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# Pharmaceutical Policy:

## Balancing Innovation, Access and Affordability

# A Primer on Pharmaceutical Policy and Economics

Huseyin Naci, MHS, PhD and Robin Forrest, MSc

Department of Health Policy

The London School of Economics and Political Science

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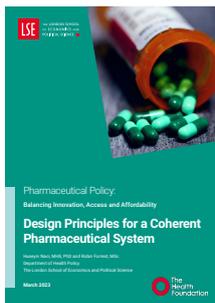
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This is the first of three reports as part of a series commissioned by The Health Foundation on pharmaceutical policy and economics. This first report serves as a primer on pharmaceutical policy and economics from a global perspective.

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# Authors



**Huseyin Naci** is an Associate Professor of Health Policy at The London School of Economics and Political Science (LSE), United Kingdom (UK). Huseyin conducts research and teaches on health care policy and practice in Europe and the United States (US). His research to date has evaluated the quantity and quality of the evidence base underpinning the approval, adoption, reimbursement and use of prescription drugs in Europe and the US. His research has appeared in leading medical and health policy journals, including the *Journal of the American Medical Association (JAMA)*, *The Lancet*, *The BMJ*, *Health Affairs* and *The Milbank Quarterly*. Huseyin has a PhD from the Department of Social Policy at LSE and a master's in Health Sciences from the Johns Hopkins Bloomberg School of Public Health, US. In 2018 to 2019, he was the recipient of the UK Harkness Fellowship in Health Care Policy and Practice, based at the Harvard Kennedy School of Government, US. Huseyin does not receive any funding from the pharmaceutical industry and does not have any conflicts of interest to declare.



**Robin Forrest** is an MPhil/PhD student (Health Policy and Health Economics) and research analyst in the Department of Health Policy at LSE. His research focuses on pharmaceutical policy and economics. Prior to joining LSE, Robin worked in the health economics and regulatory affairs divisions of various global pharmaceutical and biotechnology companies. Robin has an MSc in International Health Policy from LSE, for which he was awarded the Brian Abel-Smith Prize for Best Overall Performance on the programme. Robin also holds a BSc (Hons) in Biochemistry from the University of Bath, UK. Robin does not receive any funding from the pharmaceutical industry and does not have any conflicts of interest to declare.

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# A note to readers

## Objectives of this report

The overarching purpose of this first report is to serve as a primer on pharmaceutical policy and economics.

The aims of the report are to:

- 1** Outline the population health and industrial sector objectives of pharmaceutical policy and how these factors contribute to governmental policy setting.
- 2** Describe the process and policy environment surrounding the discovery, development, approval, pricing and adoption of pharmaceuticals.
- 3** Introduce and define key economic concepts and principles that play a role in this landscape.
- 4** Draw on broader literature from various disciplines to describe the political economy of medicines regulation, assessment, pricing and adoption.
- 5** Outline key trade-offs that policymakers must make pertaining to innovation, access and affordability in relation to new medicines.

Given the global nature of the pharmaceutical sector, our overview is not country-specific, although we do bring in examples from individual countries where appropriate.

## Methodological approach and framework

In this report, we adopt a 'bench to bedside' framework to describe the lifecycle of pharmaceutical products from discovery to use in health systems, detailing key issues and trade-offs that policymakers confront.

The contents of this report are based on a review and synthesis of the literature. We first systematically identified reference materials on pharmaceutical markets (ie, textbooks, book chapters and highly cited papers) in the health policy and economics literatures. These reference materials formed the basis for describing the supply- and demand-side factors in pharmaceutical markets. We then incorporated insights from a broader body of literature to enrich the framework with additional empirical findings and by identifying contested areas and highlighting tensions between different stakeholders.

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# Abbreviations and acronyms

<b>AIDS</b>	Acquired immune deficiency syndrome
<b>AMC</b>	Advanced Market Commitment
<b>ASMR</b>	<i>Amelioration du service medical rendu</i> (additional medical benefit rendered) (FR)
<b>BNF</b>	<i>British National Formulary</i>
<b>CCI</b>	Commercially Confidential Information
<b>CEPI</b>	Coalition for Epidemic Preparedness Innovations
<b>CEPS</b>	<i>Comité Economique des Produits de Santé</i> (France)
<b>COVAX</b>	COVID-19 Vaccine Global Access Facility
<b>COVID-19</b>	Coronavirus disease 2019
<b>CVD</b>	Cardiovascular disease
<b>DTCA</b>	Direct-to-consumer advertising
<b>EEA</b>	European Economic Area
<b>EMA</b>	European Medicines Agency
<b>EMEA</b>	European Medicines Evaluation Agency
<b>ERP</b>	External reference pricing
<b>EU</b>	European Union
<b>FDA</b>	Food and Drug Administration (US)
<b>GCP</b>	Good Clinical Practice
<b>GMP</b>	Good Manufacturing Practice
<b>HCV</b>	Hepatitis C virus
<b>HIV</b>	Human immunodeficiency virus
<b>HTA</b>	Health Technology Assessment
<b>ICER</b>	Incremental cost-effectiveness ratio

<b>ICH</b>	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
<b>INN</b>	International non-proprietary name
<b>IRP</b>	Internal reference pricing
<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency (UK)
<b>MRC</b>	Medical Research Council
<b>NHS</b>	National Health Service
<b>NICE</b>	National Institute for Health and Care Excellence (England)
<b>NIH</b>	National Institutes of Health (US)
<b>NIHR</b>	National Institute for Health and Care Research (UK)
<b>OECD</b>	Organisation for Economic Co-operation and Development
<b>P4P</b>	Pay for performance
<b>PRIME</b>	PRiority MEdicines
<b>PTE</b>	Patent Term Extension
<b>QALY</b>	Quality-adjusted life year
<b>R&amp;D</b>	Research and development
<b>RCT</b>	Randomised controlled trial
<b>RECOVERY</b>	Randomised Evaluation of COVID-19 Therapy
<b>RWE</b>	Real-world evidence
<b>S&amp;P</b>	Standard and Poor
<b>SARS-CoV-2</b>	Severe acute respiratory syndrome coronavirus 2
<b>SMR</b>	<i>Service medical rendu</i> (medical benefit rendered)
<b>SPC</b>	Supplementary Protection Certificate
<b>TRIPS</b>	Trade-Related Aspects of Intellectual Property Rights
<b>UK</b>	United Kingdom
<b>US</b>	United States
<b>VPAS</b>	Voluntary Scheme for Branded Medicines Pricing and Access
<b>WHO</b>	World Health Organization
<b>WTO</b>	World Trade Organization

# Report overview

## Intended audience

This report will be relevant to anyone interested in an overview of the key issues in the pharmaceutical sector, in particular individuals new to policy or analysis roles in government or other central agencies involved in pharmaceutical policy. Researchers and students in the field of health policy will also find this report useful for understanding the unique features of the pharmaceutical sector.

## Our Perspective

In the report, we focus primarily on the population health objectives of pharmaceutical policymaking: how governments can strive to promote innovation of, and access to, affordable medicines to improve the health of their populations. In addition, we highlight industrial policy considerations: how governments aim to leverage and benefit from the pharmaceutical industry to foster economic growth. We also discuss the trade-offs between population health and industrial sector objectives in pharmaceutical policymaking.

This report differs from other sources that describe pharmaceutical policy and economics, in important ways. Notably, our approach is multidisciplinary. We canvass different bodies of literature to provide a balanced and holistic overview of the sector. For example, reference materials in the economics literature consider the supply and demand factors that influence the development, appraisal and use of pharmaceuticals. To complement these theoretical insights from the health economics literature, we bring in examples from the political science, sociology and health policy literatures, which elucidate the political economy of pharmaceutical regulation and assessment. We also pay particular attention to the quantity and quality of clinical evidence in guiding decisions in the pharmaceutical policy landscape. This allows us to identify areas where existing evidence challenges the assumptions of mainstream theories and concepts and highlight areas of controversy where evidence is mixed or of low quality.

## Report framework

This report adopts a 'bench to bedside' framework (**Figure 1**):

### Key issues in the pharmaceutical sector

Section 1 of this report offers an introduction to the pharmaceutical sector and to several of the main themes covered in this series of reports. In this section, we cover the unique features of the pharmaceutical market. Taking both a health and an industrial policy perspective, we also introduce key objectives for pharmaceutical policymakers in promoting population health and leveraging the sector as a driver for economic growth.

### Pharmaceutical research and development

Drug development is high-cost and high-reward. In Section 2 of this report, we characterise the main health and industrial policy objectives relating to pharmaceutical research and development (R&D). We describe the role of public and private funding in drug development and outline the patent-based system of incentives that stimulate industry R&D by increasing expected returns on investment for pharmaceutical companies and the limitations of this system.

### Generating evidence in clinical trials

Clinical trials are required to generate evidence that demonstrates the benefits and harms of new drugs. These trials form the basis on which health systems approve and adopt new drugs. But not all clinical trials supporting drug approvals are of the highest quality or usefulness. In Section 3, we cover the essential design features of clinical trials in generating reliable and trustworthy data, which can be used for evidence-based decision-making in clinical practice and health policy.

### Regulatory review

In Section 4, we describe the role of drug regulatory agencies in assessing the benefit–risk profiles of new drugs both pre- and post-approval. We also describe two often-overlooked roles of drug regulatory agencies: first, their role in reducing the informational asymmetry between pharmaceutical companies and prescribers and patients; and second, their role in providing additional incentives for innovation.

