes of the approval processes can also be different. Among 100 drug/indication pairs approved by the EMA between 1995 and 2008 for 42 anti-cancer drugs, 47 indications were assessed differently by the FDA. In 19 cases (indications), one agency had approved the indication but the other had not. In the remaining 28 cases, variations were observed in the framing of the indications, but only 10 were considered to be "clinically relevant" differences.

Although it appears plausible that seeking approval from agencies applying different methods and evidentiary requirements may impose costs in the last phases of clinical trials, there is no evidence from which to assess the magnitude of these additional costs.

International co-operation in regulation can take several forms, from information sharing between agencies to mutual recognition or fully integrated processes. Reliance is an intermediary step where assessments are shared, but the receiving authority remains responsible for the approval decision (Luigetti et al., 2016).

Several international networks already promote harmonisation of regulatory requirements. The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), created in 1990, is the most influential initiative for medical products. It gathers representatives from regulatory authorities from Europe, Japan and the United States, and representatives of the pharmaceutical industry and from WHO, who work together to establish guidelines and standards for drug evaluation. Other initiatives include the *Asia-Pacific Economic Co-operation Life Sciences Innovation Forum* (APEC-LSIF); the *Pan American Network for Drug Regulatory Harmonization* (PANDRH), which supports regulatory

convergence/harmonisation in the Americas; the *International Pharmaceutical Regulators Programme* (IPRP), which facilitates the implementation of internationally harmonised technical guidelines for pharmaceuticals; and a number of WHO programmes, such as the *PAHO/WHO Collaborating Center for Biological Standardization*, providing expertise and research in developing WHO written standards and guidelines (US International Trade Administration, 2016).

A number of initiatives promote information sharing between regulatory authorities. For instance, the *International Generic Drug Regulators Programme* (IGDRP) launched a pilot in 2014, which allows the EMA or EU countries' national authorities sharing assessment reports with other members of the network, i.e. regulatory authorities from the European Union, Canada, Switzerland, and Australia (Luigetti et al., 2016). The WHO also launched in 2015 a pilot of collaborative registration for medicines approved by a stringent regulatory authority (SRA)[2] where assessment reports from these authorities are shared with African countries (Luigetti et al., 2016).

Among OECD countries, some agencies are required to take into account overseas assessment reports where a product has been approved in a country with a "comparable control system" and the applicant requests such a review. This is the case for SwissMedic, for instance. According to Luigetti et al. (2016), the review time is reduced by 20% when EU assessment reports are used in the process. Health Canada is now permitted to use assessment reports produced by other agencies in its own evaluations. Mexico uses work produced by the EMA, the FDA, Health Canada, the Australian TGA and SwissMedic to enable approvals within 60 days (Luigetti et al., 2016).

The marketing authorisation of medicines in the European Union presents the highest level of regional integration, where medicines can be approved through centralised, decentralised or national procedures. Provisions for mutual recognition enable reliance on a decision of one member state by others within the European Union.

Strengths

While the impact of greater harmonisation or co-operation on the reduction of R&D costs has not been evaluated, reliance on decisions of other agencies clearly reduces time to approval. Co-operation and coordination between agencies can generate transaction costs but reliance - or mutual recognition - where accepted by national authorities, holds the potential to reduce time and effort by both regulatory agencies and manufacturers. This can be particularly beneficial in countries with limited regulatory capacity, enabling them to draw on the expertise of stringent regulatory agencies.

Weaknesses

Regulatory authorities operate within different cultural contexts and these are reflected in attitudes towards risks and potential benefits, which in turn influence regulatory decisions. Although scientific evidence is the cornerstone of regulatory approval, the appraisal of the evidence inevitably involves discretion and judgement. While regulatory authorities already cooperate to harmonise methods and standards, issues of sovereignty, and recognition of cultural, contextual and clinical differences among jurisdictions mean that few are willing to rely entirely on judgements made by other agencies to make major regulatory decisions.

Option 2: Accelerate market access for medicines with significant potential benefit

Summary

Accelerated and adaptive approval pathways can not only provide more rapid access to treatments for unmet medical needs but also have the potential to reduce the cost of producing evidence prior to marketing approval. However, in shifting some evidence requirements to after marketing approval, they also increase uncertainty about the safety and efficacy of new treatments and pose potential risks to patients who receive treatments early. Accelerated and adaptive approval may be most appropriate when used highly selectively, for those medicines promising the greatest potential benefit and in conjunction with stringent rules for compliance with post-market evidence requirements and patient information adequately conveying uncertainty as to the risks and benefits of treatment.

Background

New drug approvals rely on well-established standards for evidence of safety and efficacy, usually based on randomised controlled trials (RCTs), which can take several years to conduct (see Chapter 2). The regulatory process itself takes several months, including review time by the competent authority and time used by the applicant to answer questions and update documentation. However, time to approval for New Active Substances (NAS) by stringent regulatory agencies has declined and converged over the past decade. The median approval time of six regulatory authorities[3] declined from 565 days in 2006 to about one year in 2016, and the difference in the median approval time between the fastest and slowest agencies decreased from 530 to 180 days (Bujar, McAuslane and Liberti, 2016).

Since the end of the 1980s and following pressure from the HIV patient community to expedite access to new treatments, many regulatory agencies have implemented accelerated marketing authorisation pathways to approve promising treatments for high unmet medical needs earlier and more quickly (i.e. for severe diseases without any available treatments). Some regulatory agencies can approve treatments earlier in their development phase, with lower levels of evidence, usually conditional on provision of further evidence post-approval. In the United States, for example, the Food and Drug Administration (FDA) Accelerated Approval Program allows for early marketing authorisation of drugs for serious conditions / addressing unmet medical needs based on surrogate endpoints[4], provided that manufacturers then submit results of phase 4 trials to confirm the expected clinical benefit (FDA, 2016). In the European Union, the EMA may grant conditional approval for medicines that address unmet medical needs – including medicines that treat life-threatening diseases, are intended for use in emergencies, or are orphan medicines – and where the benefit of early availability is considered to outweigh the risks of less comprehensive data than normally required (EMA, 2017b). Manufacturers are also required to provide comprehensive data after conditional approval to confirm that the benefit-risk balance is positive (EMA, 2017b). Accelerated assessment in the European Union, on the other hand, refers to a shortened period of review of an marketing approval application by the EMA when the application is for a product of major interest for public health and represents a therapeutic innovation (EMA, 2017a).

More recently, the *Sakigake Review Designation System* was launched by the Japanese Pharmaceuticals and Medical Devices Agency (PDMA) in 2015 to approve innovative

products within six rather than 12 months of submission of phase 3 clinical trial data. Products are targeted for the *Sakigake* system based on criteria such as disease severity and evidence of substantial improvement over conventional therapies (Mori, 2017). In 2017 Japan also established the *Conditional Early Approval System* for early approval of medicines for severe and rare diseases without an existing effective treatment and for which conducting confirmatory clinical trials is difficult (ibid.). Early approval entails restrictions to ensure appropriate clinical use, and is conditional on post-market reconfirmation of safety and efficacy (ibid).

In 2014 the EMA launched a pilot project to explore the feasibility of "adaptive pathways" (Eichler et al., 2012, 2015). In its "adaptive licensing"[5] pilot program the EMA takes a stepwise approach, with iterative phases of data gathering and regulatory evaluation; successive changes to marketing authorisation that take into account new evidence generated; and acknowledgement of remaining uncertainty at each stage (Eichler et al., 2012). Adaptive licensing can therefore enable, for example: the use of a new medicine in a restricted patient population with subsequent broadening of the marketing authorisation to a wider patient population, or a change to the indications for which a product is approved after confirming its benefit-risk balance, following a conditional approval based on surrogate endpoints. Adaptations could be based on a comprehensive development and licensing plan agreed in advance, not only between manufacturers and regulators, but also with payers that base decisions on the evidence generated (Eichler et al., 2012). Licensing frameworks based on the idea that knowledge and experience about a therapeutic product can be gained at every stage of its lifecycle have also been developed elsewhere, for example in Canada (ibid.).

While the trade-offs between the benefits and risks of earlier access and less certain treatment effects and toxicity need to remain at the forefront of decision making, accelerated marketing authorisation schemes may be useful in many situations where there is substantial potential benefit from early treatment. Beyond immediately life-threatening conditions, such as untreated HIV for which accelerated approval was initially devised, other examples include preventive therapies in situations where there is high risk of contracting the disease, or curative treatments where there is only a short period of time between diagnosis and the point at which treatment becomes impossible or futile (Eichler et al., 2015).

Strengths

Accelerated marketing authorisation has the potential to provide patients in desperate need faster access to promising treatments. It could also provide the pharmaceutical industry with earlier returns on R&D investments. Because the cost of capital to finance R&D can represent a sizable share of total drug development costs, shortening the time between cash outlays for clinical trials and cash flow from product sales can reduce the overall cost of R&D.

Weaknesses

Accelerated approval processes can pose greater risks for patients, particularly if uncertainty as to the risk/benefit balance of a treatment remains after approval. There is some evidence that drugs approved since the adoption of the Prescription Drug User Fee Act in the United States, which accelerated FDA approval processes, have been more likely to receive black-box safety warnings or be withdrawn, than drugs approved prior to it (Frank et al., 2014). On the other hand, a study of drugs approved by the EMA found

that exceptional circumstances or conditional approval procedures were not associated with a higher probability of safety warnings than standard approval (Arnardottir et al., 2011).

It is not entirely clear whether prior efforts to accelerate marketing authorisation have been accompanied by sufficient efforts to reduce uncertainty after initial approval, or whether such accelerated procedures have increased safety issues. The EMA has reported that compliance with specific obligations related to conditional marketing authorisation was generally acceptable, while critics argue that evidence submitted subsequent to conditional authorisation has not provided sufficient certainty of the benefits and harms of new medicines (Banzi et al., 2017; EMA, 2017c).

Accelerated approval might also discourage investment in additional research on new agents. Manufacturers may take the view that by not generating further evidence on clinical effectiveness following accelerated approval they avoid the risk of unfavourable publicity and adverse regulatory action if later trials demonstrate poor clinical effectiveness (Naci et al., 2017). Thus, accelerated approval could create a disincentive to conduct additional research in those therapeutic areas in which accelerated approval has already been granted (ibid). A review of the available evidence base for novel therapeutic agents granted accelerated FDA approval between 2000 and 2013 found that a majority of RCTs of these products were not designed to evaluate their clinical benefits, but rather to incorporate them into standard treatment regimens, or to evaluate them for use in indications for which they were not approved (ibid).

Accelerated approval may also reduce the evidence available for subsequent health technology assessment (HTA) and coverage or pricing decisions by payers. This can make it more difficult to align prices with the relative effectiveness of treatments and to maximise the value of pharmaceutical expenditure.

Enabling conditions

There are a number of additional issues in deciding whether and how to implement accelerated marketing authorisation (OECD, 2017b). First, it is important to consider whether patients are adequately informed of the quasi-experimental status of products approved through such pathways, and that their safety and efficacy has not been established according to the criteria applied to other treatments. Second, countries could consider whether regulatory agencies have the means to ensure that companies comply with their commitments to produce further evidence post-approval within agreed timeframes. Stringent post-marketing evidence requirements, in terms of both safety and effectiveness, may be essential to manage uncertainty, as although incentives for firms to fund studies are reduced once a new product is approved for marketing, the need remains for robust clinical data to support regulatory, treatment, and pricing or coverage decisions. Third, countries could consider the option of withdrawal of authorisation in case of non-compliance with post-approval obligations, and whether to integrate products approved under accelerated pathways into standard treatment protocols prior to their safety and efficacy being established.

Reductions in the cost of R&D *per se,* however, do not automatically increase the efficiency of pharmaceutical spending or help achieve sustainable access to innovative medicines. Efficiency can only be increased if measures that reduce the costs of R&D are accompanied by mechanisms that can reduce medicine prices and improve value.

B. Increase spending efficiency

Option 3: Facilitate international co-operation in health technology assessment (HTA)

International co-operation in HTA could improve information available to payers; potentially avoid duplication of effort by HTA agencies; and reduce heterogeneity in evidentiary requirements among agencies, thereby reducing the burden of producing evidence for firms.

Implementation of co-operation initiatives may face significant challenges in gaining agreement on methods and parameters between countries, and in harmonising national processes. When considering such initiatives, it is therefore important that policy makers take into account the similarities and differences of national systems. Decisions about the breadth of co-operation, in terms of the countries involved, and the extent of co-operation, in terms of the level of integration of capacities and processes, or the type of assessments conducted jointly, may need to be adapted to the level of similarity of cooperating countries.

At the very least, however, HTA agencies could share clinical data on efficacy or comparative effectiveness that underlie assessments, or the results of those assessments, to reduce duplication and improve information available to payers. OECD countries could also attempt to define best practices in the conduct of HTA, or to standardise the health outcome measures to be used.

Background

HTA is a mechanism for supporting coverage decisions and price negotiation processes. One option to improve the information available to payers is for countries to cooperate in assessing the comparative effectiveness of new medicines. This however, requires a certain degree of homogeneity in terms of existing standards of care. In contrast, assessments of cost-effectiveness and budget impact of new technologies must be country-specific, as they depend on the epidemiologic context, on costs of products and services and patterns of care in individual countries.

Population structures and burdens of disease, levels of income, healthcare system characteristics, standards of care and HTA infrastructure vary significantly among OECD countries. As a result, new products can have varying impacts on different healthcare systems. Co-operation in HTA can range from loose networks that share information on completed assessments to full integration of capacities and processes. Regardless of the level of integration, clinical data on efficacy or comparative effectiveness that underlie assessments could be shared across countries. Countries could also attempt to define best practices in conducting HTA, or to standardise the outcome measures to be used. Clinical studies often use a variety of outcome measures, which can make study synthesis difficult and can severely limit the generation of reliable research conclusions. A review of approximately 9 000 clinical trials in oncology, for example, found that more than 25 000 outcome measures were only used once or twice (Hirsch et al., 2013). A core set of standard outcome measures would also facilitate evidence generation by firms, as they would have a pre-specified set of outcome measures that would be accepted by HTA agencies.

Co-operation is already developing in regional and international HTA networks: examples include the Central and Eastern European Society of Technology Assessment in

Health Care (CEESTAHC), Health Technology Assessment International (HTAi), HTAsiaLink, the International Network of Agencies for Health Technology Assessment (INAHTA), and the HTA Network of the Americas (Red de Evaluación de Tecnologías en Salud de las Américas, RedESTA). The United States Agency for Healthcare Research and Quality (AHRQ) created the Systematic Review Data Repository (SRDR) to make data underpinning systematic reviews and meta analyses and review reports freely available, and to reduce duplication among HTA agencies.

At the European Union level, the *European Network for Health Technology Assessment* (EUnetHTA), for example, has issued methodological guidelines to assess the comparative effectiveness of new technologies, and is piloting joint assessment for a small number of products.[6] The European Commission made a legislative proposal for an initiative on EU-wide co-operation on HTA in January 2018, expected to be endorsed by the European Council and Parliament in 2019 (European Commission, 2018). Objectives of the proposal include improving the availability of innovative health technologies; reducing duplication of efforts by HTA agencies and industry to ensure the efficient use of resources; and strengthening the quality of HTA. The proposal foresees an amendment to the existing Directive on Cross-Border Healthcare (2011/24/EU), which provides for a network of HTA agencies of member states to facilitate co-operation and the exchange of information, to establish a joint clinical assessment process for medicines and medical devices. National assessments would be replaced by joint assessments for selected technologies and carried out by a coordination group of national authorities and bodies responsible for HTA. While non-clinical (e.g. health economic) assessments would remain national, the proposal also provides a mandate for the European Commission to support voluntary co-operation and the exchange of aspects of HTA that go beyond clinical assessment.

Some initiatives to standardise outcome measures and share information are also underway already. The development of core outcome sets (COS) has begun in recent years as a response to the heterogeneity in outcome measures, to provide standardised minimum sets of outcomes to be measured and reported in all clinical studies of effectiveness in a given therapeutic area (Gargon et al., 2014). For instance, the Core Outcome Measures in Effectiveness Trials (COMET) initiative, funded by the European Commission and the United Kingdom National Institute for Health Research (NIHR), promotes COS and published a handbook for COS development in 2017 (Williamson et al., 2017).

The BeNeLuxA initiative (involving Belgium, the Netherlands, Luxembourg, Austria, and Ireland) has included joint HTA among the potential activities listed in its Terms of Reference (BeNeLuxA, 2018). The focus is on high-cost and orphan drugs that are considered priorities in each of the participating countries, and for which assessment methods are deemed sufficiently similar to allow for such co-operation. An experimentation phase for this approach is currently underway for a small number of products.

Strengths

Greater international co-operation in HTA has the clear potential to increase the level of information that underlies coverage decisions and price regulation or negotiations. Sharing of the same information can also increase harmonisation in decision processes between countries and facilitate greater co-operation in negotiations or procurement (see Option 4).

Co-operation reduces duplication of effort among countries and can generate administrative cost savings. While greater depth of co-operation may require a greater effort of harmonisation upfront, conducting joint assessments and the full integration of capacities, for example through establishing a centralised HTA function, could lead to greater cost savings. However, costs related to the conduct of HTA are modest in comparison to the costs of the technologies being assessed.

For manufacturers, greater alignment of submission requirements and methods between countries or joint assessment processes may also lower costs to comply with these requirements. Harmonisation of requirements can reduce the number of country-specific dossiers that need to be prepared and submitted in order to gain coverage by national payers and gain agreement on prices.

Weaknesses

While the basic principles that underlie HTA are firmly established, substantial variation exists among countries in terms of the metrics used to assess technologies, assessment parameters, and other methodological choices. For example, a mapping of methods applied by 48 HTA agencies in 27 countries of the European Union and Norway found that approaches varied in terms of choice of comparators, or the use of network meta-analysis for indirect comparisons of treatments (European Commission, 2017). Co-operation may be particularly difficult where there are variations in burdens of disease, costs of health services, and treatment patterns. Domains that are context-dependent such as economic evaluation, or that require value judgments, will limit the scope for shared evaluation.

Enabling conditions

Because some domains of HTA are context-dependent or require value judgments, it is important that countries clearly define societal preferences and their parameters for HTA nationally (see Option 9), and assess the scope for co-operation accordingly. Continued and strong political commitment to co-operation will also be necessary to sustain initiatives. There may also be legal constraints on sharing of data between HTA agencies that need to be assessed.

Option 4: Encourage co-operation in negotiations, contracting or procurement

Summary

Countries could increase the efficiency of pharmaceutical procurement through international co-operation in negotiations, contracting, or procurement. This could increase their bargaining power, promote competition in pharmaceutical markets, and impose greater discipline in negotiation and pricing processes through improving the information available to buyers. Co-operation could also reduce administrative costs if duplication between countries is lessened.

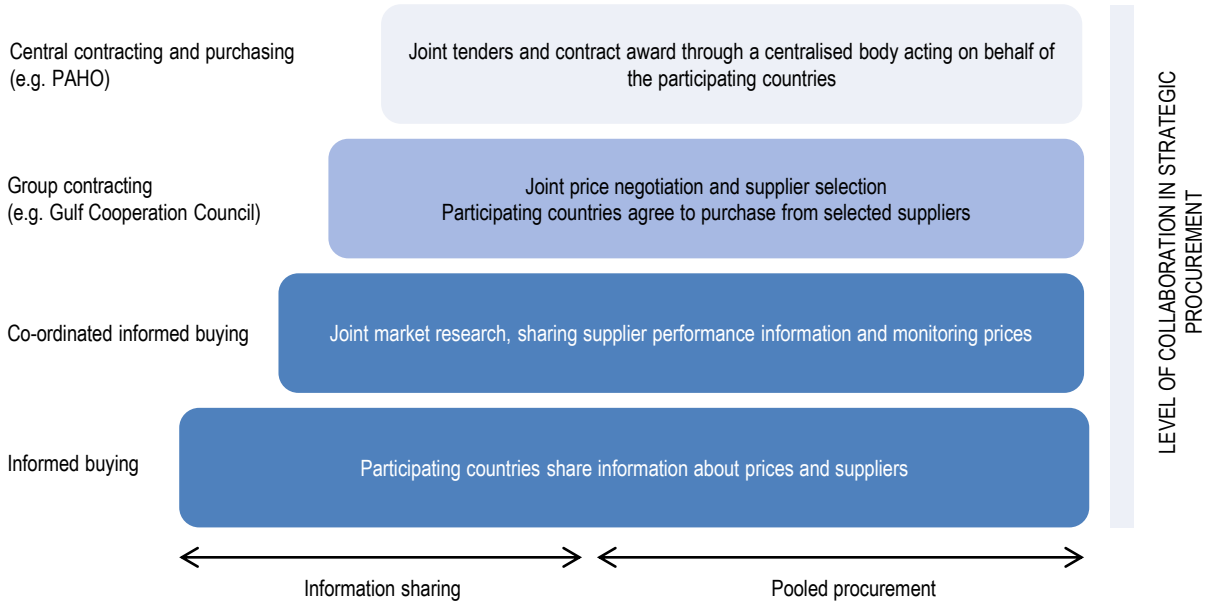
International co-operation could span the exchange of information or joint drafting of technical specifications without joint tendering, to joint tendering, joint price negotiations, or fully integrated international joint procurement. All these options have their own merits and weaknesses. Their appropriateness depends on market characteristics (e.g. the level of competitiveness), the political will to cede sovereignty and independence in order to benefit from joint contracting opportunities, and the level of intercountry harmonisation achievable in evaluating medicines and making pricing or

purchasing decisions. When substantial harmonisation effort is required, co-operation can also imply significant administrative costs. Depending on the nature and extent of co-operation, joint negotiations, contracting, or procurement may lead to greater price transparency.

Background

International co-operation in medicines procurement can take different forms, with varying levels of integration among individual countries that agree to cooperate. As illustrated in Figure 3.2, in principle, co-operation initiatives can range from rather loose arrangements of sharing information to inform procurement, e.g. on prices, suppliers or methods and results of HTA, with countries continuing to regulate prices or purchase medicines individually, to more integrated forms, where participating countries may open joint tenders, enter into contracts jointly, or set up a central buying unit that enters into economic transactions with suppliers (World Health Organization, 2016).

Figure 3.2. Levels of international co-operation



Note: PAHO: Pan-American Health Organization
Source: World Health Organization, 2016, p. 8.

Examples of international co-operation in the procurement of medicines have emerged since the late 1970s. Initially, co-operation schemes developed mainly among smaller low- and middle-income countries, with a focus on vaccines or medicines deemed "essential". As some schemes have matured, the product scope has expanded to cover medicines for a wide range of diseases, as well as other medical supplies. Examples that are considered successful, perhaps not least because of their longevity, include:

- The Pan American Health Organization (PAHO) Revolving Fund for Vaccine Procurement, a highly integrated scheme, with tendering, contracting and payment performed centrally by PAHO was established in 1979 and now comprises 41 Latin American and Caribbean countries (DeRoeck, 2003; Huff-Rousselle, 2012; World Health Organization, 2016).

- PAHO has also been operating the Strategic Fund for joint procurement of "strategic" public health supplies since 2000 – comprising 25 countries in the PAHO region as at September 2015 – to procure drugs for highly prevalent communicable and non-communicable diseases (PAHO, 2015).
- The Gulf Co-operation Council Group Purchasing Program (GCC/GPP), a joint contracting scheme for vaccines, medicines and other medical supplies for seven countries in the gulf region, was also established in 1979 (Huff-Rousselle and Burnett, 1996; DeRoeck et al., 2006; World Health Organization, 2016).
- The Eastern Caribbean Drug Service (ECDS) was established in 1986 (Huff-Rousselle and Burnett, 1996; Huff-Rousselle, 2012).
- At a global level, the Global TB Drug Facility (GDF) established in 2001 has procured tuberculosis treatments for 90 countries, including most developing countries with high TB prevalence, providing drugs procured centrally with GDF funds as well as technical assistance to local procurement mechanisms (Stop TB Partnership, 2017).
- World Health Organization Global Fund includes a pooled procurement mechanism for supplies to treat HIV, malaria and TB (Wafula, Agweyu and Macintyre, 2013; The Global Fund, 2015).

More recent examples can be found in Europe. In 2014 the European Commission established the EU joint procurement agreement for pandemic vaccines and other medical countermeasures for combating serious cross-border health threats (Azzopardi-Muscat, Schroder-Beck and Brand, 2016). By April 2016, 24 EU member states had signed the agreement (European Commission, 2016b). Formally, this mechanism represents a high degree of integration between participating member countries in that the European Commission takes central responsibility for the procurement process, opens tenders on behalf of countries, becomes the sole contractual counter party for suppliers, and allocates products to member countries (ibid.). However, there is no requirement for exclusivity, and member states can continue to contract individually with suppliers while participating in the scheme; they are also allowed to opt out of the scheme at any stage (Azzopardi-Muscat, Schroder-Beck and Brand, 2016). This EU joint procurement process has not been used thus far.

Belgium, the Netherlands and Luxembourg established a cooperative initiative in 2015, subsequently joined by Austria in 2016 and Ireland in 2018. The overall goal is to ensure affordable access to innovative medicines. The initiative comprises extensive co-operation in informing and preparing pricing and reimbursement decisions, including joint HTA, horizon scanning, and the exchange of information from national disease registries, as well as joint price negotiations with industry (BeNeLuxA, 2018; Department of Health, 2018). Internal transparency among the members of the cooperative is an essential principle. The focus is on high-cost and orphan drugs considered priorities in each of the participating countries, and for which assessment methods are deemed sufficiently similar to allow for such co-operation. The initiative is currently being piloted for a small number of products, in particular orphan drugs. Similar co-operation has been announced but not yet implemented by Bulgaria and Romania in the procurement of high-cost drugs (BMI Research, 2015; Petrovsky, 2015); by Poland, Hungary, Slovakia and Lithuania (Visegrad Group, 2017); and by ten Southern European countries that have signed the so-called Valletta Declaration (Infarmed, 2018).

There is little evidence available to assess the likely impact of this policy option in OECD countries. Joint procurement schemes in Europe are relatively new and the available literature mainly describes schemes in low- and middle-income country contexts, which may be of limited relevance to OECD countries (Azzopardi-Muscat, Schroder-Beck and Brand, 2016; Espín et al., 2016). Also, the publicly available studies were not always conducted independently, and did not always employ rigorous evaluation methods to show that prior co-operation or joint procurement schemes had been successful.

Strengths

An advantage of looser arrangements to share information could be an increase in internal transparency, i.e. among, but not beyond, the cooperating parties, which could improve, for example, their understanding of commercial strategies of pharmaceutical firms involved in negotiations.

Greater international co-operation can impose greater discipline on negotiation and pricing processes through improving the information available to payers. Structured co-operation mechanisms can improve the information available to buyers and impose greater discipline on price negotiations, through the explicit definition among cooperating parties of criteria that underlie decision making, and therefore help align prices to the "value" of treatments as evaluated by health technology assessment (HTA). This can lead to higher prices for effective medicines that provide high value and, by the same argument, lower prices for medicines of lesser value, leading to greater alignment of prices with the relative effectiveness of treatments.

The primary objectives of past co-operation schemes have been to improve efficiency of spending, achieving overall cost reductions or offsetting savings with increased volumes to improve access (DeRoeck et al., 2006; Huff-Rousselle, 2012). The creation of buyer monopsony in entire market segments that span several countries and represent a large proportion of supplier revenue can help attract more competitive offers from suppliers (Management Sciences for Health, 2012). In low- and middle-income countries, co-operation has also aimed to improve the reliability of supply and avert shortages (DeRoeck et al., 2006). Other benefits can include (Huff-Rousselle and Burnett, 1996; DeRoeck et al., 2006; Huff-Rousselle, 2012; Azzopardi-Muscat, Schroder-Beck and Brand, 2016; Espín et al., 2016; World Health Organization, 2016):

- More rational product choice through better-informed selection and standardisation.
- Reduction in operating costs and administrative burden in the procurement process, for example through reducing duplication between countries and shared processes to gather information and monitor prices and supplier performance.
- Improved quality assurance through restricted tenders and stricter up-front screening of suppliers.
- Increased equity among member countries.
- Reduction or elimination of the potential for corruption in procurement.
- Transfer of technical capacity in procurement through the formal establishment of networks of procurement professionals, especially to resource-constrained environments.
- Improvements in transparency and other aspects of supply chain management.

Aside from co-operation in operational processes for negotiation, contracting or procurement, countries could cooperate in skill development and capacity building within government agencies or payers involved in negotiation and procurement.

The limited evidence available suggests that some joint procurement schemes have been successful at achieving objectives related to efficiency, reliability of supply, and access. A review of the operating mechanisms and achievements of the GCC/GPP and the PAHO Revolving Fund found success in terms of the stated objectives of reducing cost and ensuring more reliable supply as a result of more efficient procurement and better forecasting of demand (DeRoeck et al., 2006). Both programmes were also found to have reduced prices versus local procurement and to have accelerated access to new medicines (DeRoeck et al., 2006; Organization, 2007). At a meeting on pooled procurement hosted by WHO in 2007, representatives of the Eastern Caribbean Drug Service (ECDS), the Gulf Co-operation Council Group Purchasing Program (GCC/GPP) and the Global TB Drug Facility (GDF) reported that joint procurement was successful at increasing bargaining power, achieving significant cost savings, enhancing quality control, and increasing access to medicines.

Weaknesses

Gaining and sustaining political commitment to co-operation may be difficult. For example, key problems in procurement of H1N1 vaccines and antivirals by EU countries prior to establishment of the joint procurement mechanism were seen as the main triggers for the Council and Parliament to request establishment of the mechanism by the Commission. These were related to price, liability, confidentiality, and flexibility to adjust quantities ordered to actual needs (European Commission, 2016b). However, not all member states were supportive of the proposal at first, with disinterest especially among those who already had agreements in place with the industry (Azzopardi-Muscat, Schroder-Beck and Brand, 2016). The EU mandate on public health, and the strong legal basis in the *Treaty on the Functioning of the European Union* (TFEU) for combating serious cross-border threats to health, are considered instrumental in reaching an agreement. However, focus remained strictly on vaccines for serious cross-border threats to health, and the participation of countries remained relatively flexible, with opt-out clauses and no exclusivity requirements (ibid.).

Existing co-operation schemes in the procurement of medicines within the EU mainly involve small countries. However, it has been argued that larger countries may be reluctant to join, or may even perceive joint negotiation mechanisms as disadvantageous, by weakening their sovereign right to negotiate directly with suppliers (Azzopardi-Muscat, Schroder-Beck and Brand, 2016).

Depending on the depth of co-operation chosen, joint price negotiations or tendering can engender price transparency among cooperating countries. Although countries could agree to adopt tiered pricing between them, price transparency can make tiered pricing more difficult than where discounts are confidential, for example because the general public in a given country may be reluctant to accept higher prices than in other countries that are part of the cooperative. Joint negotiations or tendering can lead to price convergence among cooperating countries, and can disadvantage countries that were previously able to negotiate favourable terms with suppliers, at least in the short term.

Finally, given that co-operation schemes are costly to establish, purchasers may be tempted to award significant proportions of the total volume of a class of medicines to fewer or even a sole supplier in order to generate savings. This could reduce the number

of different types of products in a class available to physicians and patients, and thus limit product choice, as well as leading to greater market concentration among suppliers, or eventual supplier monopolies. This may not only lead to price increases in the longer run but may also jeopardise the reliability of supply through increased dependence on few or only one supplier. Thus it is important to mitigate risk to competition by appropriate tendering and contracting mechanisms, and in particular, to avoid winner-takes-all tenders (see Option 8).

Enabling conditions

International co-operation in negotiations, contracting or procurement could be increased gradually, with initial steps including the building of capacity and co-operation in workforce training or exchange of information. These would require little effort to harmonise national processes. However, commercial information, such as prices, may be legally protected; rules that protect such information may need to be reviewed to enable information sharing.

Depending on progress and experience with initial steps, more demanding areas of co-operation that require more sustained political commitment and greater harmonisation might then be explored. Gaining and sustaining political commitment is important for deeper co-operation schemes that go beyond the sharing of information. The guide to drug procurement by Management Sciences for Health (2012), for example, concludes that continued political commitment is the cornerstone of joint procurement schemes. Noting that only a few multi-country procurement schemes have proven sustainable over time, such as the examples from PAHO, the Caribbean and the Gulf states, the guide also states that political commitment is a necessary but insufficient prerequisite to maintain buyer monopsony. Co-operation agreements could include mechanisms to enforce monopsony commitments, to avoid co-operation being weakened by the negotiations of individual members.

A significant challenge to co-operation in procurement can be that harmonisation in product registration and regulation are necessary, and that countries need to commit to aligning product preferences. Co-operation can lead to increases in overall costs if the administrative burden, for example from large harmonisation efforts, outweighs the savings generated from price reductions. This may require detailed technical feasibility assessments prior to launching co-operation schemes.

Option 5: Assess performance of medicines in routine clinical practice and adjust coverage and pricing accordingly

Summary

Instead of setting or negotiating definitive coverage conditions for medicines at market entry, adjusting them at subsequent points in time to better reflect performance in routine clinical practice could increase efficiency of spending, and could align incentives for innovation with the benefits medicines deliver to patients.

With the current capacity of health care systems to analyse routine data, this is unlikely to be practical for all products, and would be unnecessary for products for which effectiveness has been well established. However, it could be prioritised for treatments whose effectiveness is uncertain. The effective use of routinely-collected data would require countries to improve capacities and data governance to collect, link, process and analyse such data for the purpose of determining effectiveness.

Background

Prices and reimbursement conditions for new medicines are usually defined at market launch, based on evidence of efficacy and safety generated in late-stage clinical development trials that take place prior to marketing authorisation. While studies of efficacy aim to establish the "extent to which an intervention does more good than harm under ideal circumstances" (James, 2017, p. 619), they do not necessarily demonstrate effectiveness, defined as the "extent to which an intervention does more good than harm under usual circumstances" (ibid.). Indeed, the use of medicines in routine clinical practice may often reveal a gap between the benefits and risks assessed in pre-market clinical trials and those observed in routine practice, not only due to factors unrelated to the medicine, such as adherence to treatment or other patient characteristics, patient-physician relationships, but also because of the possible discovery of previously unrecognised effects (e.g. rare adverse effects that were not detectable in pre-market clinical trials).

While this gap is widely recognised, the performance of medicines in routine practice is only rarely assessed, and usually not with the purpose of revising reimbursement conditions or prices. Several obstacles, including those that are described below and related to data availability and quality, analytical methods and patient privacy, may explain why this does not happen. Randomised controlled trials (RCTs), which are most often conducted by the pharmaceutical industry to establish efficacy prior to marketing authorisation, continue to be considered the "gold standard", as they provide evidence under conditions that minimise bias and confounding. RCTs usually apply restrictive patient inclusion criteria to increase the probability of showing a treatment effect, and may exclude very young, very old and multi-morbid patients; use allocation concealment and blinding to avoid biases; and adhere to strict follow-up protocols that improve patient adherence. These methods increase the internal validity of studies and thus the confidence that an observed outcome can be attributed to the intervention (Revicki and Frank, 1999; Gartlehner et al., 2006). The hierarchies applied by most HTA agencies classify data from non-randomised studies as a lower level of evidence than RCT data.

Thus far, data from routinely collected sources have been used mainly to monitor safety and measure utilisation post marketing approval than for other purposes, largely because serious adverse events (death, hospitalisations) or other safety signals can be easier to discern. In HTA the use of routinely-collected data is more limited and policies of national HTA agencies vary (Makady et al., 2017). According to the most recent OECD surveys (OECD, 2013b, 2015a), nearly half the OECD member countries routinely collect data on pharmaceuticals prescribed or dispensed. However, linkage between these datasets and other health data is less common and limits their utility. In the European Union, several public-private initiatives have been launched to encourage co-operation between industry, regulators, HTA agencies, and other stakeholders in exploring tools and methods for the use of routine data (IMI, 2018).

Strengths

Although deriving evidence from routinely-collected data still presents some challenges, in the long run this option is a promising route for providing credible long-term evidence of a product's value to the health system. Pre-market RCTs have many advantages, such as pre-specified and well-defined endpoints and patient inclusion/exclusion criteria, randomisation of study subjects into intervention and control groups to control for bias and confounding, and blinding of patients and health care provider to provide unbiased

measures of efficacy in the trial population. However, these features of RCT study designs that ensure high internal validity of their results can also limit their external validity and generalisability. Pre-market RCTs are carried out using selected populations under ideal conditions that but say little about which interventions work best when implemented in different routine settings and on different populations.

The advantage of studies of effectiveness in routine practice relative to RCTs is their greater external validity and generalisability. Such studies are thus useful for:

- Examining clinical outcomes in a diverse study population that reflects the range and distribution of patients observed in routine clinical practice;
- Comparing multiple alternative interventions (e.g. older vs. newer drugs) or clinical strategies to inform optimal therapy choices beyond placebo comparators;
- Measuring the gaps between efficacy and effectiveness.