### Pricing and reimbursement

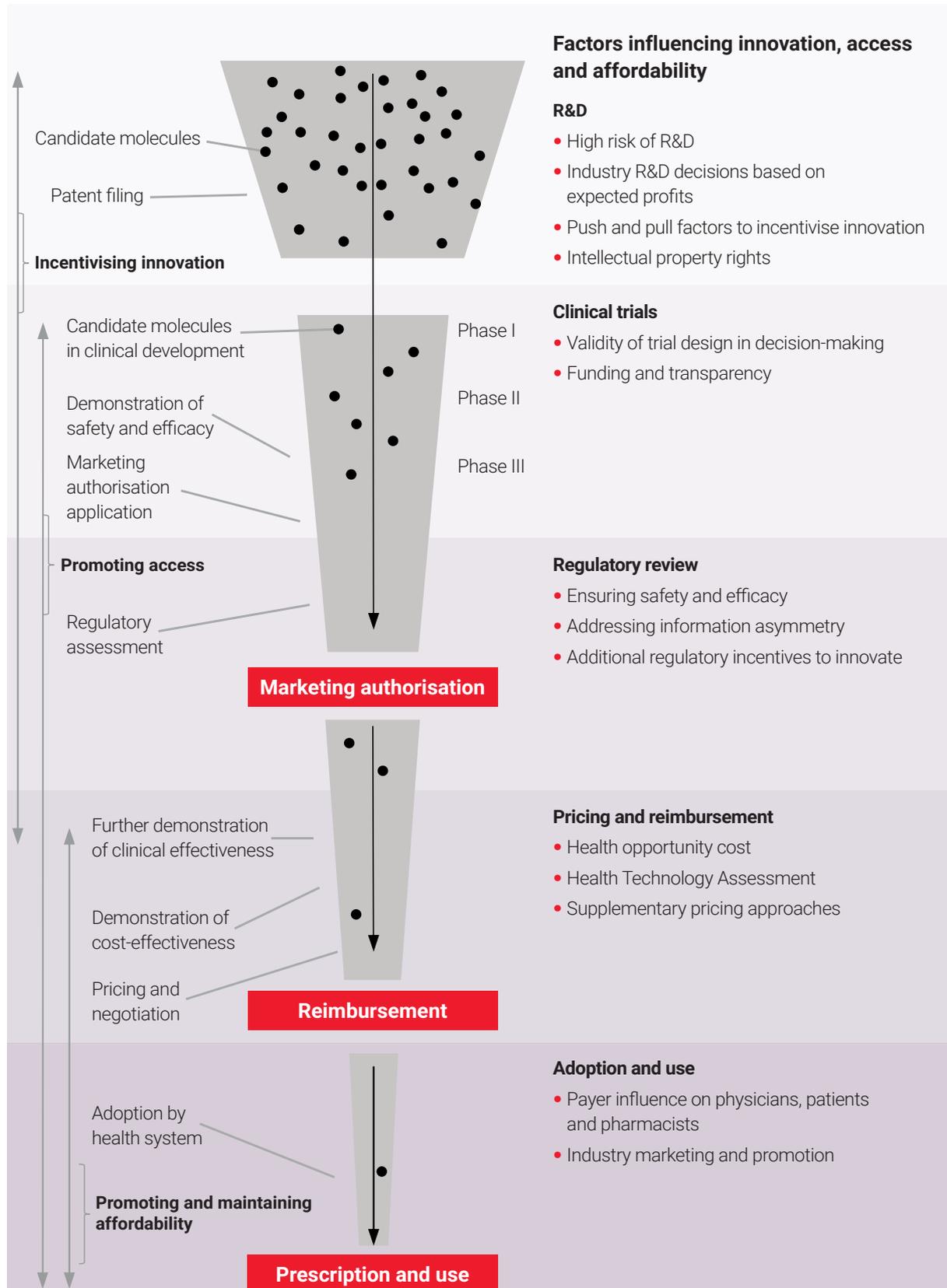
Government-granted monopolies are partly responsible for sustained high drug prices, which are an increasing concern for policymakers. In Section 5, we examine the driving factors behind high drug prices. We then turn to the main strategies that policymakers implement to regulate the prices of new drugs, focusing particularly on those which seek to align price with value, and their limitations.

### Adoption and use of pharmaceuticals

Once new drugs are approved by drug regulatory agencies and reimbursed by payers, several factors determine their adoption and use in the health system. In Section 6, we outline ways in which policymakers can influence the adoption and use of new drugs in the health system and promote the use of cost-effective drugs. We also summarise how pharmaceutical companies influence demand for their products to maximise revenues.

From bench to bedside

**Figure 1 – Pharmaceutical development: from bench to bedside**



**Notes:** This figure is for illustrative purposes. Size is not proportional to the time spent in each stage of a drug's lifecycle.

# Section 1 Key issues in the pharmaceutical sector

## Section overview

Distinct economic and policy issues characterise the pharmaceutical sector. This section introduces these issues and provides context for the remainder of the report. To begin, we briefly describe the key features of the pharmaceutical market. We then review the evidence on the clinical effectiveness of new drugs, highlight recent trends in pharmaceutical expenditure and document how the industry's drug development pipelines compare to societal needs. We also explain the contribution of the pharmaceutical sector to the economy, and the industry's role as a powerful political actor in this landscape. This section introduces the three key population health objectives of pharmaceutical policy that feature as key considerations throughout the report – innovation, access and affordability – and how these interact with industrial policy objectives.



## Overview of pharmaceutical markets

To add context to the themes, concepts and issues that appear throughout this report, we provide a highly simplified overview of the market for pharmaceuticals below (**Box 1**).

### Box 1 – The market for pharmaceuticals

The market structure of any sector of the economy is the key factor that determines the prices that companies can charge for their products and the approach that companies adopt to maximise their profits.

Economic theory suggests that if a market is perfectly competitive, companies will charge prices equal to the marginal cost of production. However, a perfectly competitive market requires:

- many buyers and sellers
- buyers and sellers to have perfect information about the product and the price
- many substitutable products
- no barriers to market entry or exit.

### The imperfect market for pharmaceuticals

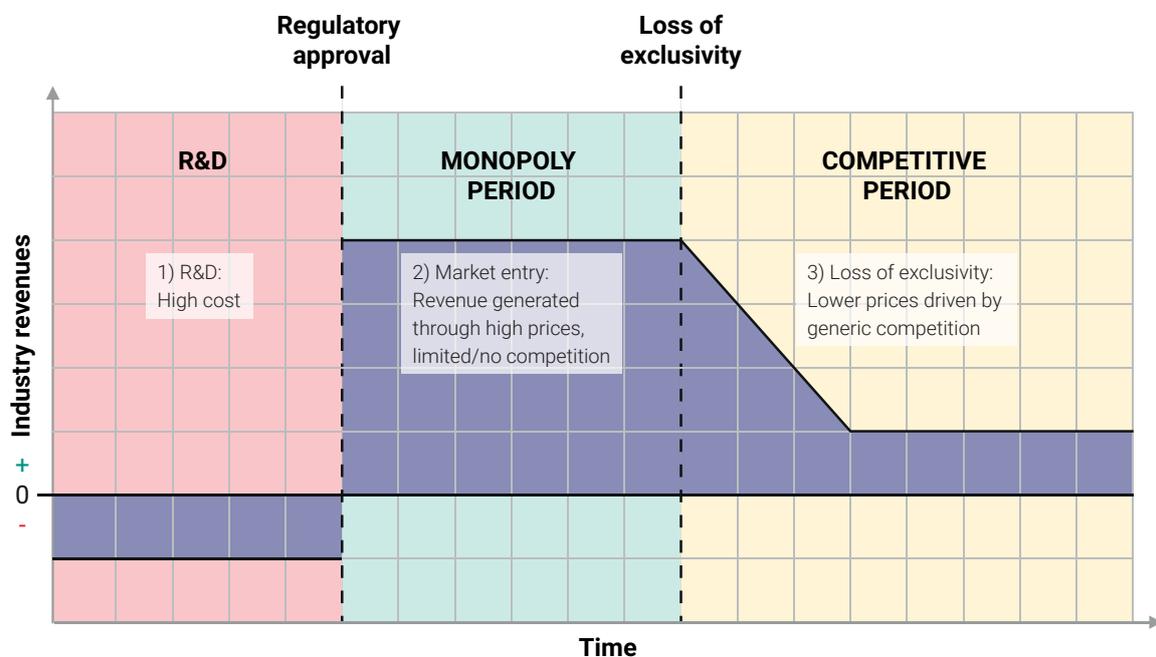
The characteristics of the on-patent pharmaceutical market are as follows:

- There are high regulatory, scientific and economic barriers to market entry, which reduce the number of sellers in the market.
- Drug regulatory agencies set evidence standards for establishing the clinical efficacy and safety of investigational drugs prior to market entry. Meeting these standards is costly. Together, these issues create high barriers to market entry, which reduce the number of sellers in the market.
- To incentivise market entry, pharmaceutical companies are granted a transient period of protection from competition through patents and regulatory exclusivity. These forms of market protection further reduce competition and the number of substitutable products on the market.
- The benefits and harms of new drugs are not easily or readily observable to consumers (physicians or patients). Asymmetric information between pharmaceutical companies and consumers has competition-reducing effects as physicians and patients may be unable to interpret the information on the benefits and risks of the already limited number of substitutable products on the market.
- Imperfect competition is a key driver of high drug prices in the on-patent market for pharmaceuticals.