Studies that use routine data are significantly cheaper to conduct than RCTs. Through secondary use of data generated from the routine processes of healthcare delivery, such studies do not require the recruitment of healthcare professionals and patients to participate and can be conducted with smaller teams of researchers. With technological advances, the costs of data collection and storage can be expected to decrease further in the future.

Ultimately, using assessments of performance in routine clinical practice to adjust coverage and pricing could lead to greater alignment of financial incentives for manufacturers with the value delivered by the medicines they produce.

Weaknesses

Data availability and quality remain problems in assessing performance in routine practice. Observational data in routine datasets are not collected for research purposes, which may imply that measures of health outcomes or confounding factors to assess performance may not be available or may be recorded with poor quality.

It is often methodologically difficult to disentangle effects of a medicine *per se* from confounding factors in non-randomised and retrospective studies based on routine data. Random allocation can balance confounding factors between intervention and control groups in RCTs if sample sizes are sufficiently large. Observational studies must instead rely on sophisticated statistical methods to control for confounding in the absence of randomisation. These methods, such as propensity score-matching, synthetic control groups, etc. are still an emerging field of research. While studies using routine data can enable greater generalisability of findings because they reflect the conditions of routine practice (in which patient populations are more heterogeneous and inappropriate prescribing or lack of patient adherence to treatment may be more common), they can have poorer internal validity and may fail to accurately isolate the effects of the treatment assessed (Revicki and Frank, 1999; Gartlehner et al., 2006). Examples of current initiatives that aim to develop methods for analysis of routine health data further, including the estimation of treatment effectiveness, include the Observational Health Data Sciences and Informatics (OHDS) initiative in the United States and the Electronic Health Records Research Group (EHRRG) in the United Kingdom.[7]

Enabling conditions

The effective use of routinely collected data would require countries to improve their capacities not only to collect and link data generated by health care providers, payers or other stakeholders in health care systems, but also to process and analyse the data for purpose of assessing effectiveness. The availability, governance and use of routinely collected data have been a recent focus of the OECD Expert Group on Health Care Quality Indicators. Based on a 2013/14 survey (OECD, 2015a), at least 15 OECD countries routinely collected data on prescription medicines. Most of these data come from reimbursement claims or billing data. In at least eight countries, prescription databases are linked with other databases such as hospital discharges and mortality data.

Assessing the performance of medicines post marketing authorisation might also entail expanding data collection and standardising the data to be collected, which can generate additional costs. For example, this could include defining minimum datasets or establishing additional registries for specific purposes. Countries would likely need to devote additional resources to expand their capacity for the collection, storage and analysis of routine data, and some countries may be unable to absorb the additional costs at current levels of health expenditure. Although studies that use routine data are cheaper than RCTs, assessments of the performance of medicines in routine practice would have to be done in addition to pre-market RCTs and other prospective studies that are currently required to support marketing authorisation or post-market surveillance. To produce generalizable results in each country, a given medicine would likely need to be assessed in each country using routine data from domestic sources, leading to some duplication.

While digitalisation has increased volumes of available data, computing power and infrastructure for analysis, not all data can be transformed into information, and not all information is relevant evidence. It is therefore important to examine the types of evidence that can be derived from different sources of routinely-collected data. There are differences in the potential value of different data sources according to their collection and storage methods. Claims data are the most commonly available source in many countries, but their purpose is to facilitate billing, so their scope is often limited to spending, utilisation and potentially appropriate use. Different databases sometimes utilise different coding schemes across different settings of care, such as physician records and hospital discharge data. Linking such sources to extract the information of interest may be difficult. The uptake of electronic health records (EHR) permits routine collection of additional information (e.g. diagnoses, test results, etc.).

Assessments of the performance of medicines from the perspectives of payers are inherently comparative. Adjustments to coverage and pricing of a given medicine may have consequences for treatments that are alternatives to the medicine assessed, and in particular, other medicines that serve as comparators. Countries may therefore need to consider more dynamic systems of iterative coverage and pricing as new evidence becomes available, as this could entail reassessments and adjustments for all products that may be compared to the product for which coverage or pricing is being changed. Such network effects may be complex to manage.

The use of routine data sources also requires robust data governance and security measures to preserve confidentiality and patient privacy. All countries that responded to the OECD surveys (OECD, 2013b, 2015a) have legislation on data privacy in general, which apply to health and health care data. Some also have laws that govern the use of health care data more specifically. A major problem, however, is that many legislative instruments governing data, privacy and security predate the digital era, and their

interpretation in the context of secondary use of electronic health data is difficult, including requirements for obtaining informed consent. Although data that have been de-identified can generally be made accessible at lower risk to personal privacy, current data protection and privacy laws may be a barrier to greater use of routine data.

While analysis of data from routine practice cannot replace the safety and efficacy data generated by pre-market RCTs, evidence hierarchies and other methodological standards employed by some HTA agencies may need to be revisited. Post-market analyses can complement pre-market data by allowing actual effectiveness versus expected efficacy and safety to be evaluated in routine clinical settings. Analytical capacity would have to be expanded to apply rigorous observational methods that in the absence of randomisation can isolate effects of the treatment under evaluation from confounding factors. Many HTA agencies in OECD countries employ a formal hierarchy of evidence, attaching lower weight to observational studies, and are generally circumspect in considering evidence of effectiveness from routine data sources (Makady, Goettsch and Willemsen, 2015; Makady, 2017).

A further issue is the assignment of risks and costs between payers and industry while routine data are collected and analysed to reduce uncertainty around the effectiveness of a medicine. One option is to have government or HTA agencies collect and analyse data independently from the industry or payers, which could minimise conflicts of interest. If manufacturers are expected to collect and analyse data, policy needs to consider financial incentives for producing additional evidence. Payers may therefore need to be circumspect in initial coverage and pricing decisions where the effectiveness of a medicine is uncertain, and offer the prospect of coverage expansion or price increases if and when a medicine is shown to be effective using routine data. Initial coverage and pricing decisions also may also need to include binding conditions, enshrined in contractual or statutory law, to ensure that subsequent changes, such as delisting from coverage or price reductions, can be implemented.

Option 6: Promote competition in on-patent markets

Summary

To improve efficiency in pharmaceutical markets one approach is to promote competition among on-patent medicines with similar indications and pharmacological profiles, as seen recently with hepatitis C medicines. However, certain market features can prevent competition from working effectively. For example, in countries with national "positive lists" and regulated prices, negotiators are not always well placed to harness competition. Since positive lists usually determine both market access for companies and patient access to alternative treatment options, national "purchasers" may not always be in a position to negotiate favourable contract terms in exchange for listing.

There are several options for promoting on-patent competition; two in particular are *tendering by indication* (or requests for proposals, RFPs), and *formulary management*. While tenders for sole supplier arrangements can lead to the largest discounts, multiple supplier contracts retain therapeutic choice, and enhance security of supply. Formulary management can encourage competition among therapeutic alternatives by giving the most cost effective options preferential placement in a tiered formulary and in formulary-compliant treatment guidelines.

Background

Tendering is well recognised as an effective mechanism for generating competition. While sole supplier tenders arguably create the strongest incentives for discounting, they are not without attendant risks. Multiple supplier arrangements can preserve therapeutic choice, support the retention of multiple suppliers in the market (thus avoiding risks of future monopoly pricing), and enhance the security of supply.

Competitive tenders could be offered at national level and be followed by a formal and transparent process to allocate market shares to the best bidders. This can provide an optimal trade-off between competitive prices and product availability sufficient to ensure that all patients have access to treatments based on need, particularly where products are not clinically interchangeable.

Norway recently shifted a large share of medicines from the outpatient market to hospital markets,[8] where they are procured through a centralised process. The Norwegian Hospital Procurement Trust (LIS) is in charge of procurement of all of these products and uses European-wide requests for tender (RFTs). LIS drafts RFTs by indication,[9] and in co-operation with physicians, to ensure that patients will be offered a choice between alternative treatments where needed, and does not adopt a winner-takes-all approach. Alternative products are ranked within treatment guidelines according to the attractiveness of the bids submitted by manufacturers, and prescribers are required to use the medicines according to their order of priority unless a different choice is justified for clinical reasons - but all products remain available. The impact on price of the Norwegian tenders by indication is not known, except for cases where biosimilars are available (see Option 8). Since 2016, LIS may no longer disclose the prices that result from its tendering process.

Formulary management can also be used to encourage competition among therapeutic alternatives, by giving the cheapest or most cost effective options preferential placement in a tiered formulary and in formulary-compliant treatment guidelines. This form of formulary management is used mainly by insurers and PBMs in the United States (see Box 3.2).

Box 3.2. Formulary management, definition

"Formulary management" is a term typically used in the United States to refer to the practice of constructing a reimbursement formulary that steers prescription and consumption towards certain categories of drugs, usually those offering the most favourable terms. Constructing the formulary includes defining a list of covered products, setting the associated co-payments for patients, and determining coverage conditions (e.g. stepped therapy, prior authorization).

The list of covered drugs (and associated co-payments) usually falls into one or more of three broad categories:

- **Open formulary**: Where the insurer pays a proportion of the cost of all or virtually all marketed drugs, although some OTC of life-style drugs may be excluded.
- **Closed formulary**: Where the insurer only covers drugs listed on the formulary.
- **Tiered formulary**: The insurer offers differential co-payments or other financial incentives to encourage the use of preferred formulary drugs, but still pays a portion of the costs of the non-preferred drugs. Over time, the number of levels in tiered formularies has tended to increase. According to a 2016 survey of employer-sponsored plans, which cover about half of the non-elderly population, one third of covered workers face 4-tiered co-payments, and about half 3-tiered co-payments. Others have only one- or two-tiered co-payments or no co-payments after an initial deductible amount (The Kaiser Family Foundation and Health research and Educational trust, 2016).

A tiered formulary thus creates an opportunity to promote price competition in return for "preferred formulary status", which provides an advantage to a manufacturer in terms of market share, particularly where products are considered to represent comparable degrees of clinical benefit. Importantly, a tiered formulary can also create opportunities to increase the value of pharmaceutical spending, by steering prescription and consumption towards medicines with higher value. This requires the selection of products, tier placements and coverage conditions to be informed by pharmacoeconomic analyses.

Many payers in OECD Member countries already use pharmacoeconomic assessments to inform not only formulary listing and coverage decisions, but also clinical treatment guidelines. While the use of pharmacoeconomics was uncommon in the United States in the 1990s, more recently there has been renewed interest in its application, and increasing recognition of its potential to enhance value through drug benefit design (Grabowski and Mullins, 1997; Neumann, 2004; Lising et al., 2017).

Source: See for example http://lab.express-scripts.com/lab/insights/drug-options/how-we-build-a-formulary.

To date, assessments of the impact of formulary management strategies by PBMs have generally focused on use, patient adherence, and health care costs, rather than effects on competition (see, for example, Huskamp et al., 2005). One study examined the impact of the implementation of a close national formulary in the Veterans Health Administration drug benefit in 1997, and found that it significantly impacted market shares and reduced the price per pill in the therapeutic classes affected by the change in the two years following implementation (Huskamp, Epstein and Blumenthal, 2003). Clearly, a

significant obstacle to assessing the impact of formulary management on prices is that actual prices paid generally remain confidential. Recent analyses show that both list prices and rebates have increased substantially in the United States in recent years (see Chapter 1), but confidentiality prevents any analysis of the impact of price negotiations on prices for health insurance plans and consumers.

Strengths

Tendering by indication has the potential to foster competition between medicines that are still patented, providing a lever to increase spending efficiency not commonly applied in countries with price regulation, particularly where the use of reference prices (maximum reimbursement amounts) discourages discounting to the payer.

A tiered formulary may be thought of as a form of value-based benefit design that can be used to promote the preferential use of high value products, and to discourage, through higher co-payments or narrower coverage conditions, the use of lower value products. Tier placement has the potential to send unambiguous signals to prescribers and patients alike regarding care choices that are of greater or lesser value.

Weaknesses

Tendering processes that reduce prices very aggressively risk creating market segments that may become unattractive to manufacturers. This can lead to future problems of supply, and with market concentration, potentially, monopoly pricing. Clinical guidelines or formulary placement driven by the results of tendering processes may be seen by some patients and clinicians as limiting their therapeutic choices. Guidelines, however, could be developed by physicians' societies or HTA agencies, and routinely incorporate cost effectiveness considerations in prioritising treatment options.

Where tiered formularies are determined by price rather than cost effectiveness, priority may not be given to the highest *value* or most effective products.

Enabling conditions

Tendering by indication is most effective in reducing prices when the outcome is "winner takes all", but as noted above, this carries attendant risks to ongoing supplier participation in the market and security of supply. By contrast, not limiting the number of potentially successful suppliers creates minimal incentive for deep discounts.

One possible approach is to limit the number of bids accepted and set the reimbursement amount at the level of the lowest *unsuccessful* bid. This ensures a profit margin for successful tenderers by paying them a price higher than their tendered price (thus encouraging them to remain in the market), but retains incentives for suppliers to offer their best prices in order to be among the successful bidders.

Tiered formulary management is widely used by PBMs and health insurance plans in the United States. Its use in countries with national positive lists is not known, though it is not incompatible with value-based pricing as applied in 4th hurdle systems.[10]

Option 7: Explore bundled payments for episodes of care in oncology

Summary

Payment per episode of care rather than for individual services and products is expected to encourage health care providers to the most efficiency mix of inputs and engage in strategic purchasing to get better prices. In oncology, current pilots suggest that episode-based payments can generate savings, mainly stemming from more efficient use of resources. The ability of such payments to contain medicine costs might be more limited, especially when there is no competition for a given indication. Countries could, however, explore the feasibility of bundled payments in oncology.

Background

In oncology, many new treatments are used in combination with existing ones and/or in step therapy protocols, leading to escalating treatment costs. Yet the prices of individual products are often negotiated with individual companies sequentially, and in some cases, with multi-year commitments.[11] In parallel, provider payments for oncology treatments sometimes create incentives to use the most expensive treatment when cheaper alternatives exist. For example in France, in order to guarantee patient access, the most expensive oncology medicines are paid for over and above DRG tariffs, creating an incentive for hospitals to use these drugs instead of cheaper medicines included in the tariffs. In the United States, providers administering chemotherapies to patients covered by Medicare Part B are paid through a "buy and bill" system in which physicians receive a payment equal to the average sale price of the drug in private markets, plus a margin of 6%, thus incentivising the use of the most expensive medicines (Newcomer, 2012).

A bundled payment is a fee intended to cover the costs of a suite of services, delivered by one or several providers, as an alternative to individual payments for each service or product used in the process of care. The term is very generic and covers a number of different concepts. Payments per case (DRG-like), used in hospitals in many countries are bundled payments. Bundled payments *per episode of care* pay for a suite of services provided around an acute "episode of care". They typically cover inpatient activities (e.g. elective surgery), and pre and post intervention visits for a set period of time (OECD, 2016).

The main objective of bundled payments is to encourage providers to be more efficient when treating patients. Increased efficiency can be derived from changes in the *mix of inputs* or from changes in the *prices of individual inputs*. In oncology, physicians typically make decisions concerning the mix of inputs. These decisions can be influenced by clinical guidelines or even constraints imposed by national or local formularies, but a bundled payment per episode could also encourage physicians to use the most cost-effective mix of inputs. The ability of individual providers to influence oncology drug prices may, however, be limited. Active formulary management or tendering may offer some opportunities to foster competition (see Option 6), but this requires the existence of several therapeutic options perceived as alternatives.

Bundled payments in oncology are currently being tested in the United States (Deloitte, 2016; Social and Scientific Systems, 2016; Spinks et al., 2017). Identified payment models falling into this category are presented in Table 3.1:

- The 21st Century Oncology's radiation bundle model, introduced in 2012, provides an episode-based payment which covers external beam radiation therapy

services for 13 common cancer diagnoses, from the first consultation to 90 days after treatment (Falit, Chernew and Mantz, 2014).

- The UnitedHealthcare Oncology Episode Pilot Program, tested between 2009 and 2012 in five sites and about 1000 patients, proposed bundled payments for 33 episodes of care related to breast, colon and lung cancer. The bundle included physician hospital care, hospice management care, and case management, while other services remained paid on a fee-for-service basis. Oncologists received a single fee for chemotherapy medications, set at the average sales prices and without a margin.
- The Head and Neck Bundled Payment Pilot provided a one-year episode payment for patients with head and neck cancer. Providers were paid through four risk-adjusted bundled payments, with stop loss provisions and the possibility of adjusting payments in case of need (Spinks et al., 2017).

Table 3.1. Oncology bundled payments tested in the United States

	Services included in the bundled payment	Contracting parties and payment arrangements
21st Century Oncology's Radiation Oncology Bundled Payments (From 2012)	The bundle includes professional and technical services delivered in its facilities for external beam radiation therapy services for 13 common cancer diagnoses, from the first consultation to 90 days after treatment. Payment does not cover indirect treatment expenses such as medications, laboratory tests, and diagnostic imaging, and are not risk adjusted.	21st Century Oncology Center (largest provider of radiation therapy, with 180 facilities) and Humana
UnitedHealthcare Oncology Episode Pilot Program (2009-2012)	Bundled payment covered physician hospital care, hospice management and case management. All other services (i.e. physician office visit, chemotherapy administration, diagnostic radiology, laboratory) were paid as per the pre-existing FFS arrangement. Drugs were paid at average sales price.	UnitedHealthcare partnered with 5 US oncology practices to pilot an episode payment model for treating nineteen discrete "episodes" in breast, colon, and lung cancer with evidence-based treatment regimens.
Head and Neck Bundled Payment Pilot	Four bundles defined for different treatment plans. Bundles included multidisciplinary cancer care for one year.	UnitedHealthcare and University of Texas MD Anderson Cancer Center (provider)

Note: FFS: fee-for-service; P4P: pay-for-performance.
Source: Social and Scientific Systems, 2016; Spinks et al., 2017.

Bundled payments for a number of chronic diseases treated in hospitals have been used in Portugal since 2007: HIV infection, multiple sclerosis, pulmonary hypertension, different lysosomal storage diseases, familial amyloid polyneuropathy and selected cancers (i.e. breast cancer, cervical cancer, and colorectal cancer). Hospitals receive an annual payment for two years, and outcomes are being monitored (survival rates at 6, 12, 18 and 24 months). Payment rates were initially defined by applying average costs of individual services to standards of care (Lourenço, 2016). Further information was not available at the time of writing.