## Box 1 – The market for pharmaceuticals (continued)

- The presence of third-party payers (eg, governments and insurers) reduces the number of buyers in the market and the price sensitivity of consumers.
- In comparison, the off-patent (generic) market for pharmaceuticals is closer to a competitive market:
- Barriers to entry are considerably lower for generic drugs. Manufacturers are required to demonstrate equivalence to originator drugs to receive marketing authorisation instead of conducting costly clinical trials.
- There is no sustained protection from competition for generic medicines. This (in theory) allows many more sellers and substitutable products in the market.
- Post-marketing data provide additional information about the benefits and harms of drugs in real-world populations. Over time, this reduces the asymmetry of information between manufacturers and consumers that exists at the time of initial market entry.
- Greater competition often leads to lower prices in the generic market than the on-patent market (**Figure 2**).

**Figure 2 – Pricing and competition throughout a drug’s lifecycle**



**Notes:** (1) Before approval, companies conduct clinical trials that build on publicly funded research to evaluate the efficacy and safety of their products prior to regulatory assessment. (2) At market entry, government-granted patents and exclusivity granted by drug regulatory agencies sustain high drug prices. Industry revenues are highest during the monopoly period. (3) After loss of exclusivity, competitors enter the market. A greater number of competitors on the market reduces prices to levels nearer that of marginal costs. Notably, the figure omits the considerable amount of early- and late-stage research that academic and public sector institutions conduct.

**Source:** Adapted with permission from Khullar *et al.* (2020)<sup>1</sup>

### Box 1 – The market for pharmaceuticals (continued)

The net contribution of any new drug to population health is the health benefit it provides relative to its cost, across its lifecycle (ie, during both the monopoly and competitive periods). Ultimately, if the drug is priced too highly during the monopoly period, then the health opportunity cost (health loss as a result of services displaced across the health care system; see Section 5) can outweigh the drug's net benefit across its lifecycle. If this is the case, then the introduction of the drug into a health system can be health-reducing.<sup>2</sup>

## Key issues in the pharmaceutical sector

**Prescription drug use has increased steadily over the past four decades.**<sup>3</sup> Around a half of adults in the United Kingdom (UK) now take at least one prescribed medicine every week, with almost a quarter of adults being prescribed three or more.<sup>4</sup> Similar trends can be seen globally.<sup>5</sup>

**The effectiveness of newly approved drugs is variable:**

- **Some drugs have had a profound effect on population health.** According to one estimate, 35 per cent of improved life expectancy in the United States (US) between 1990 and 2015 was attributable to pharmaceuticals alone, second only to the impact of public health measures (40 per cent).<sup>6</sup>
- **Some drugs have become a mainstay of medical treatment, to the extent that the World Health Organization (WHO) has deemed them 'essential'.**<sup>7,8</sup> Access to these drugs is now considered a basic human right as part of the right to good health.<sup>9</sup>
- **Many debilitating and life-threatening diseases have become preventable, treatable or curable as a result of pharmaceutical innovation.**<sup>10</sup> Some new drugs play a transformative role in treatment.<sup>10</sup> A recent example is sofosbuvir – a highly effective treatment for patients with chronic hepatitis C virus (HCV) infection.<sup>11</sup>
- **However, not all new drugs offer clinically meaningful benefits over existing treatments. The majority of new drugs provide variable (and often only minor additional) benefits to patients than existing alternatives, which are more difficult to discern.**<sup>12</sup> Cancer now accounts for the single largest therapeutic area for products in development.<sup>13</sup> However, almost half of new cancer drugs that entered the European and US markets in recent years did so with no evidence of survival or quality-of-life benefits.<sup>14–18</sup> Only about a third of newly approved drugs offer substantial clinical benefit compared with available treatment options.<sup>12</sup>

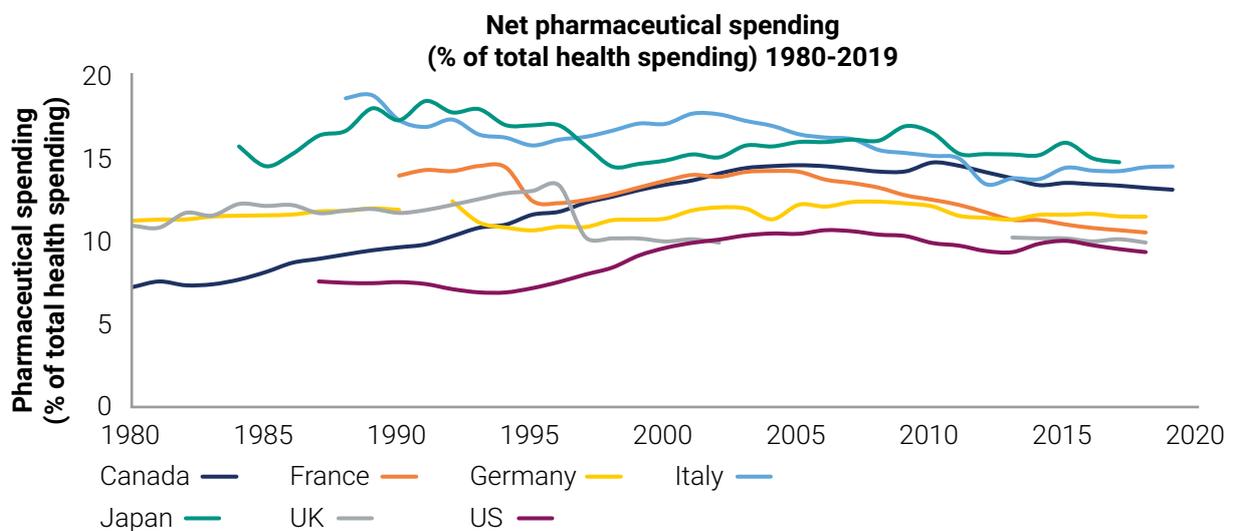
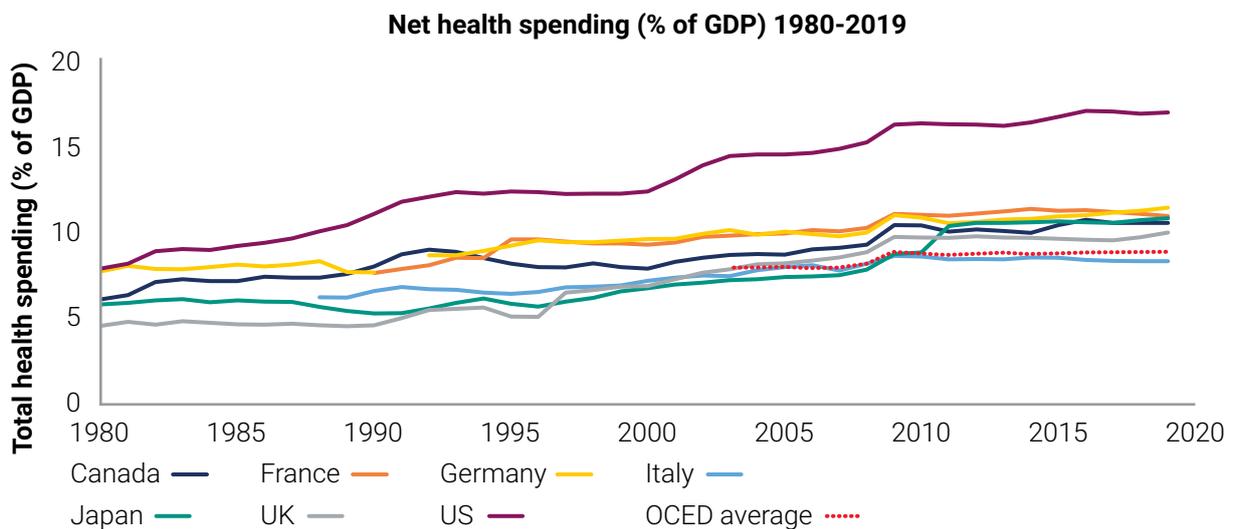
**Pharmaceutical expenditure is trending upwards.** Pharmaceutical spending now accounts for almost 15 per cent of total health spending in countries of the Organisation for Economic Co-operation and Development (OECD)<sup>19</sup> and is the third-largest cost component behind inpatient and outpatient care.<sup>20</sup>

Pharmaceutical spending includes primary care (community) and hospital spending. These broad categories are sometimes referred to as retail and non-retail, respectively.

- **Community spending** covers drugs prescribed in primary care (outside of hospitals).
- **Hospital spending** includes drugs administered or dispensed in the hospital (including drugs that are self-administered). Accurate measurement of total hospital expenditure on pharmaceuticals is difficult due to a lack of publicly available and harmonised data sources, with many countries unable to supply data on it.

**The rate of growth of community spending on prescription drugs has in many countries remained relatively stable since the mid to late 2000s, according to the OECD.** Some countries may have observed a decrease in expenditures associated with community prescribing in real terms during this time, particularly in the past decade (**Figure 3**).<sup>19</sup>

**Figure 3 – Community spending on pharmaceuticals, 1980 to 2019**



**Notes:** GDP = Gross Domestic Product. Community pharmaceutical expenditure does not include medicines administered in hospitals. There are missing OECD source data for some years due to country reporting methods.

**Source:** Adapted from OECD health spending data.

**The development of new drugs is not always reflective of disease burden or societal need.**<sup>21–23</sup> Cardiovascular disease (CVD) is the top cause of death globally, yet innovation of new drugs to treat CVD is stagnant.<sup>24,25</sup> There is also substantial unmet medical need in rare diseases, neglected tropical diseases and antibiotic-resistant diseases. Incentives for drug development are discussed in Section 2 (patents) and Section 4 (regulatory incentives).

## The importance of pharmaceutical expenditure for health policymakers

**Health systems globally are faced with increasing budgetary constraints.**<sup>26,27</sup> As expenditure on prescription drugs rises, budgets become more constrained and pressure is placed on health systems to contain increasing health care costs.

**Most of pharmaceutical expenditure is spent on patent-protected drugs.** In the UK in 2015, generic drugs accounted for 84 per cent of the volume of pharmaceuticals sold – the highest proportion among European Union (EU) countries – yet these drugs represented just a third of the total pharmaceutical spending.<sup>28</sup>

**The price of prescription drugs has increased substantially over the past few decades.**<sup>29,30</sup> This is concerning as some new drugs have become more expensive relative to the benefits they provide.<sup>31</sup> For example, the average list price of cancer drugs (adjusted for inflation) relative to the health benefits they provide increased by 10 per cent annually between 1995 and 2013.<sup>31</sup>

**Adopting new, expensive drugs in fixed-budget health care systems displaces existing health care services.**<sup>32</sup> Health lost as a result of the displacement of existing health care services is defined as the ‘health opportunity cost’.<sup>33</sup> Resources allocated to new, expensive drugs could be spent more efficiently on other (existing) services or treatments that offer better value for money in the health system, having a greater impact on overall population health.<sup>34</sup>

**Higher prices do not always correlate with meaningful innovation, which is defined as the development of new drugs that offer better clinical outcomes for patients.**<sup>35–37</sup> In fact, unique features of the pharmaceutical market that limit competition are key drivers of high drug prices (as outlined in **Box 1**).

## The contribution of the pharmaceutical sector to the economy

**New medicines developed by industry, and the resulting health gains attributed to some of them,<sup>6,38</sup> are not the only benefits of a strong pharmaceutical sector.** The pharmaceutical sector contributes to the economy.

**The pharmaceutical industry creates highly skilled, well-paid jobs, which are sought after by governments.** Industry estimates suggest that in 2017, more than 5.5 million people were directly employed (eg, in research and development [R&D], manufacturing, distribution or corporate headquarters' functions) in the pharmaceutical industry globally.<sup>39</sup> This includes around 750,000 people in Europe (2018),<sup>40</sup> 800,000 people in the US (2017)<sup>41</sup> and 60,000 people in the UK (2017).<sup>42</sup>

**The pharmaceutical sector also contributes to the upskilling and reskilling of the workforce throughout the pharmaceutical value-chain.**<sup>43</sup> Increased skills (along with increases in enterprise, technology and investment) are key drivers of productivity growth – a primary contributor to overall economic growth.<sup>44</sup>

**Governments seek to attract and sustain local pharmaceutical R&D activity.**<sup>45</sup>

Policy interventions range from direct government support for R&D to tax incentives and special programmes designed to stimulate new R&D investment from pharmaceutical companies.<sup>46</sup>

**However, the opportunity cost of government efforts to encourage domestic investment from the global pharmaceutical sector is not known.** From an industrial policy perspective, tax breaks and the public sector investment required to create and sustain pharmaceutical jobs could displace other activities that may yield similar (or higher) numbers of employment opportunities within and outside of the health sector. Empirical estimates of this are not available (or known).

## Considerations for pharmaceutical policymaking

**Pharmaceutical policy sits at the intersection of health and industrial policy.**

**The WHO defines health policy as: “the decisions, plans, and actions that are undertaken to achieve specific health care goals within a society”.**<sup>47</sup> In the pharmaceutical sector, governments shape health policy to promote the development of, and access to, safe and effective medicines, at affordable prices, to improve population health. Ensuring innovation in, access to and the affordability of medicines that offer meaningful clinical benefits to patients may be considered the *health-related* objectives of pharmaceutical policymaking.

**Industrial policy may be defined as: any type of intervention or government policy that attempts to improve the business environment or to alter the structure of economic activity towards sectors, technologies or tasks that are expected to offer better prospects for economic growth or societal welfare than would occur in the absence of such intervention.**<sup>48</sup>

In this respect, government intervention in the pharmaceutical sector aims to stimulate innovation, competitiveness, education, skills and productivity, among other objectives. These can be thought of as the *industrial* objectives of pharmaceutical policymaking.

When setting pharmaceutical policy, governments aim to strike an optimal balance between the health system goals of innovation, access and affordability with those of the pharmaceutical industry:

- **Innovation.** Health systems and the industry have a joint interest in sustaining a healthy pipeline of new drugs to advance patient care. To encourage the development of medicines that offer meaningful therapeutic benefit to patients and address unmet medical needs, governments and regulatory agencies issue incentives. However, this incentive-based reward system can inadvertently sustain high drug prices and drive pharmaceutical expenditure.
- **Access.** Patients duly expect timely access to new drugs that are safe and efficacious. Companies that develop new products are also interested in achieving fast market access. However, establishing the benefits and harms of new drugs quickly in clinical trials is difficult. More rigorous clinical testing is inevitably time-consuming and increases the cost of R&D for the industry.
- **Affordability.** Companies that develop new drugs have an interest in maximising revenues and making profits. From the health system perspective, paying high prices for new drugs is associated with significant opportunity costs and can divert funds away from existing treatments, interventions and services offered across the health system. If new drugs are not cost-effective relative to existing treatment options, the foregone health benefits from displaced services may outweigh the health benefits of new drugs.

## Industry influence on policy and practice

**Pharmaceutical companies, and organisations representing the interests of the pharmaceutical industry, are powerful political players in health systems and beyond.**<sup>49–52</sup> Given the pharmaceutical industry's important role in the economy, it has strong political influence and leverage in negotiations and national policy agenda setting.<sup>53</sup>

**Pharmaceutical companies spend heavily on lobbying governments, routinely sponsor patient organisations and often establish financial links with health care professionals and organisations.**<sup>54–56</sup> Between 1999 and 2018, the pharmaceutical and health products industry recorded the highest spending on lobbying of all industries in the US, totalling \$4.7 billion (equivalent to £3.5 billion in 2018).<sup>57</sup> In the UK, studies show substantial industry financial support for patient organisations,<sup>58,59</sup> as well as for groups that contribute to resource allocation decisions, including clinical commissioning groups and parliamentary groups.<sup>60,61</sup>

## Key issues in the pharmaceutical sector – summary

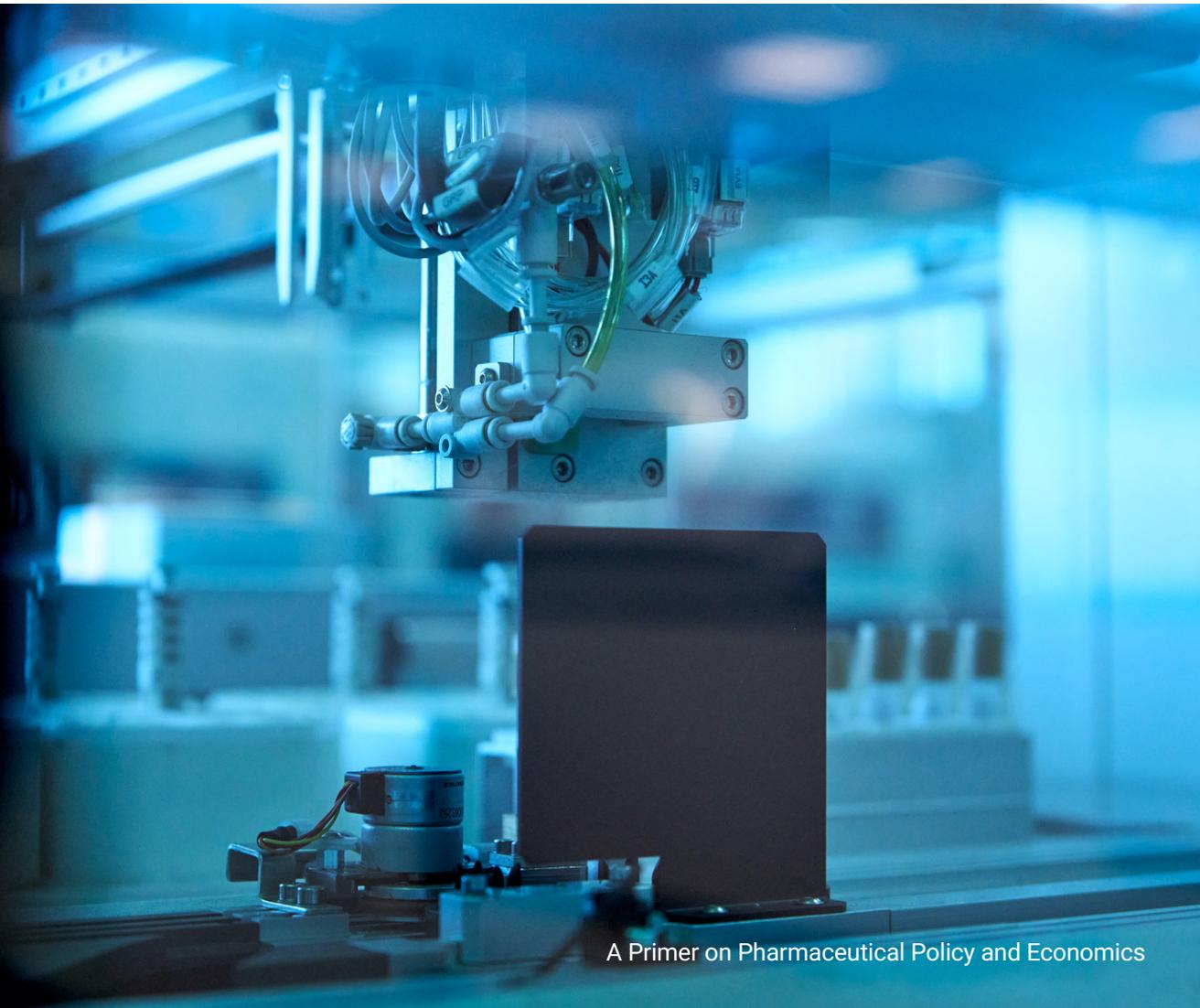
### Box 2 – Summary of key objectives, issues and trade-offs in the pharmaceutical sector

- The structure of the pharmaceutical market determines the price companies can charge for their products and the approach they adopt to maximise profits. The key features of pharmaceutical markets, from which many policy issues arise, include (but are not limited to) high barriers to entry and limited competition.
- Pharmaceutical policy sits at the intersection of health and industrial policy.
- Promoting the innovation of medicines that offer meaningful therapeutic benefit to patients, ensuring timely access and achieving affordability are the key objectives of pharmaceutical policymaking.
- Maximising population health given limited resources is the primary goal of health systems.
- Improving or altering the business environment to increase economic activity and foster economic growth is the key objective of industrial policy.
- The interests of the industry, patients and policymakers converge and diverge across different stages of the product lifecycle. Policymakers are faced with the challenging task of balancing the interests of health systems and the industry to promote health and economic growth.