Strengths

Evidence on the impact of bundled payments for episodes of care in oncology or other expensive treatment settings is emerging. In the United States, for example, the costs of

erythropoiesis-stimulating agents were included in Medicare payments for end-stage renal disease (ESRD) in 2011, to replace payments for the medicines on top of the treatment. Erythropoiesis-stimulating agents were one of the largest cost line-items for the Medicare program. The new bundled payment has been successful in containing spending growth (Levinson, 2014). In oncology, an assessment of the United Healthcare Oncology pilot program showed a 34% cost reduction for the entire episode of care, in spite of a 179% increase in chemotherapy costs (Newcomer et al. 2014). Interestingly, studies show that other alternative payment models, such as "clinical pathways" or add-on payments to providers for enhanced care delivery (e.g. Oncology Care Models tested in the United States[12]), also have the potential to improve cancer care and reduce costs, even though they may not affect pharmaceutical costs (McClellan and Thoumi, 2015).

Weaknesses

If a payer's objective is to contain medicine prices and costs, bundled payments may not be the solution. Even though providers might be incentivised to negotiate prices or tender to get better prices for the medicines they use, they will only be able to obtain price advantages if several treatments compete within a given indication. Opportunities for intra-class competition in oncology would need to be assessed. For example, approval of multiple PD-1 and PD-L1 inhibitors might trigger price competition (Seiden, 2016). However, competition may remain limited among medicines recently approved for a previously unmet need. The advent of precision medicine, with treatments increasingly tailored to individual patient characteristics, may also reduce opportunities for competition. Finally, evidence from one pilot of bundled payments showed an increase in pharmaceutical costs – not specifically attributed to a price increase - despite a decrease in total costs.

If poorly designed or executed, systems that provide bundled payments may potentially put providers or patients at risk. These problems, and possible mechanisms to avoid them, have been widely documented in the literature on DRGs (Busse et al., 2011). Because bundled payments shift some financial risk from payers to providers, the latter may respond to financial incentives inherent in the system by providing sub-standard care, engaging in risk-selection among patients, denying high-risk patients access to innovative treatments, or choosing inferior products. This may happen, for example, if payment tariffs are too low or not updated frequently enough, or when the quality of care is not rigorously monitored. Bundled payments are therefore only suitable where treatments are homogeneous enough to establish meaningful average costs across providers, appropriate payment tariffs can be set and updated regularly, and sufficient data are available to monitor the quality of care and take remedial action if sub-standard care is observed.

Enabling conditions

Bundled payments for episodes of care have the potential to increase efficiency in cancer care delivery through more efficient use of inputs. Given the financial incentives that bundling can create for providers, appropriate quality and outcome indicators would be needed to ensure quality and protect patients from risks of substandard care (Mcpherson, Hedden and Regier, no date; McClellan and Thoumi, 2015). In addition, if bundled payments were to include pharmaceutical costs – which has not always been the case in pilot projects – tariffs defined for episodes of care would require regular revision to stay abreast of rapid treatment evolution in oncology. Otherwise, patient access to new treatments could be compromised by the emergence of large gaps between actual costs and payments. It would also be necessary to take into account the common practice of

off-label prescribing in oncology.[13] Payers may need to decide whether to encourage or discourage this practice, which would in turn influence approaches to tariff setting.

The ability of bundled payments to influence medicine purchase prices would depend on the existence of intra-class competition. If bundled payments were introduced with this objective, they would need to target conditions, indications, and stages of treatment in which several drugs can be reasonably considered as suitable alternatives.

Option 8: Promote competition in off-patent markets

Summary

To improve efficiency of spending through savings derived from generics and biosimilars it is important to promote and maintain competition in off-patent product markets. Increasing the penetration and uptake of generics and biosimilars can deliver savings without loss of benefit for patients, by moving prices closer to marginal costs of production.

A number of policies can support the uptake of generics and biosimilars, such as encouraging early entry of new suppliers upon loss of exclusivity (LoE) of originator or reference medicines, encouraging physician prescribing by INN, strengthening the role of pharmacists, and incentivising and educating patients. In addition, price competition can be fostered by appropriate procurement mechanisms, provided that several manufacturers are active in each market segment.

Mechanisms to influence generic and biosimilar prices include competitive tendering, albeit avoiding sole-supplier or "winner-takes-all" arrangements, as these can lead to suppliers exiting the market, creating risks not only to the security of supply but also of market concentration that can increase prices in the long run.

Background

The potential of generic markets is not yet fully realised in all OECD countries. For example, while the market share of generics by volume exceeds 80% in countries such as Germany and the United States, it is only approximately 52% across all OECD countries and below 30% in countries such as Greece, Italy and Switzerland.[14] The penetration of biosimilars also varies significantly between countries, depending on the therapeutic class (Rémuzat et al., 2017). The savings potential of increased generic and biosimilar uptake therefore remains substantial (QuintilesIMS Institute, 2016).

In the United States, where the overall market share of generics is near 90% of the total volume of medicines dispensed by community pharmacies (OECD, 2017a), a recent study found that the market is highly concentrated: 40% of generic molecule-dosage-forms are supplied by a single manufacturer, 20% by two or three manufacturers, and the remaining 40% by more than four manufacturers. In addition, the share of molecule-dosage-forms supplied by one or two manufacturers increased between 2004 and 2016, and price increases were positively correlated with supplier concentration (ibid.). Although increases in the prices of off-patent drugs have so far had limited impact on overall spending (see Chapter 1), there is a risk that in the future prices of single-source generics will increase further due to the lack of competition.

Countries can improve policies to increase the efficiency of spending through greater use of generics and biosimilars, and can implement mechanisms to ensure that markets remain competitive. The 2017 OECD report on "Tackling Wasteful Spending in Health"

suggested a number of policies in two main categories: 1) policies that aim to increase the availability of generics on the market, including entry-level legislation and pricing methods; and 2) policies that steer behaviour of main stakeholders – physicians, pharmacists, and patients – towards the use of generics already available on the market (OECD, 2017d).

Market entry of generic products after loss of market exclusivity (LoE) of originators could be facilitated through several mechanisms. For example, allowing generics manufacturers to complete regulatory requirements prior to LoE allows for more rapid entry to market. Readily accessible and easily searchable databases could be created to compile patents and exclusivity status of originator medicines. This is already the case in the United States, for example, where all approved small molecule pharmaceutical products, information on associated key patents and their expiry dates, and dates of LoE are available in a single database, known colloquially as the "Orange Book"[15]. Regulators could also identify areas where generic competition is limited or lacking, to prioritise generic approval in these areas. In June 2017, the US Food and Drug Administration (FDA) began publishing a list of branded medicines that had lost exclusivity but for which there were no approved generic competitors. It also expedites the review of generic approval applications for products with fewer than three approved generic suppliers (FDA, 2017).

Competitive processes that aim to balance short- and long-term efficiency and sustain strong competition could also be used to moderate generic and biosimilar prices. In general, evidence suggests that systems that use direct price regulation of generics, for example by imposing fixed discounts relative to originator products or using therapeutic reference pricing, are less effective in reducing prices than systems in which prices are established through competitive mechanisms such as tendering or negotiations (OECD, 2017d).

Countries could consider increasing the use of tendering for multi-source products. The three cornerstones of efficient tendering are: binding bids; a mechanism for setting the tender price that incentivises manufacturers to reveal their real costs of production; and appropriate selection of the number of suppliers (OECD, 2013a). Tenders can be designed to take into account criteria other than price, such as product quality or reliability of supply, and to avoid awarding the entire market volume in a segment to a single manufacturer. Reducing prices too aggressively can be counter-productive in the longer term, as individual market segments may become insufficiently attractive for manufacturers to remain active (Kanavos et al., 2012). Sole-supplier contracts can be particularly counter-productive in terms of preserving long-term competitiveness and avoiding monopolies, and can lead to higher prices in the longer run.

In countries where retail price competition in off-patent markets is impacted by the use of internal reference pricing,[16] competition for market shares may take the form of discounting in the supply chain, and discounts may not be passed on to either the payer or the patient. To benefit from this type of discounting, in 2007 Australia introduced a programme of "price disclosure" (see Box 3.3).

Box 3.3. Use of price disclosure in Australia

Under Australia's price disclosure policy, suppliers of multi-source medicines to the Pharmaceutical Benefits Scheme (PBS) are periodically required to submit data on sales revenue, sales volume, and the value of incentives (such as discounts or bonus stock) offered to community pharmacies to preferentially dispense their products.

Based on this information, the reimbursement price paid by the government is adjusted to reflect more closely the true average market price at which the medicines are supplied.

First introduced in 2007, price disclosure arrangements now apply to more than 400 products. The policy has resulted in very significant price reductions and the consequent savings to the PBS are expected to reach approximately AUD 20 billion by 2019-20.

As part of its price disclosure policy, Australia has also implemented moderating policies which aim to ensure that more than one supplier of each off-patent medicine remains in the market. This is intended to minimise the risk of exposure to large price increases that could arise if competition were to reduce prices to a level at which suppliers dropped out of the market leaving a single monopoly supplier of the remaining brand of a medicine.

Source: http://www.pbs.gov.au/info /industry/pricing/eapd/faq-for-pharmacies-and-wholesalers.

Policies that encourage generic or biosimilar penetration through steering the behaviour of main stakeholders, include (OECD, 2017d; Rémuzat et al., 2017):

- Mechanisms that encourage or incentivise physicians to prescribe generics or biosimilars, such as guidelines; prescribing software that highlights price differences or selects the cheapest alternative by default; financial incentives for pharmacists to dispense, and for patients to accept generic/biosimilar products; and mandating prescribing by international non-proprietary name (INN).
- Allowing or requiring (unless explicitly precluded by the prescriber) pharmacies to substitute originators with generics (and reference products with biosimilars where appropriate) and avoiding pharmacy remuneration schemes that encourage the dispensing of more expensive drugs (e.g. use of progressive mark-ups).
- Educating professionals and patients through information campaigns and incentivising patients to be sensitive to product prices, for example through larger co-payments for more expensive products.

Finally, countries could also implement a system to monitor market dynamics and allow purchasers to report sharp price increases if procurement mechanisms are unsuccessful in avoiding market concentration. When the number of competitors becomes low (for example, less than three) payers could begin negotiating with generics manufacturers to re-enter the market. This might entail a commitment to a minimum price for a limited period of time in order to increase the reliability of supply. Enforcement of competition and antitrust laws could also provide recourse for countries.

Strengths

Creating conditions that promote competition in the off-patent market using tendering or price disclosure can dramatically reduce generics prices.

Encouraging generic and biosimilar uptake is a straightforward means of increasing spending efficiency without reducing benefits to patients. Fostering competition in off-patent markets, through facilitating market entry of competitors and appropriate procurement mechanisms that avoid the formation of monopolies, can help moderate prices while avoiding the need for direct price regulation.

Making information on patent content is an integral part of the social contract that underlies patent protection, which aims to make innovations widely available to society. It could also be argued that access to readily available information on the status of patents and of other forms of market exclusivity is in the public interest. Providing such information in an easily accessible format is a simple way of enhancing transparency and facilitating competition. In the longer run, legal action against firms that abuse dominant market positions can act as a deterrent.

Weaknesses

Overly aggressive discounting by manufacturers in order to gain market share can drive competitors out of the market and reduce competition in the longer term. Policy approaches may therefore need to include mechanisms that increase the likelihood that several suppliers remain active in each market segment, such as tenders that allocate specified market shares to competing manufacturers. Competitive mechanisms that lead to market concentration, such as sole supplier arrangements are best avoided. Policies may also need to include mechanisms for monitoring the competitiveness of market segments and provide for remedial action when segments become overly concentrated.

Enabling conditions

Mechanisms for making patent information readily available are inherently valuable and should not be associated with the imposition of barriers to generic market entry, in particular patent linkage. Patent linkage refers to linking marketing approval of a generic medicine to the patent status of the originator. This requires the regulatory authority to delay marketing authorisation until either the expiry of patents covering the originator (or reference product in the case of a biologic) or a decision that the relevant patents are not infringed, or are invalid or unenforceable (Roox et al., 2008; Bhardwaj, Raju and Padmavati, 2013). While this policy is intended to protect originators from lost sales caused by infringing products, it can lead to delays in market entry or unwarranted delay in authorisation if, for example, a patent is subsequently challenged successfully. Allowing generics manufacturers to receive marketing authorisation while the originator is still under patent can accelerate the entry of generic products upon LoE.

C. Determine willingness to pay for new treatments and health benefits

Option 9: Define explicit and firm criteria for coverage and pricing

Summary

Aligning coverage and pricing of new medicines with societal preferences and willingness-to-pay for healthcare may enhance both efficiency of spending and patient access. National authorities responsible for pricing and coverage could establish clear criteria for coverage and pricing decisions that reflect societal preferences, through a transparent and procedurally fair process. This could improve dynamic efficiency by making coverage and payment decisions more predictable to industry, rewarding effective

treatments and providing consistent signals to guide investment decisions in the development of innovative treatments.

However, to achieve these goals, countries would need to adhere firmly to their stated criteria and not deviate from established rules. Governments or payers may nevertheless want to retain some flexibility in decision making to take into consideration constraints or circumstances specific to a decision that were not foreseen in pre-specified criteria. Willingness to pay for a given drug may legitimately vary across countries and decision rules will therefore generally be defined at the national or sub-national level, where health care budget decisions are made.

A rules-based process to make coverage and pricing decisions could also provide for resolution mechanisms that are invoked when the pre-specified rules preclude coverage of a new medicine at the price offered by the manufacturer, and negotiations to reach an agreement within the rules are unsuccessful. Such mechanisms may need to take into account budget constraints and afford significant authority and flexibility to governments, payers or independent arbiters to incentivise manufacturers to operate within the pre-specified rules, and avoid imposing decisions on payers that are not affordable.

Background

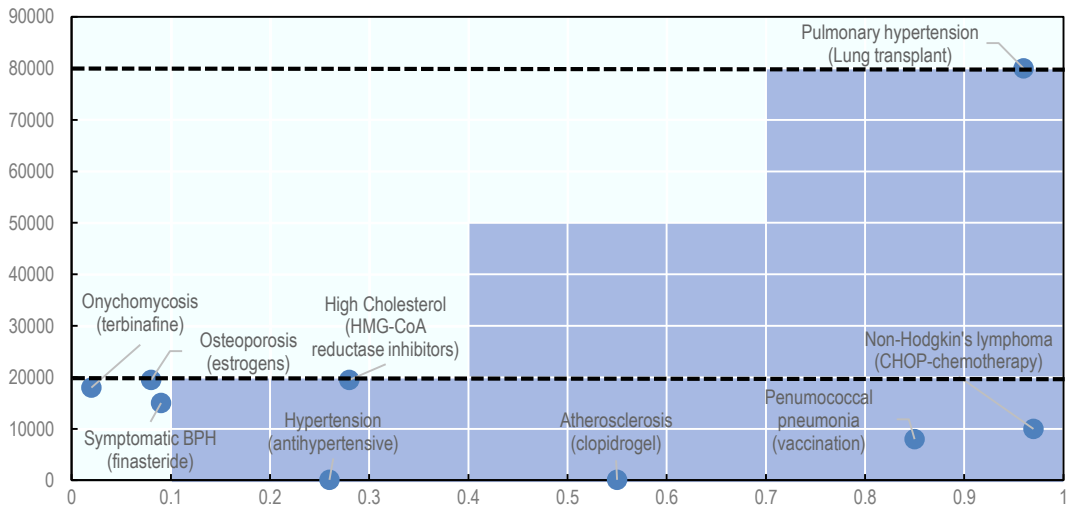
Most OECD countries regulate the prices of publicly funded on-patent drugs, with the objective of striking a balance among access to medicines, efficiency of public spending, and encouragement for companies to invest in R&D. While some countries directly regulate prices,[17] others impose coverage conditions that affect prices indirectly. Both types of regulation require that authorities make decisions centrally on what the right price of a medicine ought to be. Decision makers use a mix of methods or criteria to make such decisions, and the methods and criteria are not uniform across countries. These methods include, for example, international benchmarking; internal reference pricing (reference to the price of existing competitors); and economic evaluation (OECD, 2008; Panteli et al., 2016).

In OECD countries that use economic evaluation, assessments of value are often based on comparative cost-effectiveness analysis (CEA)[18] to determine whether the price of a treatment is "acceptable", or to express its value to the healthcare system in terms of its opportunity cost. CEA[19] is usually preferred over cost-benefit analysis for two reasons. First, most experts consider that health budgets should only be used to maximise health improvements and not for other purposes (such as increasing labour productivity). Second, using cost-benefit analysis requires the monetisation of health gains, which raises many theoretical questions and practical issues. In principle the use of CEA requires the definition of a cost-effectiveness threshold, beyond which new medicines would not be covered (Culyer, 2016).

Cost-effectiveness is, however, generally not the sole criterion and new treatments may be accepted with very different levels of cost-effectiveness due to a number of factors (see Figure 3.3). The market for anti-hypertensives, for instance, is crowded with multiple products, many of which are relatively inexpensive off-patent drugs. This makes it challenging for manufacturers to develop new treatments with sufficient incremental benefits and prices that would allow them to approach a pre-determined cost-effectiveness threshold. On the other hand, some treatments may be accepted with incremental cost-effectiveness ratios (ICERs) higher than the implicit or explicit pre-defined threshold (see Chapter 1 and OECD, 2017d). This is currently the case in particular for oncology and orphan medicines, which are often funded through "special

access" paths that circumvent rules applied in other areas. This is partly explained by the fact that the assessment of the "value" of a medicine may include factors other than cost-effectiveness (see Box 3.4).

Figure 3.3. Incremental cost-effectiveness ratios and burden of disease associated with some treatments



Note: X-axis represents the burden of disease expressed as "proportional shortfalls".
Source: Adapted from Stolk et al., 2004) and Zwaap et al. (2015).

Box 3.4. Value-based pricing and societal willingness to pay

Value-based pricing commonly refers to one of the strategies firms can use to set the prices of their products. "Value-based pricing is the setting of a product or service's price based on the benefits it provides to consumers. […] it relies on the consumers' perception of the value" (Investopedia, 2017). More precisely, "Value-based pricing is the method of setting a price by which a company calculates and tries to earn the differentiated worth of its product for a particular customer segment when compared to its competitor." Setting such a price requires referring to a specific market segment; identifying attributes that differentiate this product from existing competitors; and understanding how consumers value this differential or how much they are willing to pay for it (Dholakia, 2016). Market research, such as consumer surveys, can help to determine this amount. A company can for instance determine how much a consumer is willing to pay for a TV with a larger screen -all other things being equal- or how much a consumer values a specific brand in fashion products (ibid.).