# Section 2 Pharmaceutical research and development

## Section overview

Drug development is high-cost and high-reward. Companies invest in time-consuming and risky R&D based on expected future revenues, expected costs of drug development and policies that influence demand for new drugs. However, disease areas in which there is an unmet societal need for new drugs are not always those which are most profitable for industry. A complex mix of incentives to mitigate the risk and cost of R&D, through limiting competition for a defined period of time, characterises the pharmaceutical innovation system. This section outlines the key stages of pharmaceutical R&D, the rationale for using incentives to foster innovation in the sector, currently used incentives and their shortfalls.



## Characteristics of pharmaceutical R&D

**Prescription drugs can improve patient outcomes.**<sup>62</sup> R&D that leads to new drugs is key to ensuring that society captures the potential health benefits of new drugs in the future.

### **Pharmaceutical R&D is risky, time-consuming and therefore costly:**

**Risk:** Overall, around 10 to 15 per cent of investigational drugs that enter clinical trials (studies in humans) will eventually obtain regulatory approval.<sup>63–66</sup>

**Time:** The time taken from identifying a drug target to testing in clinical trials can often take around three to five years. Subsequently, the time taken from early clinical trials through to regulatory approval typically takes another eight years.<sup>64</sup>

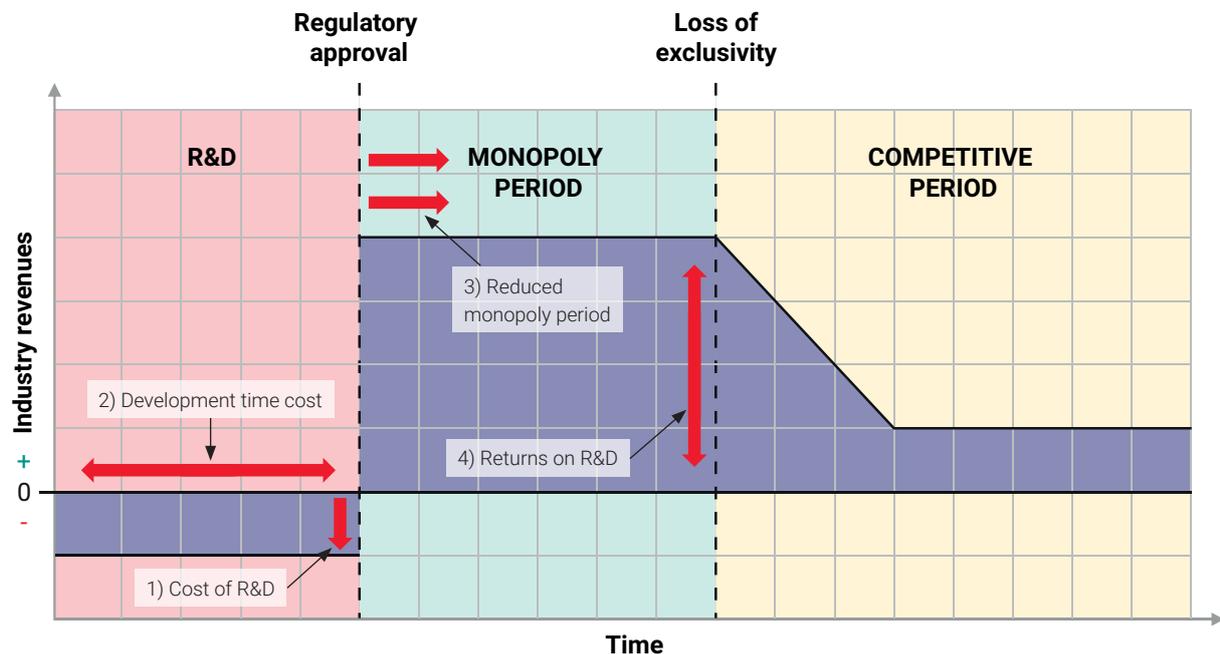
**Cost:** The cost of pharmaceutical R&D is often referred to as a global ‘sunk’ cost. R&D for novel drugs takes place once globally, with firms incurring costs before a product reaches the market. After this point, the marginal costs of production are relatively low.<sup>67</sup>

Studies suggest that the median capitalised R&D cost per new drug is around \$1,142 million (2018 US\$) (£844 million; 2018), including expenditure on failed trials.<sup>68</sup> Phase III clinical trials that support regulatory approval (so-called ‘pivotal trials’) account for the largest share of R&D costs.<sup>69,70</sup>

**Although R&D investment is high-cost, it is often high-reward.** Several strategies are used to account for the cost of pharmaceutical R&D (these are discussed below). These mechanisms afford industry with protection from competition for a defined period, during which they are able to charge higher-than-competitive prices (**Figure 4**).

**R&D spending as a share of net revenues (R&D intensity) is high in the pharmaceutical sector.** Pharmaceutical companies spent about one-quarter of their net revenues (after expenses and buyer rebates) on R&D in 2019 (up from around 19 per cent of net revenues spent on R&D over the past two decades).<sup>71</sup> This compares to 15 per cent for other highly R&D-intensive industries such as software and semiconductors, and an average of 2 to 3 per cent for all Standard and Poor (S&P) 500 companies.<sup>71</sup> In 2018, 13 of the top 35 firms globally by total R&D expenditure were pharmaceutical or biotechnology companies.<sup>72</sup>

**Expected global lifetime revenues (which depend on price and volume sold), expected costs of drug development and policies that influence the demand for prescription drugs determine industry investment in R&D.** Empirical evidence links potential profits with increased R&D activity.<sup>73–80</sup> Several studies show that growth in market size and potential profits (from expansions in insurance coverage, patent protections, disease prevalence and other factors) have a strong impact on R&D activity.<sup>81</sup> A meta-analysis of these studies suggests that a 1 per cent increase in company revenues increases the number of new drugs by 0.20 per cent, considering the average quality of pharmaceutical innovation.<sup>82</sup> The estimation of expected profits can distort industry priorities towards those areas that are most lucrative, and away from unmet health need.<sup>83</sup>

**Figure 4 – Costs and rewards in pharmaceutical R&D**

**Notes:** (1) The cost of R&D can be substantial and creates a significant barrier to entry. (2) The time taken for R&D increases costs further through missed opportunities for returns on investment and the opportunity cost of capital that is tied up in R&D. (3) The patent life of new drugs is partly used up during R&D, reducing the monopoly period once the product is approved. (4) Following regulatory approval, protection from competition during the monopoly period ensures high returns on R&D investment.

**Source:** Adapted with permission from Khullar *et al.* (2020)<sup>1</sup>

**The US pharmaceutical market (which accounts for approximately 50 per cent of global sales),<sup>84</sup> plays a disproportionately large role in influencing global R&D trends.** Empirical evidence links legislation, regulation and payment policy in the US to measurable changes in sector-wide R&D activity.<sup>36,74,81,85–88</sup>

**Industry and health policy interests do not always align during R&D.** From a health policy perspective, R&D should primarily target areas of unmet medical need (areas without adequate treatment options),<sup>89</sup> where new drugs make a clinically meaningful difference for patients. Predictably, industry seeks to develop treatments based on highest expected profits.

**Companies prioritise disease areas and patient populations that are most lucrative and for which there is a high societal willingness to pay.<sup>90</sup>** Oncology is one of the riskiest (in terms of development failure),<sup>64,66</sup> and therefore costliest,<sup>68</sup> therapy areas to conduct R&D. Yet, oncology represents the most active therapeutic area in terms of the numbers of clinical trials and products in development, reflecting decision-makers' high willingness to pay for cancer medicines in many settings.<sup>66</sup>

**Increased R&D spending is not always truly 'innovative' and does not always lead to the development of drugs that offer meaningful clinical benefits to patients.**

Pharmaceutical companies often argue that high profits drive future investment in R&D.<sup>91,92</sup> However, much of the increased R&D spending due to higher profits contributes to developing drugs that duplicate the action of existing drugs and targets patient populations that already have effective treatment options.<sup>36,37,87,93</sup>

## Incentivising pharmaceutical innovation

**To incentivise drug development, policymakers use a mix of ‘push’ and ‘pull’ incentives to stimulate private investment in R&D.<sup>94</sup>**

### **Policymakers use ‘push’ incentives to reduce or subsidise costs during R&D**

**(Figure 5).** Traditionally, early-stage ‘basic’ R&D activity is funded through grants to public sector research institutions and academia. Examples of public sector research institutions include the National Institutes of Health (NIH) in the US and the Medical Research Council (MRC) in the UK. The NIH alone is the single largest public funder of health research globally, contributing \$42 billion (equivalent to £35 billion) to medical research in 2020.<sup>95,96</sup>

- **Public funding of R&D is aimed at maximising the societal value of drug development. Drugs that benefit from publicly funded research have a disproportionately large effect on public health, and often prioritise unmet medical needs.**<sup>97–100</sup> In recent years, almost all vaccines and many drugs developed to treat cancer and infectious diseases were developed (at least in part) through publicly funded research.<sup>97,98</sup> Public sector funding has also been instrumental in the development of coronavirus disease 2019 (COVID-19) therapeutics and vaccines.<sup>101</sup>
- **Early-stage public funding complements later-stage industry investment in R&D and the commercialisation of new products.**<sup>102–105</sup> Although public funding of early-stage R&D is important for stimulating R&D, it does not replace industry investment in R&D, which further develops drug candidates, evaluates candidates in clinical trials and commercialises them. In Section 3, we discuss the role of industry-funded clinical trials.
- **Industry funding of R&D is substantial.** OECD estimates suggest that in 2016, industry (private) funding of pharmaceutical R&D (\$100 billion; £70 billion) was approximately double that of public funding (\$53 billion; £37 billion) globally.<sup>20</sup> Of this private investment in pharmaceutical R&D, over half occurred in the US.<sup>20</sup>
- **The combination of public and private funding, which contributes to new drug approvals, can lead to criticism and concerns over the public ‘paying twice’ for new drugs.** Critics argue that the public pays once through initial funding of R&D and then again once the drug is approved for use in health systems.<sup>106–108</sup> Sofosbuvir is an illustrative example from the US. The development of this hepatitis C drug benefited significantly from an estimated \$60.9 million in NIH public funding.<sup>109</sup> When approved in 2013, its list price in the US was \$84,000 (roughly around \$1,000 – equivalent to £655 in 2013 – per pill) and during the first year of approval cost the US health system around \$8 billion.<sup>110,111</sup>

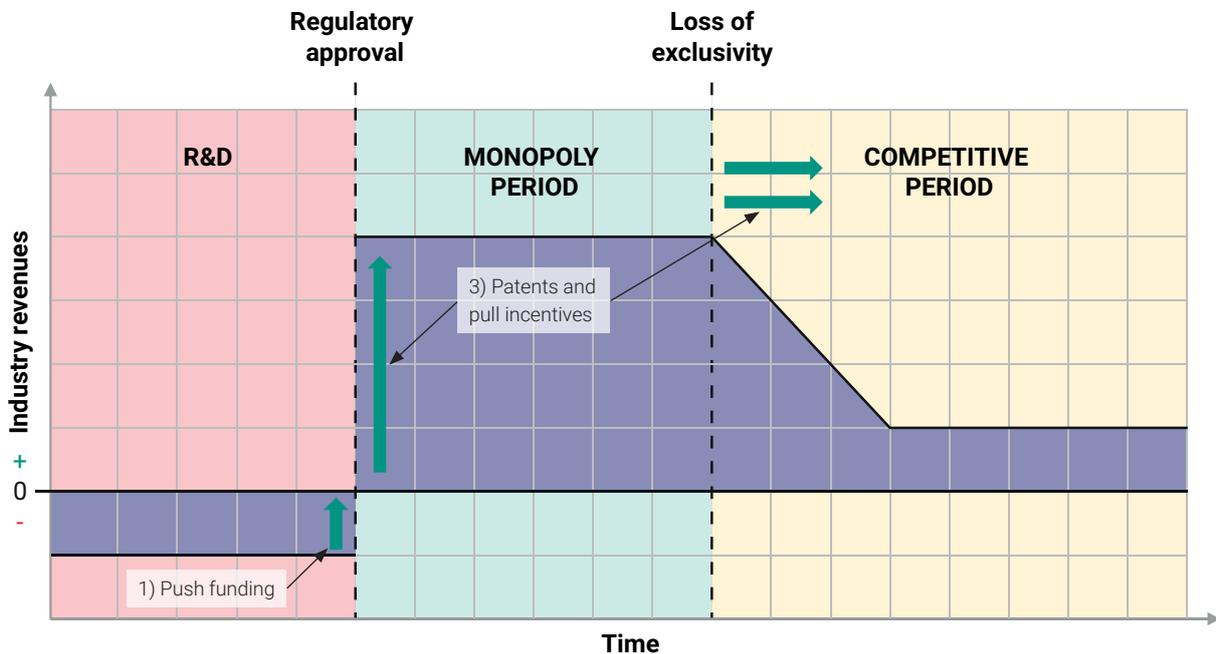
- **‘Push’ incentives also address industrial policy objectives.** Governments seek to improve the ‘attractiveness’ of their markets to encourage private investment and maximise the economic benefits of pharmaceutical R&D. As also outlined in Section 1, governments employ a range of strategies to do so, including direct public investment in research, the facilitation of industry links with academia, tax incentives, public–private partnerships, data infrastructure enhancements or maintaining a favourable political and regulatory landscape for investing companies.<sup>45</sup> The industry responds to ‘push’ incentives in different ways (**Box 3**).

### Box 3 – How does the industry respond to ‘push’ incentives?

- Push incentives effectively attract industry investment in pharmaceutical R&D.
- According to economic theory, advances in public basic research can stimulate industry follow-on investment. Empirical evidence supports this. In the US, NIH-funded basic research has had a significant effect on the market entry of new drugs.<sup>103</sup>
- One study shows that over the four decades preceding 2011, at least 153 drugs that the Food and Drug Administration (FDA) approved were discovered through research carried out in public sector research institutions.<sup>97</sup> Over half of these drugs were indicated for the treatment or prevention of cancer or infectious diseases.
- Between 1988 and 2005, public funding supporting early- and late-stage research occurred in almost half of the drugs that the FDA approved and in almost two-thirds of priority-review drugs.<sup>99,112</sup>

**Policymakers use ‘pull’ incentives to increase potential future profits to reward companies for drug development (Figure 5).**<sup>113</sup> The main pull incentives for pharmaceutical R&D are protection from market competition provided by patents (which governments issue pre-approval) and market exclusivity (which drug regulators grant around approval).

**Figure 5 – How do ‘push’ and ‘pull’ incentives impact pharmaceutical costs and expected returns on R&D?**



**Notes:** (1) Push funding reduces the initial cost of investment for R&D. (2) Patents increase revenues post-approval by creating a monopoly period in which firms can charge higher-than-competitive drug prices. In theory, together these factors create incentives for drug development by increasing expected returns on investment and profit.

**Source:** Adapted with permission from Khullar *et al.* (2020)<sup>1</sup>.

- **Patents allow government-granted monopolies to charge higher-than-competitive prices for a defined period of time.** Since 1995, the World Trade Organization (WTO) agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) established a 20-year protection period from the time of filing (which is usually shortly after drug discovery).<sup>114</sup>

## Shortfalls of patents in pharmaceutical R&D

**Protection from competition that the patent-based system of incentives affords is a key driver of sustained high drug prices.**<sup>115</sup> In the US, almost 80 per cent of pharmaceutical expenditure is on these on-patent drugs, which account for only 10 per cent of all dispensed prescriptions.<sup>116</sup> Post-patent expiry, generic drugs offer much greater value for money for health systems, providing the same clinical benefit, at a fraction of the cost of their on-patent counterparts.

**Patents are a ‘one-size-fits-all’ legal regime.**<sup>117</sup> The patent system applies the same broad rules to innovation across different industries, from pharmaceuticals to the automotive industry, despite the fact that the need for intellectual property protection for these industries differs greatly.

**One key shortfall of the patent system for the pharmaceutical industry is that the monopoly period is fixed from the date of patent filing early in the R&D process, regardless of the drug approval date.** Due to the lengthy process of R&D, at the time of product approval, much of the patent life may have expired. Further pull incentives and market exclusivities are used to remedy this reduction in effective patent life.<sup>118</sup> The additional forms of market protection that drug regulatory agencies grant are discussed in Section 4.

**The patent-based system may also prevent timely and affordable access to new drugs in resource-constrained health systems.**

- **Since 1995, the WTO's TRIPS agreement has governed the international protection of intellectual property.**
- **'Flexibilities' in the TRIPS agreement (further clarified in the Doha Declaration in 2001) provide a legal framework for governments or courts to grant compulsory licences in the case of a health emergency or to address public health needs.** Such flexibilities permit the use of a patented intervention (domestically, for public health) without the authorisation of the patent holder. For example, during the human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic, compulsory licensing was used to allow some low-income nations to import generic anti-retroviral medicines.<sup>119</sup> Evidence suggests that compulsory licensing is rarely implemented outside of low-income countries.<sup>120</sup>
- **A patent 'waiver' temporarily removes the rights and protections that the TRIPS agreement affords from the manufacturer.** Under such a waiver, the patent holder is not able to prevent the local production and import or export of health technologies on intellectual property grounds. The aim of a patent waiver is to expedite the availability of a product during a public health emergency (**Box 4**).