Pharmaceutical companies may use value-based pricing to determine their pricing strategies. If a new product has no comparative advantage over existing competitors, it might be expected to enter the market at a lower price to capture market share. If the product offers some benefits over existing treatments, it is likely to command a premium over the price of competitors. The US Senate report on Gilead's pricing strategy for Sovaldi® describes an example of how companies may think when setting the price of their products according to such a rationale (Committee on Finance of the US Senate,

2015, pages 29-30).

In many countries, however, governments or compulsory health insurance schemes are the main payers for "covered" pharmaceuticals. Their willingness to pay (on behalf of tax payers or the insured population) is therefore what companies need to understand in order to propose a price that will be considered acceptable. Many dimensions may be taken into account when assessing the value of new products: improvement in length and quality of life, obviously, but also convenience or cost-savings in other parts of the health system; gains in labour productivity for patients and carers, etc. Previous studies of "value-based pricing" have shown that countries most often adopt a health system perspective, rather than a wider societal perspective when making coverage or pricing decisions, but also that added therapeutic benefits (QALYs in the most formal and quantified approaches) are not the only attributes public payers value when they determine their willingness to pay. The rarity and the severity of the disease treated, as well as a high unmet medical need, often lead payers to accept higher prices for products for some disease categories (Paris and Belloni, 2013).

Many public payers have been reluctant to publish an explicit cost-effectiveness threshold beyond which they would decline to cover products. Most countries using cost-effectiveness as a criterion for coverage and/or pricing, such as Australia and the United Kingdom, use an implicit or explicit threshold to support decisions, but remain flexible in taking into account other factors that may be relevant to the decision. Signals about willingness to pay for different factors, such as rarity or severity of the disease or degree of unmet need, are thus not always clear and consistent.

While value-based pricing remains an appealing mechanism in principle, a consistently workable way to apply it in practice has yet to be found. Defining the concept of value and corresponding assessment methods may require additional debate among stakeholders (including government, payers, patients, the industry and the general public) to reach agreement. This would help payers to behave consistently in their decision making so that signals to industry reflect this concept of value. For example, formal Multi-Criteria Decision Analysis (MCDA) methods could be developed to incorporate factors other than health gains into a definition of value (Angelis and Kanavos, 2016). Such methods allow an explicit consideration of stakeholder and public preferences in trade-offs.

One option to account for severity while retaining a central role for the cost-effectiveness criterion is to adopt different ICER thresholds for different levels of disease severity. In 2015, the Dutch Health Care Institute proposed ICER reference values that varied with the level of severity of the disease treated, measured in terms of proportional shortfalls[20] (see Zwaap et al., 2015 and Figure 3.3). In Norway, rules and criteria for priority setting in health care were recently updated after several commissions and a wide consultation on priority setting (see Box 3.5).

Box 3.5. Priority setting in Norway

In the past 30 years, five government commissions have been appointed to evaluate principles for priority setting in the health care sector, in 1987, 1997 (2), 2014 and 2015. In 1997, the Lønning II Commission recommended that priority setting in the Norwegian health care services should be based on three criteria: severity, expected benefit and cost-effectiveness. These criteria have been further defined and recommendations submitted to a consultation. Updated criteria for priority setting are the following (Norwegian Ministry of Health and Care Services, 2017):

- The benefits of a new intervention are assessed qualitatively and quantitatively. Clinical benefits include direct health improvements, as well as indirect benefits such as improvement in family members' health. The economic value of increased productivity at work is not included. In HTA, quality-adjusted life years (QALYs) are used as a quantifiable measure of healthy life years.
- An intervention is assessed against its opportunity cost, which is the benefit to other patients that could have been realised with the same resources. A cost-effectiveness ratio is calculated to assess opportunity cost. Any ICER below or at NOK 275 000 (~ USD 32 000) per QALY is acceptable.
- This ICER threshold is adapted to take into account the severity of the disease treated. Disease severity is assessed using the criteria of absolute shortfall. Absolute shortfall expresses the *number*[1] of healthy life years lost by a patient group as a result of a disease as compared with the average expected healthy life years for the population of the same age. Six severity classes are proposed, with different ICER thresholds and the threshold for the highest level of severity is set at NOK 825 000 (three times the lowest level).
- Additional discretionary assessments must be used, along with HTA to make decisions, which are: the quality and uncertainty of the documents (greater uncertainty justifies a lower priority) and the overall budget impact of an intervention. Interventions with a high overall budget impact will have higher opportunity costs, which may justify phased adoption.
- The rarity of a condition does not in and of itself justify a different set of criteria for priority setting. However, less stringent requirements for documentation may be acceptable when assessing interventions targeted towards small patient groups with a severe condition where it is difficult to perform controlled outcome studies. In addition, higher resource use may be accepted for interventions targeted towards very small patient groups with an extremely severe condition, such as children with congenital genetic diseases, where there is often a lack of good documentation of the benefit of an intervention.
- There are no discrete criteria for "end-of-life" therapies.

The transparency of the process facilitates equitable health care services and ensures the democratic legitimacy of decisions. However, it means that buyers, i.e. the hospitals and the authorities, could miss out on substantial discounts. The Norwegian government acknowledges that, ideally, discounts should be public, but this may require greater coordination at the European level to safeguard the principle of tiered pricing.

1. By contrast, proportional shortfall (suggested to assess severity by the Dutch Health Care Institute) expresses *the proportion* of anticipated life expectancy and quality of life lost by a patient group as compared with the average anticipated life expectancy and quality of life for the population of the same age. In the opinion of the Norwegian working group, it is more serious to lose 20 of 40 remaining healthy life years than to lose one of two remaining healthy life years.

Some OECD countries give explicit consideration to budget impact when determining their willingness to pay for particular products, such as those that treat large populations. Given that production costs of medicines are often relatively low, high volumes (e.g. due to high prevalence and/or life-time treatment) may still be attractive for investors even if the unit price of the product is lower than it would be if the cost-effectiveness of the product were considered as the sole criterion for pricing. For example, many payers have already entered into agreements with manufacturers that maximise the number of patients treated with the available budget or that include volume-price discounts. This approach was eventually taken in several countries for direct-acting antivirals (DAA) for hepatitis C. Rather than ending up with this outcome after some negotiations, the conditions which would trigger this could also be defined in advance. Even though the occurrence of such events is likely to be infrequent, it is nevertheless important to give innovators an indication of what they can expect to receive for a breakthrough treatment for a high-prevalence disease, with the obvious example being a treatment for Alzheimer's disease.

In the Netherlands, for example, horizon scanning is used to anticipate the market entry of new drugs that, based on list prices in other countries, are expected to have a high budget impact. Medicines with a budget impact estimated to exceed EUR 40 million per year, or those exceeding EUR 10 million per year and a cost per patient of EUR 50 000, are temporarily suspended from reimbursement and subject to HTA and price negotiation by the Ministry of Health, Welfare and Sport. In England, the National Institute for Health and Care Excellence (NICE) introduced a "budget impact test" in 2017 whereby NHS England may enter into price negotiations for health technologies with an anticipated NHS budget impact exceeding GBP 20 million in any of the first three years of marketing (NICE, 2017).

A rules-based system could also provide for a resolution mechanism, to ensure that effective medicines are available to patients even if national authorities or payers are not able to agree prices with manufacturers within a reasonable timeframe after marketing authorisation. Such a system exists in Germany, for example, where an arbitration board (composed by an impartial chairman, two other impartial members, in addition to two members appointed by both parties to the negotiations) is empowered to determine a price for the German market within three months of a failed negotiation (Wenzl and Paris, 2018). Mechanisms like this may need to take into account budget constraints and confer significant authority and flexibility on governments, payers or an independent arbiter in order to avoid imposing decisions on payers that are unaffordable and to incentivise manufacturers to operate within the pre-specified rules. In Germany, for example, prices set by arbitration have been found to be significantly lower than those offered by the industry during preceding negotiations (Ludwig and Dintsios, 2016). Other countries, such as Australia, only allow for judicial review of procedural issues in coverage decisions, with the authority to invalidate decisions for procedural reasons, but not to overturn or invalidate decisions on their *merits*. Such a mechanism avoids introducing parallel routes to coverage decision making, which could produce decisions that are unaffordable for the public payer.

Strengths

Transparent consensus criteria would make coverage and pricing decision more acceptable to societies and relieve decision-makers of some of the costs of making decisions on a case-by-case basis. As there is no purely technical solution, the legitimacy of any decision-making criteria would be enhanced were they to be widely debated and agreed.

A rules-based process for making decisions on coverage and pricing that includes firm indications of the willingness-to-pay of national authorities or payers, would increase their ability to align their expenditure better with public preferences. Enshrining pre-defined resolution mechanisms to stalled negotiations in legislation could ensure that public authorities are able to enforce these rules. Efficient resolution mechanisms, such as arbitration, could also help ensure that decision outcomes are aligned with pre-defined criteria while ensuring each party due process. Such mechanisms could be designed to give manufacturers an incentive to operate within the rules and avoid situations where rules may be circumvented through parallel paths to coverage.

At the same time, a more rules-based process would provide clearer signals and predictability for pharmaceutical companies, and align their incentives for R&D with public preferences. It would provide manufacturers with larger rewards for treatments to which society attaches high value, and smaller rewards for those valued less highly.

Weaknesses

There is no straightforward means of setting an optimal spending cap for highly prevalent diseases for which effective medicines become available. What constitutes an adequate but not excessive budget reflects social value judgments, and would need to be determined through a political process and by authorities responsible for insurance coverage and pricing decisions.

An important factor to take into consideration when defining pricing criteria is that explicit thresholds or reservation prices can have powerful anchoring effects for subsequent negotiations, as well as for other mechanisms used for setting transaction-specific prices. Anchoring effects have been documented widely in the psychology and behavioural economics literature (see Box 3.6).

Conducting economic evaluations, such as cost-effectiveness analysis, requires resources and skills that may not be readily available in all OECD countries. More co-operation between countries has the potential to create efficiencies, especially in the assessment of clinical benefits. However, due to differences in the patterns of care and costs of health care inputs, including prices of comparators, economic evaluation can generally only be performed at the national level.

Box 3.6. Behavioural economics and anchoring effects

Anchors are cognitive heuristics that allow people to process numerical information but lead to biases because, when required to value an option under uncertainty, any relevant information presented subsequent to exposure to the anchor induces people to adjust their valuation from the anchor rather than valuing it based only on the relevant information (Tversky and Kahneman, 1974). Research has shown that these adjustments are usually insufficient given the information people receive so that an initial anchor has a significant effect on the final outcome of the valuation (ibid.). This can be applied directly to price negotiations and it has been shown consistently, across a wide variety of settings and population groups, that exposing people to a number prior to a price negotiation biases subsequent offers and final negotiated prices significantly (Furnham and Boo, 2011). People who have significant knowledge of the field in which prices are negotiated, such as professional purchasers, are also prone to this bias, although anchoring effects have been found to operate differently in experts (ibid).

Buyers can improve negotiation outcomes from their point of view by defining their optimal prices ahead of negotiations and making optimal prices the anchor. The literature suggests that there are risks in only defining a reservation price. Indeed, evidence shows that when buyers anchor their negotiation in a reservation price, subsequent offers and the final prices negotiated are significantly higher than when buyers make their first offer based on their optimal price (Galinsky and Mussweiler, 2001). Subsequent offers and final negotiated prices are also higher when sellers make the first offer, for instance by offering a discount from a high list price (ibid.). The latter scenario currently occurs when pharmaceutical manufacturers negotiate confidential discounts from a list price with individual purchasers.

Enabling conditions

Eliciting public preferences coherently is methodologically difficult, in part people need to be presented with decisions that involve complex trade-offs, and extensive data collection is also required. All of the proposals described above require value judgments. This calls for a more structured and transparent approach to eliciting such preferences. Possible approaches include broad public consultations, population surveys, or a political process that debates these concepts and aims to enshrine preferences in explicit rules or legislation.

To ensure predictability for stakeholders, it is important that clear criteria are established in each country as to when resolution mechanisms may be invoked as a response to stalled negotiations. The criteria could, for example, include the absence of therapeutic alternatives, limits to delays between marketing authorisation and reimbursement and pricing decisions, minimum thresholds of effectiveness, or budget impact.

Option 10: Optimise the use of Managed Entry Agreements

Summary

Performance-based managed entry agreements (MEAs) could be used in a targeted manner for new medicines whose effectiveness or cost-effectiveness is particularly uncertain, in order to align coverage and pricing with clinical outcomes. Similar to using

routinely collected data, information generated from data collected under MEAs can be used to adjust prices and coverage conditions to reflect "real world" performance of new medicines, increasing efficiency of spending and aligning incentives for innovation with the benefits that medicines deliver to patients.

The following policies may increase benefits of performance-based agreements to health systems: 1) making evidence of clinical benefits and effectiveness generated under such agreements available to the scientific community; 2) designing agreements to incentivise firms to demonstrate performance of the product; 3) disclosing the existence of agreements in order to reduce opacity in international markets; and 4) clearly defining performance measurements. At the same time, MEAs can impose additional administrative burden on providers, payers and patients, which may offset some of the potential benefits.

Background

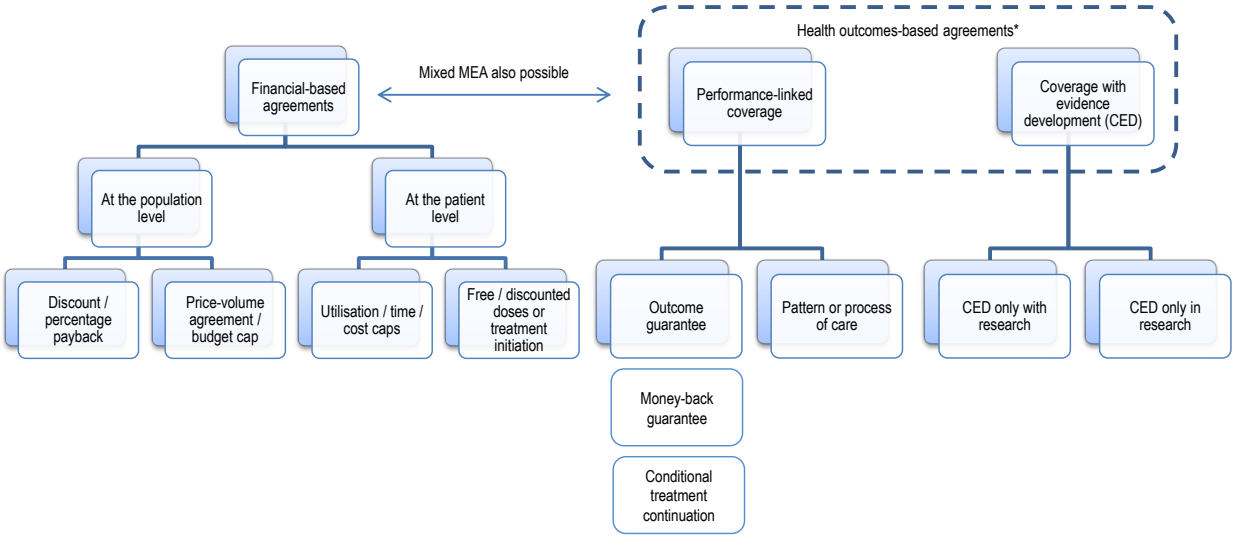
In some OECD countries, MEAs (sometimes also referred to as risk-sharing agreements, special pricing arrangements, performance-based agreements, outcome-based agreements or patient access schemes) have increasingly been adopted between payers or regulators and pharmaceutical companies to accelerate access to innovative medicines or manage their financial impact. However, recent reviews find that little is known as of yet about the actual effects of MEAs and that evaluations are often limited to perceived advantages and disadvantages (Gerkens et al., 2017; Kanavos et al., 2017). In many countries confidentiality about the existence of MEAs and their content also makes it difficult to provide a complete and accurate overview of the agreements currently in place.

The main goals of MEAs are to reduce uncertainty about the safety, effectiveness or cost effectiveness of treatments (often present at the point of marketing authorisation or reimbursement decision), or to manage the financial impact of new medicines on healthcare budgets, for example, through confidential price discounts or rebates (Kanavos et al., 2017). Based on their goals, MEAs can be grouped into two broad types. These can then be broken down into further categories as illustrated in Figure 3.4, which shows the taxonomy of MEAs developed by the Belgian Healthcare Knowledge Centre (KCE).

Financial agreements often consist of confidential discounts or rebates, which may or may not be conditional on factors such as volume or expenditure thresholds, but are not linked to the performance of treatments and do not require the collection of data on health outcomes. Such agreements may reinforce opacity in the pricing of medicines, allowing net prices to remain below list prices that are referenced by other payers or regulators, or to serve as anchors in price negotiations elsewhere.

Performance-based agreements entail the collection of data on health outcomes, and make insurance coverage, payment or rebates contingent on the clinical performance of the product in practice. These agreements contain a financial provisions but are mainly prompted by the need to reduce uncertainty about the clinical or cost effective of a medicine through additional data collection. They also occasionally serve as a mechanism through which to pay different prices for different indications of a single medicine.

Figure 3.4. A taxonomy of managed entry agreements (MEA)



Source: Gerkens et al., 2017.

Recent studies of MEAs in Australia, Canada and European countries, as well as a number of non-OECD member countries, have reported a proliferation in MEAs in the recent past, with the majority of agreements being financial (Ferrario et al., 2017; Kanavos et al., 2017; Pauwels et al., 2017; Rotar et al., 2018). A large number of MEAs are now found in Australia, Belgium, Italy, the United Kingdom and in a number of Central and Eastern European countries, such as Bulgaria, Estonia, Hungary and Slovenia. Significant activity related to MEAs has also been reported, for example, in France and Sweden.