#### **Box 4 – 2022 COVID-19 vaccine patent waiver**

In October 2020, India and South Africa submitted a proposal to the WTO on all intellectual property rights in relation to COVID-19 vaccines and treatments.<sup>121</sup>

The proposal was met with fierce opposition from industry, which argued that an intellectual property waiver would jeopardise future innovation.<sup>122,123</sup> Many countries, including Germany, Switzerland and the UK, also opposed the waiver, arguing that TRIPS flexibilities (ie, compulsory licensing) already permit countries to override intellectual property rights during emergencies, negating the need for such a waiver.<sup>124</sup>

In June 2022, the WTO endorsed a partial waiver for COVID-19 vaccines.<sup>125</sup> The decision text contained a set of clarifications of existing public health safeguards and issued a limited exception for compulsory licensing for the export of COVID-19 vaccines by eligible countries, for five years.

## Pharmaceutical firms can engage in practices that unduly extend the patent term for their products:

- Patent thickets:** Companies can register several different types of patents (compound, composition, method-of-use or process) to create a 'patent thicket' on a single drug at the same time. This delays and deters generic entry due to the risk of patent infringement and the cost of litigation.<sup>126</sup>
- Evergreening:** Companies can register new 'secondary patents' on features of existing drugs during the original 20-year patent term to extend the period of market protection.<sup>127</sup> Of the drugs with new patents in FDA records, 78 per cent are not new drugs coming on the market, but existing drugs.<sup>128</sup>
- Product hopping or switching:** Companies can switch a market onto a newer, similar product, before the patent expires. This limits the price-reducing capability of generic entry.<sup>64,65</sup>
- Pay-for-delay:** Companies can engage in illegal, anticompetitive practices through which they 'pay off' a generic manufacturer, out of the courts, to delay market entry, allowing higher prices to be charged. This practice is not uncommon.<sup>129</sup>

## Innovation of vaccines, antimicrobials and drugs for rare diseases

### Incentivising vaccine development

**Vaccines are highly cost-effective strategies for improving population health.**<sup>130,131</sup>

However, several factors that discourage private sector investment in R&D characterise the market for vaccines:<sup>132</sup>

- Many countries affected by infectious diseases are unable to pay high prices, effectively reducing the expected profits of manufacturers.
- Increasing vaccination rates reduces the risk of infection for the unvaccinated, reducing their willingness to pay and leading to what economists refer to as 'free-riding' behaviour.<sup>133</sup>
- Low- and middle-income countries that benefit from vaccine research may have limited willingness and ability to pay. Vaccines may ultimately be sold at a fraction of their social value in some settings.<sup>132</sup>
- Willingness to pay is typically higher for treatments than for preventive products such as vaccines.

- Once approved, governments of low- and middle-income countries may have the ability, as arbiters of intellectual property rights, to reduce price levels or even make a case for the compulsory licensing of vaccines.
- Compounding the factors listed above is the high risk (and cost) of R&D for vaccines.

**In theory, guaranteeing a market for vaccines in an Advanced Market Commitment (AMC) provides a strong ‘pull’ factor for companies developing vaccines.**<sup>132</sup> In

an AMC, “donors commit to a fund from which a specified subsidy is paid per unit purchased by low-income countries until the fund is exhausted”.<sup>131</sup> This grouped commitment strengthens suppliers’ incentives to invest in R&D. An AMC for vaccines was first piloted successfully on a large scale by Gavi, the global vaccine alliance, to create incentives to conduct R&D and invest in manufacturing capacity for pneumococcal vaccines.<sup>131</sup>

## Global health emergencies

**The International Health Regulations define a health emergency as an “extraordinary event that constitutes a public health risk through the international spread of disease and potentially requires a coordinated international response”.**<sup>134</sup>

Examples of health emergencies include the H1N1 influenza pandemic (2009), Ebola (2013), Zika (2016) and more recently COVID-19 (2020) and monkeypox (2022). In such health emergencies, governments and regulators can mobilise exceptional levels of incentives for drug and vaccine development (**Box 5**).

### Box 5 – Incentives for vaccine development – the exceptional case of COVID-19

The COVID-19 pandemic showcased the role of public institutions and government-led efforts in incentivising innovation globally. This global R&D response was several orders of magnitude larger than that implied by its market size, with public institutions playing an unprecedented role in vaccine R&D.<sup>135</sup> Public sector funding was also instrumental in the late-stage development and manufacturing of COVID-19 vaccines, shifting the traditional paradigm of industry funding late-stage clinical trials.

In monetary terms, the greatest push response to COVID-19 came from the US government, which allocated more than \$10 billion to vaccine R&D, increasing pre-COVID government funding of R&D by roughly one-third.<sup>136</sup> The US government prioritised the coordination of public and private funding, and the prevention of duplicative research.<sup>137</sup> A US-focused programme (‘Operation Warp Speed’) was also set up to support the late-stage clinical development and early manufacturing of COVID-19 vaccines, along with agreements to purchase the vaccines once developed.<sup>138</sup> In the EU, similar exceptional levels of push funding were committed to vaccine development.<sup>139,140</sup> In the UK, public funding contributed to the development of the Oxford/AstraZeneca (ChAdOx1) vaccine (**Box 6**).

## Box 5 – Incentives for vaccine development – the exceptional case of COVID-19 (continued)

Outside of high-income countries, the Coalition for Epidemic Preparedness Innovations (CEPI) committed funding to a portfolio of vaccine candidates. Globally, a prominent pull mechanism to stimulate COVID-19 vaccine development and equitable access was the COVID-19 Vaccine Global Access Facility (COVAX) AMC. The COVAX AMC was set up as a pooled procurement initiative, allowing 92 low- and middle-income countries to receive vaccines at a reduced price of less than \$2 (£1.70) per dose.<sup>141,142</sup> Therefore, the COVAX AMC was designed to provide a guaranteed market to manufacturers, pulling vaccine candidates through development.

### Challenges that the COVAX AMC encountered

Although economic theory supports the use of an AMC, in practice, the COVAX AMC was fraught with vast logistical, political and other challenges.<sup>141,143–145</sup> Early on in the pandemic, high-income countries brokered large-scale bilateral deals with companies across a portfolio of vaccine candidates ahead of manufacturing, leaving COVAX unable to compete and secure doses.<sup>146</sup> Middle-income countries such as Brazil and India also negotiated deals as part of manufacturing agreements.<sup>147</sup> Other countries used clinical trial infrastructure as leverage to secure purchase deals with manufacturers.<sup>148</sup>

These bilateral deals undermined pooled procurement through COVAX, meaning COVAX became reliant on high-income countries' willingness to give up doses.<sup>146</sup> Ultimately, COVAX has fallen short of its aim to provide equitable access to COVID-19 vaccines. As of August 2022, only 20 per cent of people in low-income countries have received at least one dose, compared with around 80 per cent in high-income countries.<sup>149</sup>

## Box 6 – COVID-19 vaccine development in the UK

Researchers at the University of Oxford in the UK were among the first groups to begin work on a new vaccine to treat COVID-19, in January 2020. Initial work on the vaccine was funded through existing resources available to the UK Vaccines Network, with joint funding from the Department of Health and Social Care and UK Research and Innovation.

In March 2020, an additional £2.6 million grant, provided by the National Institute for Health and Care Research (NIHR), galvanised the vaccine research. In April of the same year, the University of Oxford formed a non-profit collaboration with UK-based pharmaceutical company AstraZeneca to scale up R&D, manufacturing and distribution.<sup>150</sup>

On 23 November 2020, positive interim phase III trial results were released, confirming that the vaccine provided a high level of protection against COVID-19.<sup>151</sup> On 24 June 2021, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a Conditional Marketing Authorisation for the vaccine. Since then, more than two billion doses of the vaccine have been administered globally, in 185 countries.<sup>152</sup>

## Antimicrobials

**Economic returns to companies that develop new antimicrobials are highly uncertain.**<sup>153</sup> This uncertainty stems from unknown future demand corresponding to health need, low demand due to controlled volumes of prescribing (to prevent overuse) as well as due to generic competition from existing antimicrobials, and negative externalities associated with treating infectious diseases (the use of antibiotics can reduce future demand).<sup>154</sup> In recent years, the pharmaceutical industry's R&D of novel antibiotics has declined. One novel approach to overcoming these issues has been to adopt a subscription or so-called 'Netflix model' in which payments are fixed and therefore 'de-linked' from the volume of products sold.<sup>155-158</sup> Under such a model, health systems secure either a fixed or an unrestricted supply of the medicine for a recurring fee.<sup>159,160</sup>

## Rare diseases

**The small patient population with rare (orphan) diseases means that it is unlikely that market size alone will attract pharmaceutical companies to invest in R&D for them.** In the EU, a disease is considered rare if the prevalence is fewer than five in 10,000 people. In some cases, payers have been willing to pay a higher price for drugs for rare diseases.<sup>161-164</sup> In Section 4, we outline the array of additional incentives that drug regulatory agencies use to incentivise drug development for rare diseases.

## Pharmaceutical research and development – summary

### Box 7 – Summary and trade-offs relating to pharmaceutical R&D

- Pharmaceutical R&D is risky, time-consuming and costly. But it is also high-reward.
- Industry funding of R&D is substantial, with R&D spending as a share of net revenues (R&D intensity) remaining relatively high in the pharmaceutical sector.
- Expected future profits, expected costs of drug development and policies that influence demand for new drugs drive industry R&D decisions.
- Governments and policymakers implement several ‘push’ and ‘pull’ mechanisms to further incentivise pharmaceutical development.
  - Public funding and tax subsidies for research are the primary push mechanisms used to incentivise R&D. The COVID-19 pandemic has highlighted the importance of public investment in early- as well as late-stage R&D.
  - The patent-based system of intellectual property protection is the primary ‘pull’ mechanism used to mitigate the financial risk of drug development.
- Intellectual property protections alone do not act as sufficient financial incentives for industry to invest in all product or disease categories (eg, vaccines, antimicrobials and rare diseases). These pull mechanisms also do not distinguish between rewarding the development of drugs that offer important value to society and R&D that yields new drugs without meaningful clinical benefit over existing alternatives.
- From an industrial policy perspective, local pharmaceutical R&D has the potential to contribute to economic growth. Domestic industrial policy therefore aims to increase investment in pharmaceutical R&D. However, increased levels of pharmaceutical R&D investment may not yield proportional increases in new drug approvals that address unmet medical needs – a key priority for health policy. Policymakers must therefore aim to strike a balance between health and industrial policy on innovation.