- In Australia, 98 active agreements were reported in 2015, most of which were financial arrangements, although some performance-based agreements were also implemented (Lu et al., 2015). By March 2018 the number of agreements had increased to more than 150 (Australian Department of Health, personal communication) but information on their nature and content was not public.
- In France, neither the existence nor the content of MEAs is made public. A total of EUR 1 billion in refunds related to MEAs was reported for 2016, of which more than EUR 400 million was derived from price-volume agreements and only some EUR 120 million was attributed to performance-based MEAs (CEPS, 2017). This does not include *ex post* rebates on direct-acting antivirals (DAA) used for hepatitis C, which are subject to a specific budget cap.
- In Italy, as at March 2018, there were 88 active MEAs using registries to monitor patient-level data. Of these 88, 46 were performance-based between payers and manufacturers, including discounts for non-respondent patients (locally referred to as "risk sharing") and full refunds for manufacturers for all non-responding patients (referred to as "payment by results"); 42 were financial MEAs, through upfront discounts or volume caps beyond which manufacturers are liable for costs (AIFA, 2016, 2018). This number increased from 29 MEAs as of October 2012 (11 financial and 18 performance-based, related to 25 different products)

(Gerkens et al., 2017). In 2016, EUR 693 million in refunds related to all active agreements were reported by AIFA (OsMed, 2017).

- In Sweden, in 2017 the national Dental and Pharmaceutical Benefits Agency (TLV) reported 22 active MEAs at both the national level and the level of individual county councils. Refunds under all active agreements were estimated to amount to SEK 940 million in 2017 (TLV, 2017). Agreements were implemented to manage uncertainties regarding use and effect in clinical practice, cost-effectiveness (for example of cancer treatments) or high budget impact and displacement of alternative therapies (for example of HCV treatments) (ibid.); the exact nature of the agreements was not reported.

A survey of the experience in 16 Central and Eastern European countries[21] identified 678 MEAs across these countries, of which 668 were financial agreements (Ferrario et al., 2017). The largest number of agreements took the form of confidential discounts (495, 73%).

According to the KCE review (Gerkens et al., 2017), information on the impact of performance-based MEAs on filling knowledge gaps or decisions related to coverage were either not publicly available or reported to be relatively minor. Reasons for the latter related to, among other factors, concerns over study quality (e.g. an inability to adjust for confounding factors in analysis based on observational study designs) or the accumulation of evidence outside the MEA which increased the redundancy of the agreements. In the Netherlands, for example, while evidence of insufficient cost-effectiveness was found for three orphan drugs, for none of them was coverage withdrawn, however (ibid.).

Strengths

MEAs can have a number of advantages in theory, which include (Gerkens et al., 2017; Kanavos et al., 2017):

- Accelerating access to innovative and potentially effective treatments while uncertainty remains, and avoiding rejection of insurance coverage as a result of uncertainty.
- Improving the alignment of prices with comparative effectiveness.
- Greater flexibility in funding new and expensive treatments, for which coverage may not be possible with more rigid payment methods.
- Expanding the time horizon for data collection, thus enabling the capture of information on safety, effectiveness and cost-effectiveness in routine clinical practice (rather than in a controlled clinical research context) over longer follow-up periods than in pre-market RCTs.

Performance-based agreements can help focus treatment on patient groups likely to benefit most from an innovation, and can make use of existing sources of routinely collected data (see Option 5) to increase scientific knowledge (Gerkens et al., 2017).

Weaknesses

General weaknesses of MEAs and related challenges include (Gerkens et al., 2017; Kanavos et al., 2017):

- Significant administrative burdens and costs for providers, manufacturers and payers involved in executing the agreement and collecting data. Pure financial agreements are easier to administer than performance-based agreements and their proliferation suggests that payers consider that their benefits outweigh their costs.
- Payers may face difficulties in reducing prices, recouping payments already made to manufacturers, or de-listing treatments from coverage if the data collected under MEAs show that the treatment is less effective (or less cost effective) than expected.
- Regulators or payers may face challenges in generalising results to settings of care or countries other than those in which the data were collected, in particular when agreements take the form of coverage with evidence development (CED).
- Confidentiality clauses can prevent the dissemination of new knowledge on the performance of medicines that is generated from performance-based agreements.
- Uncertainty for manufacturers as to the financial returns from additional research produced, and the potential impact that the new evidence could have on future prices or revenues, can create dis-incentives for additional data collection once an agreement has been put in place.

In Italy, where experience with performance-based MEA has accumulated since 2006, the absence of transparency, high administrative burdens for payers and providers, and difficulties in obtaining refunds from manufacturers have been identified as issues (Garattini and Casadei, 2011; Garattini, Curto and van de Vooren, 2015). In 2016, the Italian Medicines Agency (AIFA) reported that registries captured 1.2 million treatments for 1.1 million patients as well as EUR 693 million in related refunds (OsMed, 2017). Recent evaluations of the effectiveness of MEAs in terms of accelerating access or reducing uncertainty, administrative costs, or the proportion of contractual refunds recovered by payers are not available. However, in 2012, of EUR 46 million in MEA-related refunds reported by AIFA, only EUR 31 million could be collected, representing 5% of the total expenditure for the products subject to the agreements (Garattini, Curto and van de Vooren, 2015). Disputes with manufacturers and delayed requests by hospitals were reported as the main causes of difficulties in collection.

Enabling conditions

A number of practical difficulties need to be overcome for MEAs to be implemented effectively. Difficulties have been reported thus far in establishing clear governance structures to determine when MEAs are appropriate, which data should be collected, how success and failure should be defined, what conclusions should be drawn from failures, or when the execution of an agreement should be discontinued (Gerkens et al., 2017). The increased use of MEAs and post-market data collection may undermine the role of RCTs before marketing approval and increase uncertainty regarding the safety and efficacy of treatments at the time of initial introduction into clinical practice (ibid.).

Capacity for data collection and analysis might need to be expanded in some countries. Performance-based MEAs have thus far been difficult to implement in many countries, among other reasons because data infrastructure and governance is not adequate to support the determination of outcomes. For example, few countries have adequate electronic health or medical records that can capture all the data necessary to determine outcomes.

D. Develop new push and pull incentives to encourage innovations in areas with high unmet needs

Option 11: Develop push incentives targeting product development

Summary

This policy option focuses on push incentives designed to encourage the development of specific products in therapeutic areas with unmet medical needs and suggests models to ensure wide accessibility of treatments subsidised by the public sector.

Background

Public private partnerships (PPPs) can take multiple forms and their number has been increasing steadily in recent decades. *Precompetitive PPPs* "aim to generate novel scientific concepts (e.g. disease targets and research models) and infrastructures (e.g. databases) through effective collaboration between multiple public and private entities based on mutual trust, pooling of complementary expertise and knowledge, and sharing of rewards" (de Vrueh and Crommelin, 2017). They can involve a wide range of stakeholders (universities, industry, charities, patient organisations, regulatory agencies). The Innovative Medicines Initiative (IMI) for instance, which was set up to enhance the competitiveness of the pharmaceutical sector in Europe in 2008, is the largest life sciences R&D PPP. It is jointly and equally supported by monetary contributions from the European Commission and in-kind contributions from company members of the European Federation of Pharmaceutical Industries and Associations (EFPIA). The performance of precompetitive PPPs can be assessed against their capacity to generate immediate tangible scientific knowledge, products and/or services (ibid). They play an important and growing role in pharmaceutical R&D processes but do not generally aim to deliver new medicines.

Product development partnerships (PDPs) are a type of PPP that focuses on the development of a specific product. Examples include the Medicines for Malaria Venture; the Drugs for Neglected Diseases initiative (DNDi), the International AIDS Vaccine Initiative, and the Pediatric Praziquantel Consortium. PDPs were originally developed to address the gap between R&D investments and the unmet need for new treatments for diseases with a high burden in the developing world. For these diseases, market-based incentives are not sufficient for private sector organisations to invest in the discovery, development, and deployment of new interventions.

PDPs enable the development and introduction to market of products at affordable prices. In the DNDi model for example, R&D costs are funded up-front through public and philanthropic institutions. DNDi has built close collaborations with several pharmaceutical companies. Since 2007, it has delivered one new treatment per year and met its 2007 target of six novel treatments for malaria, Human African trypanosomiasis ("sleeping sickness"), visceral leishmaniasis and Chagas disease by 2014. All of these were able to be developed rapidly and with a high probability of success as they involved either re-purposing existing drugs or developing combination therapies. Development costs are low[22] by comparison with available estimates for the industry, partly due to the unique features of the project (Maxmen, 2016).

Other options exist to encourage the development of specific products. For example, governments could fund development through long term contracts awarded on a

competitive basis, with government retaining IP rights to the developed product to enable generic manufacture. Using the current grant-funded medical research model in most countries, a health research agency could offer grants to develop drugs vital for public health that are of no commercial interest to for-profit companies. An alternative could be that the firm that undertakes the R&D retains IP rights, but commits to share them through a patent pool (see Box 3.7).

Box 3.7. The Medicines Patent Pool

The Medicines Patent Pool (MPP) was created in 2010 and is funded by Unitaid. Its goal is to provide access to affordable, quality assured HIV, hepatitis C and tuberculosis medicines in low and middle-income countries (LMICs). In May 2018 the MPP announced expansion of its mandate to include licensing of other patented essential medicines, such as those included in the WHO Model list of Essential Medicines.

The MPP signs licence agreements with patent holders to allow generic manufacturers to develop and supply licensed medicines in a large number of LMICs.

As of now, the MPP has signed agreements with 9 patent holders for 17 products. The MPP partners with multiple generic manufacturers to promote competition and drive further price reductions. These partners have already delivered 17 million patient-years of treatment in approximately 130 countries. Each licence agreement specifies in which countries generic medicines may be manufactured and/or distributed. The access-oriented voluntary license agreements signed through the MPP are negotiated from a public health perspective and are publicly available on the MPP website.

Importantly, the MPP licences enable generic manufacturers to develop new formulations (e.g. paediatric formulations or fixed-dose combinations) that may be particularly important for treatment scale-up in LMICs. High-demand for some of these formulations in LMICs (e.g. first line HIV combination products, pan-genotypic hepatitis C regimens) provide a suitable incentive for the development of these new formulations. A good example is the new fixed-dosed combination of tenofovir/lamivudine/dolutegravir developed by MPP licensees and first approved by the FDA in August 2017.

The quality of the generic medicines manufactured and distributed by the MPP licensees is assured through the WHO Prequalification programme or approval by a stringent regulatory authority, which to date has generally been the FDA though its "tentative approval" programme. A tentative approval from FDA signifies that although the product cannot be sold in the United States (due to existing patent protection or marketing exclusivity), the product meets all safety, efficacy and manufacturing quality standards for marketing in the United States.

Originator companies can receive royalties from MPP licensees. Sliding-scale royalties, linked to the income level of purchasing countries have also been included in some licences. In other cases, however, there are no royalties (e.g. licences for paediatric formulations).

Delays in access to new medicines in developing countries have been reduced significantly. The time it takes from first FDA approval of a new drug and "scale-up" of generic production/procurement for low-income countries is decreasing – from 11 years for tenofovir (standard HIV treatment) to 4-5 years for more recent products such as dolutegravir.

The licences concluded through the MPP are wide in geographical scope and generally cover all low-income countries, all countries in Sub-Saharan Africa and all lower middle-income countries. A number of licences also include additional upper middle-income countries in other regions of the world, which are not considered by companies as "commercial markets".

The recent expansion of the MPP model could facilitate affordable access to essential medicines in other therapeutic areas over the coming years, including non-communicable diseases. It could also help facilitate access and stewardship for new antibiotics able to address antimicrobial resistance.

Source: http://www.medicinespatentpool.org/who-we-are/strategy and personal communication.

Governments could also encourage the development of publicly-funded clinical trials to generate evidence about existing or new treatments that could benefit patients and health systems. The Belgian Health Care Knowledge Centre (KCE) identified cases where publicly-funded research would be of clear benefit: 1) comparative effectiveness trials of medicinal products, 2) trials of medicinal products in children and in rare diseases, 3) non-commercial trials to counteract possible publication bias, 4) trials of medical devices, 5) trials of diagnostics and screening, and 6) trials in medical areas not addressed by private companies (Neyt et al., 2015). For example, the Australian Government is providing AUD 69 million through the Medical Research Future Fund (MRFF) for clinical trials over two financial years (2017-18 and 2018-19), to support researchers in their efforts to find cures for rare cancers, rare diseases, and other areas of unmet need; to support research into cancers with low survival rates, such as brain cancers; and improve treatment outcomes and quality of life. This work will sponsor new drugs, devices and treatments to prevent, better diagnose and cure illness and disease available to Australians and global markets.

Strengths

PDPs allow the targeting of push incentives to the development of products responding to a high unmet health need that are insufficiently addressed by the private sector. Experience shows they can be very powerful vehicles to promote the development of such products. Mossialos et al. (2010), for instance, provide examples of medicines developed through PDPs for malaria, leishmaniasis, and tuberculosis. In a systematic review and assessment of incentives for the development of new antibiotics, Renwick et al. listed a number of advantages of PDPs. They allow sponsors to set the target product profile and guide development. They have the potential to attract both large firms that would not find the project attractive enough without public participation, as well as SMEs that struggle to raise the capital to overcome early-stage development barriers (Renwick, Brogan and Mossialos, 2016). Non-profit PDPs also remove the incentive to pursue high sales volumes, which is useful in the case of antibiotics for example.

Funding trials upfront and making drugs available without patent protection, or with a commitment to pool patents and agree to voluntary licensing, has the potential to enhance access and thus health impact.

Weaknesses

On the downside of PDPs, Renwick et al. noted that the sponsor bears the risk of failed projects and that sponsors/governments may not be the best placed to evaluate the viability of a project (Renwick, Brogan and Mossialos, 2016). Firms who perform the

R&D have better information about the quality of the R&D project and, for example, its chances of success, so that there is informational asymmetry between the funder and the funding recipient.

The Belgian KCE review identified several key hurdles to the option of conducting publicly-funded RCTs, among which were insufficient funding; difficulties in recruiting patients and persuading and incentivising clinicians to participate; lack of research infrastructure; and access to relevant industry-owned comparator products (Neyt et al., 2015).

Enabling conditions

Clearly defined research priorities are crucial to use push incentives effectively. Priorities that are global in nature would need to be defined and based on burden of disease and high unmet needs. Pooling funds from different countries would be desirable, as is the case in the development of antibiotics.

Public-private partnerships require long-term commitment from governments, which may not align with electoral cycles and related changes in government priorities. Another significant challenge for partnerships is the management of intellectual property rights given the multiple and sometimes divergent interests of consortium partners.

Option 12: Explore alternative pull incentives to encourage R&D for unmet medical needs

Summary

One option to spur drug development in areas of unmet need is the use of alternative pull incentives that are publicly-funded, such as market entry or innovation rewards. Alternative pull incentives are particularly appropriate in OECD countries for neglected areas of research, and for diseases where the current framework of incentives, including patent protection and market exclusivity, has not delivered needed innovation, such as in antibiotics. Orphan diseases may be another area where innovation rewards could be beneficial.

Alternative pull incentives have the potential to align pharmaceutical industry incentives more closely with public health needs. They could further improve population access to the treatments developed as a result of such incentives by requiring, for example, that specified population groups be treated, or that firms may not inhibit competition or set prices that pose barriers to access.

Background

The current framework of incentives for innovation, together with manufacturer remuneration based on price and volume, encourages investment in R&D of treatments with large market potential (through high volumes and/or high prices) in populations with high ability to pay. This can lead to the neglect of disease areas where markets are small. Examples of areas with small market volumes include antibiotics, which should only be prescribed where absolutely necessary to prevent further development of resistance, or rare diseases that only affect small populations. Medicines for neglected tropical diseases prevalent in low-income countries are examples of areas with limited revenue potential due to inability to pay.

The idea of providing innovation inducement prizes dates back to the 19th century and prizes have been used in other fields (Williams, 2012). More generally, various types of alternative pull incentives to reward firms for innovation have been proposed in the past. Most of these mechanisms follow a similar economic rationale, though they differ in terms of the suggested timing of disbursements and the conditions attached to them. These characteristics, however, can have a significant impact on "if" and "to what extent" they can harness competition among innovators, as well as on their ultimate effects on encouraging R&D activity and ensuring population access to treatments. Examples of alternative pull incentives that have been put forward so far include:

- A substantial one-time payment for the treatment of a specified disease shortly following marketing approval, based on development costs incurred and the therapeutic value of the novel medicine. Such payments have also been referred to as "innovation prizes" (Stiglitz and Jayadev, 2010; UNITAID, 2016).
- A variation of innovation prizes could be a staged approach, in which a base payment could be made to compensate manufacturers for the costs of development and distribution, followed by subsequent periodic payments. This may be especially appropriate where there is high uncertainty around the therapeutic value of the new medicine so that payments can be increased on verification of clinical effectiveness (Hollis and Pogge, 2008).
- Advance market commitments (AMCs) or advance purchase commitments, under which sponsors make a firm commitment before a new treatment is available, to purchase a specified volume of the new treatment at a specified price, as long as it meets predetermined requirements. Such mechanisms have already been piloted for vaccines (Kremer, Towse and Williams, 2005; Levine, Kremer and Albright, 2005). AMCs do not decouple incentives from price and volume, however. Rather, they set a fixed price and volume upfront in return for a commitment by the manufacturer to supply units beyond the committed volume at a lower price.

A pilot advance market commitment (AMC), with a total value of USD 1.5 billion funded by the governments of Canada, Italy, Norway, Russia, and the United Kingdom as well as the Gates Foundation, was set up in 2007 for a vaccine against pneumococcal disease (Cernuschi et al., 2011). The AMC guaranteed a price per treatment that was deemed affordable, supplementing this price up to a specified number of treatments, and has so far been considered successful in accelerating access to a life-saving product (GAVI Alliance, 2013). Because AMCs have so far been designed to supplement the existing market-based system and provide incremental sources of revenue for industry, they have received substantial political support (Hollis and Pogge, 2008).

Depending on the need for incremental innovation following a breakthrough in an area, alternative pull incentives might be structured in a way to foster competition and encourage improved follow-on products (Farlow et al., 2005; Kremer, Towse and Williams, 2005). One-off prizes that lead to "winner-takes-all" competition may therefore not be suitable in all cases. Rewards staggered in several tiers could favour follow-on innovation, by providing substantial payments to the first manufacturer that meets specifications, but also by reserving funds for subsequent competitors that offer improved treatments in the same class or for certain target populations or conditions (Berndt and Hurvitz, 2005; Levine, Kremer and Albright, 2005). This argument may also favour solutions that do not entirely decouple incentives from price and volume, but aim to make price and volume commitments up-front, such as AMCs. Mechanisms that allow follow-on products to take market share and thus portions of the rewards

from earlier entrants could also provide additional incentives for first movers to develop highly effective treatments and bring products to market more quickly (Kremer, Towse and Williams, 2005; Levine, Kremer and Albright, 2005).

If alternative pull incentives are to harness competition among private firms and expect private capital to bear the risk of failure, they have to meet two fundamental conditions (Hollis and Pogge, 2008). First, the conditions for receiving the reward must be specified in a sufficiently clear and detailed manner, so that innovators understand the ultimate goal and deliver the innovations society values. Second, the magnitude of the reward must considerably exceed the amount of investment each competitor expects to make in delivering the innovation. This is because firms face two main sources of risk: they can fail because they are unsuccessful in developing an effective new treatment, or because a competitor is able to develop an effective treatment more quickly. Although staggered rewards discussed above may reserve some funds for follow-on products and reduce the risk arising from being slower than a competitor, rewards must compensate private capital for the risk of failure (ibid.).

Innovation rewards might be coupled with conditions that firms cannot use exclusionary rights to inhibit generic competition once the reward has been disbursed, and extract economic rents (Stiglitz and Jayadev, 2010). At the same time, because a part of the R&D process may need to continue to rely on publicly funded push incentives, the magnitude of the rewards might also be reduced to account for the net public contribution across the entire development process, for example through "clawback" provisions in the reward.

Strengths

While there is limited empirical evidence thus far, there are some compelling arguments in favour of alternative pull incentives for the development of medicines. For example, a key strength of mechanisms that provide a reward for a pre-specified treatment is that, similar to current price- and volume-based incentives, they encourage competition among manufacturers. They provide an incentive to work quickly and efficiently towards approval of a successful treatment. Also, the risk of failed research is borne by private investors. Such pull incentives can avoid problems of informational asymmetries associated with push incentives by encouraging self-selection of projects that are pursued and abandoned based on information in the possession of the innovating firms (Kremer, Towse and Williams, 2005; Hollis and Pogge, 2008). If the conditions for receiving a reward are sufficiently general, for example by specifying only the disease and the level of efficacy that has to be achieved, such mechanisms can leave substantial leeway for the private sector in selecting the best avenues of research to achieve the desired outcomes.

Another argument in favour of alternative pull incentives is that they can define explicit conditions for the disbursement of reward payments that improve both access to the treatments and efficiency of spending. This could, for instance, include a requirement as a condition of payment that specified populations receive the treatment, or that generic competition is permitted as soon as the reward has been disbursed, to encourage lower prices. However, areas where market volumes are small may not be attractive for generic competition.

Other potential advantages of alternative pull incentives include (Kremer, 1998; Hollis and Pogge, 2008; Williams, 2013; UNITAID, 2016):

- Accelerating development of follow-on products using the newly developed technology because patent protection would not be necessary to ensure return on investment;
- Improving alignment of incentives for private R&D with public health priorities and a reduction of socially wasteful spending on promotional activities;
- Enhancing efficiency in healthcare spending by precluding the extraction of profits beyond what public policy determines to be the "appropriate" reward for innovation.

Weaknesses

There is also little empirical evidence of potential disadvantages of the use of alternative pull incentives and only very limited experience in applying these to medical technology or medicines. Prior experience is limited to vaccines for diseases of high burden in developing countries (see, for example, Levine, Kremer and Albright, 2005). Arguments against such mechanisms are largely theoretical or based on hypothetical problems in their implementation.

Designing effective alternative pull incentives may encounter significant practical obstacles in, for example, defining technical specifications, setting eligibility criteria for disbursing rewards, or determining the optimal amounts to be allocated to individual innovations. Such incentives are likely to be less effective in incentivising R&D in areas where there is significant uncertainty surrounding the costs of development and the value of the desired treatment, and which may make it impossible to specify the goals of research upfront (Williams, 2012). These areas could continue to rely on push incentives (see Option 11).

One argument against alternative pull incentives that involve reward payments is the difficulty of specifying rewards (Stiglitz and Jayadev, 2010; Williams, 2012). This applies both to the criteria to be fulfilled for receiving the reward and the amount to be awarded. The challenge of determining an amount sufficient to spur innovation while avoiding overpaying relative to the societal value of the product exists with all types of pull mechanisms, and indeed, is arguably similar to setting the optimal duration of patent protection or market exclusivity. A number of approaches have been suggested for determining the magnitude of innovation rewards, such as using the net present value of comparable compounds already developed (Levine, Kremer and Albright, 2005; Fisher and Syed, 2010) or auctions (Kremer, 1998). However, all have major shortcomings and no straightforward solution is currently available.

If alternative pull mechanisms condition the payment of a reward on development milestones that are unrelated to the diffusion of the medicine to patients, their effectiveness in achieving patient access may be reduced. This may be a particular problem if, for example, public entities acquire drug development projects early in the development process as a result of disbursing a reward and subsequently provide insufficient incentives for trials to achieve marketing approval (Kieff, 2001).

Alternative pull mechanisms that condition payments on entry of a new medicine to market may also provide insufficient incentives for continued investment post marketing authorisation. Post-marketing studies may be required to demonstrate long-term and

relative effectiveness, and these might not be undertaken if there are no commercial incentives (Hollis and Pogge, 2008). For example, the trade association Pharmaceutical Research and Manufacturers of America reports that approximately 17% of its members' R&D expenditure in 2014 was for post-approval research (PhRMA, 2016).

Enabling conditions

Depending on the treatments targeted, alternative pull incentives may require substantial amounts of funding and long-term commitments to be effective. If these treatments address a global need, they may require broad international co-operation to raise the necessary funds and ensure that countries contribute to development of novel drugs.

To provide effective motivation for private investment, alternative pull incentives would ideally be based on credible commitments made long before disbursements, which must be honoured once conditions for disbursement are met. The highest level of certainty would be provided by rewards established in law, as these would provide some protection from political interference and changes in leadership. Drug development cycles are typically longer than electoral cycles and critics have argued that investors and industry executives are unlikely to trust successive governments to honour commitments on entry rewards over the long periods of time required to bring new medicines to market (Farlow et al., 2005). If the institutions charged with assessing the value of novel products are able to undervalue the technology and soften commitments to releasing funds, incentives may be ineffective (Berndt and Hurvitz, 2005; Kremer, Towse and Williams, 2005).

AMCs for vaccines have been criticised for requiring detailed technical specifications, that can be difficult to develop (Farlow et al., 2005). These specifications may also discourage the pursuit of unexpected but beneficial options in the development process. In addition, this implies that AMCs can only be issued once product characteristics are reasonably well known, and thus restrict their utility to incentivising late-stage development (Hollis and Pogge, 2008). The pneumococcal vaccine pilot, in particular, was criticised for allocating a large sum to late-stage development of a vaccine that might well have been commercialised without the AMC (ibid). Other commentators have argued that the vaccine was adopted much more quickly in developing countries than vaccines developed without AMCs (Williams, 2012).

Option 13: Amend orphan drug policies to target more closely areas of unmet need

Objective: Encourage the development of affordable medicines to treat rare diseases

Summary

Although a more precise assessment of the benefits and shortfalls of different orphan drug policy frameworks would be needed, a number of policy options are proposed to improve the targeting of incentives, such as limiting financial inducements, restricting eligibility conditions, and developing other push and pull incentives.

Background

A number of policy options have been suggested to repurpose orphan drug policies (especially in the United States) to ensure that they provide appropriate incentives for the development of medicines that *would not be developed otherwise,* and that patients are able to access them (Drummond and Towse, 2014; Daniel et al., 2016).

The first option is to limit financial incentives to ensure that societies do not pay more than is necessary to encourage the development of drugs for rare diseases. This could be achieved through a reduction in the market exclusivity period (where it exceeds the exclusivity afforded to non-orphan drugs), or through a claw-back on sales beyond a certain threshold. This already exists in some jurisdictions. In Europe, for example, the period of marketing exclusivity can be reduced from ten years to six, if, at the end of the fifth year criteria for orphan designation are no longer met, and thus that the extended market exclusivity is no longer justified. The process must be initiated by an EU Member State, but it is worth noting that this has not been used to date. Japan introduced a clawback system to recover a share of grant monies awarded for the development of orphan indications between orphan drug designation and marketing approval.[23] Companies whose orphan-designated drugs are later approved and generate over JPY 100 million in sales are required to pay back 1% of the amount over the threshold to the National Institute for Biomedical Innovation (which disburses grants). This requirement is effective during the first ten years of the drug's approval or until the amount of the grant funding provided to the company is paid back in full (Kelley, 2016).

Box 3.8. Review of the period of market exclusivity of orphan medicinal products

In Europe, according to Articles 3 and 5 of Regulation (EC) No 141/2000, a medicinal product shall be designated an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than five in 10 thousand persons in the Community when the application is made (so-called "prevalence" criterion),

or

that is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected.

The prevalence criterion is much more frequently used by companies to obtain an orphan designation. Between 2000 and 2015, only one orphan designation was granted on the basis of insufficient return on investment.

Article 8(2) of Regulation (EC) No 141/2000 establishes that the period of market exclusivity may be reduced from ten to six years if at least one of the designation criteria on the basis of which market exclusivity was granted is not met. This can only happen at the request of one member state, which triggers and assessment by the Committee on Orphan Medicinal Products (COMP) or the MEA. COMP will first review the criteria on which orphan designation was granted. If these criteria are still met, nothing will happen. If they are not, COMP will assess whether other criteria for orphan designation are met. If it is the case, COMP will recommend to not reduce the period of exclusivity. If none of the criteria for orphan designation are met, COMP may recommend a reduction of the period of exclusivity.

Source: European Commission, 2008, 2016a; Kelley, 2016.

Another option is to restrict eligibility for orphan designation to situations in which market-based incentives are insufficient. New products used in oncology, for example, may have mechanisms of action that make them potentially suitable therapies for several indications with small population targets (QuintilesIMS Institute, 2017). Companies may already have sufficient incentives to develop as many indications as possible for a given product, without benefitting from advantages granted to orphan medicines.

Other options could be considered, such as pull and push incentives developed in policy options 11 and 12. Not-for-profit development of indications for rare diseases could also be envisaged. Models such as the DNDi's have shown that repurposing existing drugs for treatments without viable markets can sometimes be done at low cost. Since in many countries orphan medicines are fully paid for by the government or compulsory insurance schemes financed through social contributions, public payers might have an interest in subsidising product development for these indications and making products available at affordable prices for patients with rare diseases.

Strengths

Limiting financial returns for orphan medicines that achieve high levels of sales, through truncated market exclusivity or partial refunds beyond a revenue cap, would enable public payers to save money. This could improve access, if prices fall as a result of increased competition after the loss of market exclusivity. The option of targeting incentives to those developments that would have not occurred in their absence, if possible (see below), would result in better value from public spending.

Not-for-profit development and/or publicly-funded trials could also potentially support the development of orphan medicines at lower costs than at present, especially when repurposing or developing a new indication for an existing product. This type of redevelopment is usually quicker and cheaper than developing an entirely new product, and the medicines could be made accessible at affordable prices to patients.

Weaknesses

Reducing market exclusivity, or using a 'clawback' for successful products, may not solve problems related to patient access and unaffordable prices. In addition, there is no straightforward way to define a "cap" beyond which sales would be considered "high enough" to trigger limitations on orphan drug status.

Targeting incentives to limit eligibility to those medicines or indications that would not have been developed without specific inducements is not straightforward. The extent to which specific incentives (such as tax rebates in the United States, extended exclusivity, regulatory fee waivers) and the possibility of charging an "orphan price" play a role in the development of each indication is only known to the companies themselves.

As discussed under Option 11, publicly-funded trials raise a number of difficulties that would need to be overcome, among them the lack of research infrastructure and access to relevant industry-owned products (Neyt et al., 2015).

Enabling conditions

Orphan drug policies have spurred the development of treatments for rare diseases and any potential changes should be undertaken cautiously to ensure that R&D continues. Some basic research aimed at gaining an understanding of the impact of particular government-provided incentives would be needed in order to assess the potential impact of policy changes.

E. Strengthen the information base to better inform policy debates

Option 14: Publish authoritative information on industry activities and the risks, costs and returns from R&D, to better inform policy decisions.

Summary

An authoritative dataset assessing industry activity and performance would allow for a more fact-based debate of pharmaceutical policies, and would benefit all stakeholders, including the general public, policy makers and the pharmaceutical industry. It would also help restore trust among stakeholders.

OECD countries accounted for about 70% of global drug sales in 2016 (QuintilesIMS Institute, 2016). About 70% of global business expenditures in pharmaceutical R&D were incurred in OECD countries in 2015 (OECD, 2017a)[24] and all but two of the top 50 pharmaceutical companies have their headquarters in OECD countries (Christel, 2017), thus reporting of industry activity across the OECD would capture a large share of global activity.

This reporting could be done in a number of different ways. For example, it could draw on periodic data collection of industry activity and performance. The data would be most effective if they were collected in accordance with an agreed set of indicators and used consistent reporting standards. Data could be submitted to and published by an intermediary, such as the OECD Secretariat. Indicators would have to be agreed internationally because many pharmaceutical firms are multinational. They could span subjects such as key financial metrics and R&D activity.

Background

Public debates on pharmaceutical policy are often marked by a lack of authoritative and commonly accepted information supporting the arguments of the stakeholders involved, and this has arguably compromised trust among them. The absence of commonly accepted information to underpin debate may also undermine the ability of policy makers to make informed and balanced decisions. This is a particular issue in the pharmaceutical market, as demand is largely subsidised by public funds, the industry often benefits from publicly funded R&D, and policy makers use a range of policy instruments in an attempt to strike a balance between providing the necessary incentives for the industry and ensuring patient access to treatments.

While the private sector plays an essential role in health and pharmaceutical R&D, only firms possess rich information about their own activities. Information in the public domain is often unreliable, inaccurate or incomplete. For example, estimates of the average R&D costs of a successfully launched newly developed medicine range widely, from several hundred million to USD 2.6 billion (Morgan et al., 2011; Mestre-Ferrandiz, Sussex and Towse, 2012; DiMasi, Grabowski and Hansen, 2016; Prasad and Mailankody, 2017). The data used to develop these estimates are often not disclosed and the methods have been the subject of controversy and debate (Reuters, 2013; Avorn, 2015).

Publicly listed firms are already required to publish certain financial information to ensure functioning of capital markets and taxation systems, but the information is not structured in a way that facilitates pharmaceutical policy analysis. Furthermore, accounting methods and standards vary between countries, allowing some leeway for individual firms in defining their accounting and reporting policies. This can limit

comparability and make data aggregation difficult. Smaller firms that engage in early-stage R&D are often not publicly listed and are financed through private equity and venture capital, with the result that no data on their activities are publicly available. When estimating R&D costs, for example, relying only on reports by publicly listed firms introduces a risk of bias because project failure rates are high at early stages of R&D. Industry costs from unsuccessful R&D might therefore be underestimated when considering only data from firms traded on the stock market.

A number of commercial databases provide access to firm-level financial reporting data, such as the ORBIS database, and the Bloomberg database used in this report (see Chapter 2). Some information on the R&D pipeline and on existing technologies may also be available from commercial databases, such as Adis Insight or GlobalData. The representativeness, accuracy and suitability of existing databases would need to be assessed in detail for the purposes described in this policy option.

Additional data collection and reporting of industry activity and performance could encompass topics such as key financial metrics and R&D activity. Financial metrics could include, for example, total revenue, operating and capital expenditures, profits, assets and liabilities and cash flow, a breakdown of expenditures and cash outflows by purpose, such as R&D, employee and executive compensation, sales and marketing, and/or returns to shareholders through dividends or share buy-backs. Breakdowns of R&D activity could include the number of active and discontinued product development projects or R&D expenditure by disease area, project or development phase. Data collection could be established or executed in co-operation with other OECD directorates and working parties, in particular the Directorate for Financial and Enterprise Affairs, the Directorate for Science, Technology and Innovation and the OECD Working Party of National Experts on Science and Technology Indicators, to ensure consistency with existing reporting standards.

Strengths

Greater transparency and the availability of a common dataset for assessing industry activity and performance would provide at least three broad advantages for the general public, policy makers and the pharmaceutical industry. First, it would increase the legitimacy and accountability of pharmaceutical policy and allow the general public to scrutinise more objectively whether public funds are spent responsibly to serve public interests. Second, it would inform policy making and reduce the susceptibility of decision-making to be capture by stakeholder groups promoting their own rather than the broader public interest. Third, it would help restore trust between the industry and other stakeholders.

Weaknesses

Primary data collection, validation, anonymization, and analysis via a survey of companies could be costly. Using existing data sources, such as the databases of financial reports or R&D pipeline information, may be a cheaper alternative, albeit with some potential limitations in the scope of possible analyses. However, available databases are subscription-based, so access would also involve financial costs.

The release of data on pharmaceutical R&D and industry performance may carry the risk of disclosure of some strategic information. However, the risk could be mitigated through anonymising data submissions by firms and publishing indicators only in aggregate to prevent re-identification (e.g. for all companies or for sub-groups of companies).

In addition, greater transparency of R&D costs may encourage countries to introduce cost-plus criteria into pricing and reimbursement decision frameworks. However, cost-plus pricing could create undesirable incentives for the industry, such acting inefficiently in R&D resource allocation or inflating R&D costs, and is at odds with tiered pricing based on societal willingness-to-pay.

Enabling conditions

Collecting and publishing such information would require significant effort to achieve consensus among countries and stakeholders on the identification of relevant metrics, detailed reporting standards, and collection methods that would ensure that data are accurate and comparable.

Implementation of this option would also require substantial effort in at least two other areas. First, preparatory work would be necessary to define the relevant indicators more specifically and to review in detail the availability of data from which to compute them. Second, a neutral third party would have to be identified to oversee data collection and ensure the protection of data privacy where necessary.

Option 15: Increase price transparency in pharmaceutical markets

Summary

Improving the information available to health care systems has the potential to enhance the efficiency of spending, as well as the transparency, legitimacy and accountability of decision making by public payers. The increasing divergence of list prices from net prices actually paid by purchasers, in part a result of the proliferation of financial managed entry agreements, not only raises concerns regarding the accountability and legitimacy of decision-making by public authorities but also has a number of practical drawbacks. While full transparency could compromise tiered pricing and have uncertain effects on the results of price negotiations, payers and other stakeholders in health care systems would benefit from increased transparency.

Background

Price opacity is increasing in pharmaceutical markets both, within and between countries, due to the development of confidential agreements between the industry and private and public payers (see Chapter 1). Price opacity allows for tiered pricing, or price discrimination, between purchasers. This benefits firms because they can price products according to the ability and willingness to pay of each purchaser, thereby increasing revenues. Tiered pricing can also benefit payers and increase patient access, especially in settings where ability to pay is low and firms are willing to offer prices that are below the average.

Yet, price opacity also has a number of practical shortcomings. First, in coverage schemes where patient out-of-pocket payments are proportional to the price of the medicine, patients may not benefit from confidential discounts or rebates negotiated further upstream in the supply chain. Second, confidential prices may compromise comparisons of the costs and benefits of medicines competing for a given indication, undermining the capacity of decision-makers and providers to take comparative cost effectiveness into account when making coverage or treatment decisions. Third, list prices serve as an anchor in price negotiations between payers and manufacturers, and thus may lead to poor negotiation outcomes if anchors are far from the *true* price of the product

(see Box 3.6 on anchoring effects). At the international level, price opacity blurs international price benchmarking, which is used by many OECD countries to regulate the prices of medicines, and makes price comparisons between countries partially irrelevant. Finally, while confidential agreements are often promoted as a way to adapt to countries' ability to pay, there is no guarantee that low-income countries get lower prices.[25] Indeed, anecdotal evidence suggests that prices are not necessarily lower in low-income countries (Iyengar et al., 2016; Vogler, Vitry and Babar, 2016).

In addition, confidential prices prevent the general public from scrutinising coverage and pricing decisions made by *public* authorities. This poses a problem for both the accountability and legitimacy of public policy, because the public cannot discern whether tax or social health insurance contributions are spent efficiently. Opacity also impedes analyses of net prices and price trends, and leads the public to overestimate pharmaceutical prices. This is not conducive to informed debate between stakeholders and the pharmaceutical industry, and may expose the latter to undue criticism of its pricing strategies.

To balance these concerns, national payers could cooperate to increase price transparency. A study on enhanced cross-country coordination in pharmaceutical pricing in EU countries, suggests making transparent the existence of a discount for a given product, so that the use of its list price as a reference in international benchmarking can be subject to appropriate caveats (Vogler et al., 2015).

Strengths

Price transparency would enhance the capacity to integrate economic considerations into decision making and increase efficiency of spending. Price transparency improves the utility of economic evaluation in HTA and, crucially, enables the results of such evaluations to be shared with other stakeholders and the general public. Economic considerations could be included in establishing treatment guidelines and can help prescribers and patients make more informed treatment choices based on cost-effectiveness or other measures of value.

Increased price transparency would also increase the accountability and legitimacy of coverage and pricing decisions, allowing the general public to scrutinise more objectively whether public funds are spent efficiently. It would also allow for more accurate analyses by researchers of prices and price trends that inform policy debates. This would help restore trust between the industry and other stakeholders in pharmaceutical policy.

Weaknesses

While policymakers and other stakeholders frequently call for price transparency to inform negotiations with manufacturers or to address legitimate concerns about the accountability of decisions made by public authorities, it is not clear how increased price transparency would affect prices across different countries. For example, increased transparency could lead to price convergence and potentially result in higher prices or lower patient access in countries with low ability to pay. Many OECD countries use international benchmarking to regulate pharmaceutical prices and some of them reference a wide range of countries with varying income levels. If prices were transparent, firms might be less willing to agree to reduced prices in low-income countries if these could influence prices in higher-income countries. In addition, the pressure from public opinion in high-income countries to reduce prices to match those obtained elsewhere could become intense if prices were made fully transparent.

In regions such as the European Union with free movement of goods between countries, the combination of price transparency and tiered pricing encourages parallel export[26] from lower-income countries (e.g. Greece and Spain) to higher-income countries (e.g. Denmark and Germany). Parallel exports may undermine patient access in exporting countries and create shortages. In addition, parallel trade represents a loss of revenue for companies, which means that they may be less likely to consent to discounted prices if these are in the public domain and arbitrage cannot be effectively prevented.

Enabling conditions

Partial price transparency, such as revealing the existence – but not the magnitude – of confidential discounts can mitigate the risks associated with full transparency. For example, Australia discloses the existence of confidential discounts or rebates in a note linked to the name of the corresponding medicine in the national reimbursement formulary and in associated "therapeutic relativity sheets".[27] Partial transparency does not address, however, the problems price opacity poses for international price benchmarking, the financial burden for patients charged co-insurance based on list price, or the lack of information about value to inform treatment decisions by doctors and patients.

Another option that could be considered to reduce the incentive for parallel trade within the EU would be to allow companies to charge lower prices in countries with lower incomes by agreeing transparent, ex-post rebates. Such an approach, however, would require commitments from countries with higher incomes not to use these prices as benchmarks.

Box 3.9. A game theory approach to assessing the effects of price transparency

A game theory model of sequential price negotiations between a single pharmaceutical firm in a monopoly position and several national buyers suggests that, on average, prices would be lower under price transparency than under price opacity. This is because subsequent buyers learn about the "impatience" of manufacturers to close a deal by observing prices negotiated between the firm and prior buyers, and can better anticipate the minimum price the firm is willing to accept in a negotiation. The patience or impatience of a firm depends on the cost of revenues forgone while a negotiation is ongoing and negotiated prices crucially depend on the patience of firms to close a deal. Transparency decreases the information asymmetry of this parameter between the firm and buyers.

The model also suggests that transparency would increase overall welfare because, as a result of improved buyer information about the firm's negotiation parameters, deals would be closed quicker, allowing firms to earn higher profits and buyers to treat patients earlier.

However, these results are contingent on a number of assumptions that, at best, may only approximate the structure of actual pharmaceutical markets:

First, the model assumes that the firm is a monopolist. If more than one firm competes in an oligopoly and prices are easily observable to all firms, this can risk tacit collusion between firms. This contrasts with a scenario of price opacity, where firms are uncertain about prices offered by competitors and try to undercut each other.

Second, the model assumes that firms are not forward-looking and do not anticipate the effect of closing a deal on subsequent negotiations. If firms are forward-looking, they have an incentive to signal patience by rejecting low prices in earlier negotiations, and this can lead to higher prices for earlier buyers and lower prices for subsequent buyers. The overall effect depends on whether the signalling effect that leads to higher prices for earlier buyers is stronger or weaker than the learning effect for subsequent buyers.

Third, the model assumes that all buyers commit to transparency. If prices of only some buyers are disclosed, then forward-looking firms have an incentive to take a particularly tough negotiation stance with those buyers that disclose prices. This phenomenon can also explain why buyers currently accept opacity. As long as some buyers believe that they can negotiate better deals under opacity and do not disclose prices, all other buyers face the high cost of unilaterally disclosing their own prices.

Source: Ettinger and Sidartha (2016), "Would Transparency in Negotiations Between Countries And Pharmaceutical Firms Lead To Lower Drug Prices?", Université Paris Dauphine, unpublished.

Option 16: Improve horizon scanning activities and encourage co-operation at regional level

Summary

Improving the capacity to anticipate the opportunities and challenges represented by new medicines, emerging technologies, and disruptive innovations could speed patient access, enhance uptake by professionals, and improve budget provision. A number of OECD countries have been using horizon scanning (HS) to better prepare for market launches and adoption of new technologies. Given the globalised nature of health innovation, the process of identifying upcoming technologies and assessing their likely impact on health systems could benefit from international exchange, and regional co-operation could reduce duplication of effort. Some elements of HS would need to remain country-specific, such as epidemiology or forecasting of economic impacts, but international and multi-stakeholder co-operation has the potential to reduce duplication and be more comprehensive and less costly for individual countries.

Efforts have been launched at regional level, the most recent being the BeNeLuxA Initiative, which includes HS among the set of cooperative activities undertaken by the four countries involved (BeNeLuxA, 2018). The OECD would be well positioned to convene interested stakeholders to share information on the status of technologies and discuss methods of ensuring appropriate access (OECD, 2015b). Whether this occurs in the form of a data-sharing platform or additional data gathering on the part of the OECD Secretariat in collaboration with national and international partners, the information obtained would help member health systems prepare more effectively for the potential impact of innovative therapies on patient care, outcomes, costs, and society.

Background

Drawing on public and private sector horizon scanning initiatives, many countries are already thinking proactively about medical technologies not yet on the market. Most OECD countries have some form of publicly-supported health horizon scanning, either undertaken within the government itself or contracted to non-profit organisations (Slawomirski, Colbert and Paris, 2017). These systems create a repository of information

on emerging technologies with high potential impact on health care systems. They include information on patient needs, implementation barriers, and the benefits of new technologies in comparison with current alternatives. The functionality of horizon scanning activities varies widely across OECD countries. For example, the Italian Horizon Scanning Project (IHSP) is developing a forecasting model to predict impact of emerging medicines on the health system, including economic analyses, while the ECRI-AHRQ platform in the United States does not include predictions of the future costs of any health care technology (ECRI Institute, 2015). HS systems recently introduced in Nordic countries such as Sweden or Norway, aim to promote timely diffusion of cost-effective technologies in health systems (WHO Regional Office for Europe, 2017). The Dutch HS system established in 2012 aims to identify the financial risk associated with new inpatient or outpatient drugs, in terms of cost per patient and total budget impact and to determine drugs eligible for price negotiations[28] (Lepage-Nefkens et al., 2017).

When budgeting for health, however, countries often adopt "siloed" budgets with spending caps based on historical allocation of resources rather than on prioritising and disinvesting where needed to free up resources for the most (cost-) effective health care interventions and technologies. Costs can be particularly difficult to project before a new therapy comes to market, however failure to do so can also have a detrimental effect on patient access through overburdening budgets unprepared for the new technology. This was illustrated in the health care systems of many OECD countries with the launch of highly effective direct-acting antivirals (DAAs) for hepatitis C in 2013 and 2014. An effective HS system would have alerted decision makers and budget holders not only that a new, very promising medicine was about to be approved, but also that it would be followed very quickly by potential competitors likely to help drive prices down.

Given the globalised nature of drug development, co-operation in HS, at least at the regional level, could potentially avoid duplication of effort and promote information sharing. The role for OECD could be defined in relation to existing national and international initiatives or projects. It could potentially range from brokering knowledge produced by others to the production of new information in partnership with various stakeholders, including regulatory agencies and industry.

Strengths

Sharing information could reduce the information asymmetry between manufacturers and payers, which is currently pervasive in pharmaceutical markets. While manufacturers hold confidential information on their product development pipelines and the likelihood and timing of market launches, payers are currently reactive to launch strategies adopted by manufacturers. Manufacturers would nonetheless benefit from better preparedness by health care systems and more rapid adoption and diffusion of the most effective technologies.

Improved capacity and collaboration in horizon scanning would also allow health systems to assess whether emerging therapies adequately address unmet health needs in their populations. This could prompt alternative mechanisms to propel the development of needed therapies.

Horizon scanning is a resource-intensive endeavour, and it is arguably inefficient for countries to conduct horizon scanning activities in parallel. Pipelines and pharmaceutical R&D are global in nature, which means that the identification of products likely to have a significant impact on health systems could take place at a global level, even though entry to national markets is often sequential. While publication of horizon scanning reports

already enables other countries to benefit, achieving a greater degree of cooperation and participation would allow the information gathering to address the specific needs of contributing countries.

Areas where international collaboration could be quite straightforward include capacity-building, in terms of people, data (epidemiologic, consumption, patent expiries, and upcoming treatments) and modelling. EuroScan has published a methods toolkit outlining a three-step process to identify new technologies, prioritise those which must be assessed, and then assess their potential impact (Simpson and EuroScan International Network, 2014).

Weaknesses

Prior experience with horizon scanning has shown a number of limitations (OECD, 2017c). First, the impact of horizon scanning on technology diffusion is not straightforward. A study assessing its impact on the diffusion of six technologies in ten EU countries from 1995 to 2004 revealed that initial recommendations (positive or negative) did not have a significant impact (Packer, Simpson and Stevens, 2006). One reason for this might be that the results of horizon scanning do not always reach their target audience, i.e. governments and/or health providers (Martino et al., 2012).

A key element in assessing the feasibility of an international horizon scanning collaboration is determining the objective and scope. Such an initiative could focus on analysing public health priorities and unmet needs proactively, or could be more "reactive" in gathering information on forthcoming technologies.

Enabling conditions

In order to provide timely information to policy makers, the choice of the time horizon is important and may vary according to the technology. Drug development has a well-defined development and regulatory route, and horizon scanning usually aims to identify drugs in phase 3, or at least phase 2. However, orphan drugs may be eligible for expedited development, making the time horizon more difficult to define.

Collaboration on assessment of dimensions such as health impact, expected utilisation, time to adoption, and process impact could help health systems improve their forecasting activities. The following dimensions could be examined in an international horizon scanning exercise: potential health impact at population level (impact on morbidity, mortality); at patient level (data on effectiveness derived from clinical trials); expected utilisation of the technology (ease of acquisition, manner of administration, concomitant resource utilisation; ease of compliance; degree of invasiveness; physical and mental capacity required for use; anticipated side effects, risks, and adverse events). Time to adoption and budget impact are likely to be more country-specific, as well as effect on the healthcare system at an organisational level (e.g. structural changes, and staff training).

Several questions remain to be answered in assessing the feasibility of an integrated horizon scanning platform. Aligning group participation, objectives, and methods to ensure consistency would be a key challenge, as would be division of labour among relevant topics to ensure adequate coverage. Ideally, such a platform would also include a feedback loop on accuracy of predictions to further refine future scanning. Existing initiatives such as EuroScan, EUnetHTA and regional horizon scanning collaborations could be used as a potential model or input to any broader initiative under consideration.

Notes

1. See Option 6 for a definition of "formulary management".
2. SRAs are defined as regulatory authorities in countries that are members or observers of the International Conference on Harmonisation (ICH), or regulatory authorities associated with an ICH country through a legally binding mutual recognition agreement.
3. The European Medicines Agency (EMA),the United States Food and Drug Administration (FDA), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA).
4. A surrogate endpoint is a proxy measure, such as a laboratory marker or physical sign or other measure that is expected to predict clinical benefit, but is not itself a measure of clinical benefit. A valid surrogate endpoint must be a correlate of, and fully capture the net effect of treatment on the true clinical endpoint.
5. In this context, the EMA uses the term licensing to refer to the granting of marketing authorisation.
6. See http://eunethta.eu/eunethta-guidelines.
7. See http://ohdsi.org and http://ehr.lshtm.ac.uk.
8. "H-prescription medicines" are medicines used in the outpatient sector but prescribed by specialists and financed by Regional Health Agencies (RHA) rather than National Insurance. In the past decade, a number of therapeutic classes have been transferred from National Insurance to RHA funding, such as TNF-inhibitors (2006), multiple sclerosis (2008), some oncology indications (2014), hepatitis C, growth hormone, colony stimulating factors, coagulation factors and treatments for anaemia (2016), pulmonary arterial hypertension and the majority of oncology indications (2017).
9. In 2016, LIS launched a call for tender for pharmaceutical treatments used in rheumatoid arthritis, ankylosing spondylitis / axial spondylitis, juvenile idiopathic arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, psoriasis and psoriatic arthritis. In December 2016, LIS launched a call for tender for pharmaceutical treatments used in the treatment of hepatitis C.
10. The term "4th hurdle" refers to the requirement imposed by many OECD Member countries that pharmaceutical manufacturers demonstrate that their products represent good value for money as well as being of good quality, effective and safe in order to be included in a national formulary and eligible for public subsidy.
11. In the United States, prices for oncology drugs are most often negotiated between contracting parties. By contrast, the prices of oncology medicines administered by physicians and covered by Medicare Part B are regulated. The reimbursement basis y are based on the average sales price (ASP) - the reimbursement basis for Medicare Part B drugs - on the prices negotiated in the private sector.
12. See https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2016-Fact-sheets-items/2016-06-29.html.
13. Off-label use is estimated to account for 20-30% of annual spending on oncology medicines in the United States (Polite et al., 2016).
14. Based on volumes, in the market of reimbursed medicines in Germany and Greece and the community pharmacy market in the United States, see Chapter 1.

15. Approved Drug Products with Therapeutic Equivalence Evaluations. See https://www.accessdata.fda.gov/scripts/cder/ob/. However the Orange Book does not list all small molecule patents, nor does it include patents on biological medicines.

16. Where internal or therapeutic reference pricing is used to set a single reimbursement price for all versions of a product or for all products within a therapeutic class ("reference prices" or fixed reimbursement amount), there is little incentive for suppliers to offer discounts to the payer.

17. Authorities often set price caps, leaving the firm free to price products below the cap for individual purchasers (e.g. wholesalers or insurers). For the sake of simplification, this price cap is often referred to as 'the regulated price'. Many countries only regulate the prices of patented medicines dispensed to outpatients and publicly covered. Two OECD countries, Canada and Mexico, regulate the (maximum) prices of all patented drugs, covered or not, to prevent abuse of monopoly power and protect consumers.

18. Cost-effectiveness analysis (CEA), which is one form of economic evaluation, entails computing the incremental benefit of a new medicine relative to standard treatment and its incremental cost per unit of incremental benefit. The ICER is then benchmarked against a pre-defined ICER threshold, beyond which the treatment is usually not funded. Defining such a threshold is in principle necessary to support decision-making (Culyer, 2016).

19. Strictly speaking, HTA bodies most often use cost-utility analysis, weighting health gains with utility derived from different health states to define benefits in terms of quality-adjusted life years (QALY) gained. However, stakeholders often refer to this analysis in a generic sense as cost-effectiveness analysis.

20. Proportional shortfalls refer to the proportion of anticipated life expectancy and quality of life lost by a patient group as compared with the average anticipated life expectancy and quality of life for the population of the same age.

21. Albania, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Kosovo, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovakia and Slovenia.

22. The Drugs for Neglected Diseases initiative (DNDi) has produced several drugs in the past decade for a fraction of what pharmaceutical companies are said to spend. Factoring in the cost of failed candidates, the DNDi estimates that it can develop combination therapies for between USD 10 million and USD 45 million, and make a completely new drug from scratch for USD 110 million to USD 170 million.

23. These grants cover 50% of direct costs incurred up to three years.

24. The OECD database does not include information on BERD in all OECD and non-OECD countries in 2015. For non-OECD countries, data is only available for four countries, including China and Russia. Therefore, this figure is likely to be over-estimated.

25. Economists could argue that what counts for price discrimination is willingness to pay (WTP) and not ability to pay, but ability to pay obviously acts as a constraint on WTP.

26. "Parallel trade" refers to cross-country imports/exports operated by intermediaries – usually wholesalers- without the consent of the manufacturer. It is likely to occur when the price difference is high enough to make this trade profitable.

27. See http://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets and http://www.pbs.gov.au/pbs/home.

28. If budget impact is expected to exceed EUR 10 million and annual cost per patient is likely to exceed EUR 50 000 or if budget impact is expected to exceed EUR 40 million, the government will seek a price agreement with the company.

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