# Section 3 Generating evidence in clinical trials

## Section overview

Before a new drug can enter the market, its benefits and harms are evaluated in clinical trials and assessed by drug regulatory agencies. Such evidence on the benefits and harms of a new drug is also fundamental for decision-making downstream of regulatory approval, for example to determine whether the health system adopts the new drug and at what price. In this section we provide an overview of the most important design features of clinical trials and the key pillars of clinical trial transparency.



## Overview of clinical trials

**A clinical trial is a prospective study comparing the effects of an intervention(s) against a control.**<sup>165</sup> Over the past half-century, randomised controlled trials (RCTs), in which study participants are randomly assigned to either a treatment group or a control group, have emerged as the 'gold standard' of clinical trial design to elicit the benefits and harms of new drugs.<sup>166,167</sup>

**Evidence generated through clinical trials is fundamental for decision-making around the time of new drug approvals.**<sup>168</sup> Regulatory agencies use clinical trials to determine whether the benefits of new drugs outweigh their harms prior to approval.

**In addition to regulatory approval, data generated in clinical trials are used to inform downstream pricing, reimbursement and coverage decisions in health systems.**<sup>169</sup>

Data obtained from clinical trials form the basis of evidence that is used to inform whether payers should reimburse drugs that are newly approved, and at what price. This is discussed further in Sections 5 and 6.

**Clinical trials also play a key part in detecting safety events and aiding ongoing surveillance of newly approved drugs following market entry.** At the time of marketing authorisation, evidence of safety and efficacy is limited to data gained from a small number of clinical trials, whereby patients are selected and monitored closely throughout treatment, for a limited period of time.<sup>170</sup> Following approval, a drug is prescribed to many more patients who might use the medicine in different ways or concomitantly with other drugs (ie, 'real-world use'). Under wider and prolonged exposure, safety concerns or side effects may emerge. Indeed, it is not uncommon for approved medicines to have post-approval safety events. Approximately a third of new drugs that the FDA approved between 2001 and 2010 had these events.<sup>171</sup>

### Box 8 – Importance of well-conducted randomised controlled trials

The power and importance of well-designed RCTs to detect the benefits and harms of new drugs were once again illustrated during the COVID-19 pandemic. In early 2020, there were no approved treatments for the coronavirus. The antimalarial drug hydroxychloroquine was promoted as having high therapeutic potential in COVID-19 patients on the basis of a controversial uncontrolled study.<sup>172</sup> Contrary to what low-quality observational (non-randomised) studies suggested, findings from the UK Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial quashed claims of the effectiveness of hydroxychloroquine, while identifying dexamethasone as a treatment that lowered mortality in COVID-19 patients.<sup>173</sup> The WHO later recommended the treatment of severe and critical COVID-19 using dexamethasone.<sup>174</sup>

**The pharmaceutical industry sponsors most clinical trials that lead to new drug approvals ('pivotal studies').**<sup>175,176</sup> In the EU, around 61 per cent of clinical trials are industry-sponsored, of which higher proportions are likely to be found in later stages of clinical trials.<sup>177</sup> Research suggests that the methodological quality of industry-sponsored studies is equal to, or better than, non-industry-sponsored studies, with low risk of bias.<sup>178,179</sup>

**However, not all clinical trials produce useful information to guide reimbursement and clinical decisions.**<sup>180</sup> Very few industry-funded trials elicit information on the comparative effectiveness of new drugs (how well they work compared with existing treatments), as regulatory agencies do not typically require such comparative studies.<sup>181,182</sup> Compared with studies that public sector research institutions sponsor, industry-sponsored studies are more likely to yield more favourable efficacy results and conclusions for the industry's products,<sup>178,179,183</sup> likely due to the research questions they address.<sup>184</sup>

**Clinical trials are regulated both nationally and internationally.** Since 1990, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has issued technical guidelines for clinical trials, which regulatory authorities around the world implement. These guidelines aim to contribute to the safe development and manufacturing of new medicines.<sup>185</sup> A number of international codes of conduct and guidelines also exist to protect the rights and welfare of trial participants in their respective countries.<sup>186–188</sup>

## Optimising clinical trial design: ensuring clinical trial data are high quality, valid and useful for decision-making

A large body of literature has identified the following design features as key drivers of trial validity and relevance in decision-making. These factors also impact the duration, complexity and cost of clinical trials.

### Random treatment allocation

**Random treatment allocation is the assignment of study participants to treatment groups in a clinical trial using a random process.** Randomisation removes the potential of selection bias, meaning that any individual is equally likely to be assigned to either the intervention group or the control group. This process leads to comparable groups with similar baseline characteristics in a clinical trial, ensuring that any differences in outcomes observed between the two groups can be attributed to the treatment, and not to other factors.<sup>189</sup>

**Calls for alternative approaches to clinical evidence generation that are more flexible and efficient than randomised trials are becoming common, particularly with the emergence of 'big data' from electronic health records and other routinely collected data sources.**<sup>190,191</sup> Real-world evidence (RWE) stems from observational data obtained during routine clinical practice. Such non-randomised, observational studies play an important role in the post-market evaluation of safety by identifying rare adverse events or in complementing the evidence generated before approval.<sup>192</sup> However, non-randomised studies have a higher likelihood of generating false-positive and false-negative (ie, biased) results than randomised studies.<sup>193</sup>

## Endpoints

**Clinical outcomes are what ultimately matter to patients.** In treating cancer, for example, the main goal of treatment is to improve the patient's length and quality of life.<sup>194</sup> Accordingly, two highly relevant clinical trial endpoints are overall survival and patient-elicited health-related quality of life.

**It may not always be possible, or desirable, to use clinical endpoints in trials.** For example, many patients with early-stage cancer may live for many years. Therefore, trials that use survival as an endpoint could be too long and costly. In these circumstances, an alternative approach is to use a marker of disease (surrogate) for which there is a well-established and reliable correlation with the preferred clinical endpoint.

**Surrogate endpoints are used as short-term substitutes for outcomes that ultimately matter to patients.**<sup>195</sup> For example, high blood pressure is strongly associated with death or complications from CVD.<sup>196–198</sup> It is therefore able to serve as a 'surrogate' to the preferred clinical endpoint. Surrogate endpoints can help to achieve timely access to new medicines as well as shortening and reducing the cost of clinical trials.

**However, surrogate endpoints do not always reliably correlate to therapeutic benefit.**<sup>199,200</sup> The use of surrogate endpoints in new drug approvals is increasing rapidly. Between 2012 and 2014, almost half of all new drugs were approved based on surrogate endpoints, many of which remain non-validated.<sup>201,202</sup> In a recent evaluation, none of the surrogate endpoints that the European Medicines Agency (EMA) used were found to be validated.<sup>203</sup> Drugs approved based on evidence from unvalidated surrogate endpoints can lead to high levels of uncertainty about their clinical effectiveness (**Box 9**).<sup>204,205</sup>

## Box 9 – Surrogate endpoints in cancer trials

It is inappropriate to use surrogate endpoints if they do not strongly correlate with important clinical outcomes.<sup>199</sup>

In cancer trials, the time taken from treatment initiation to disease progression or death (progression-free survival) is often used as a surrogate for overall survival. However, progression-free survival does not always correlate with overall survival or quality of life.<sup>14,206–209</sup> This has resulted in new and often-costly cancer drugs being approved that do not offer any clinically meaningful improvements in the standard of care.<sup>210</sup>

As an example, in 2008 the FDA approved bevacizumab for treating advanced breast cancer. The clinical trial supporting bevacizumab's approval had shown that it almost doubled progression-free survival from 5.9 to 11.8 months compared with standard chemotherapy.<sup>211</sup> However, trials later showed that it had no positive effect on overall survival, leading the FDA to withdraw its approval for bevacizumab to be prescribed for the treatment of advanced breast cancer in 2011.<sup>212</sup>

## Choice of comparators

**Direct comparison of new drugs to existing alternatives is the best way to understand their relative benefits and harms (comparative effectiveness).** Currently, fewer than half of new drugs have data on their benefits and harms compared with existing treatments at the time of regulatory approval.<sup>213–215</sup>

**Comparative effectiveness data are most useful for clinical decision-making and deciding which new drugs to reimburse and at what price.**<sup>216</sup> In the absence of direct evidence on the comparative benefits and harms of new and existing drugs, decisions about which treatments to promote in clinical practice and health policy rely on indirect comparisons.

**Despite its usefulness, the assessment of comparative effectiveness remains outside the remit of regulatory agencies.**<sup>215</sup> Pharmaceutical companies do not routinely collect such data before approval.<sup>214</sup> In few circumstances, comparative research may not be legitimately possible, for example if a new drug is the first to treat a disease.

**Costly drugs that are adopted without comparative clinical effectiveness evidence can have a negative impact on public health.** For example, RCTs found bevacizumab and ranibizumab to be equally effective in patients with neovascular age-related macular degeneration despite the 40-fold difference in their price.<sup>217,218</sup>

## Clinical trial validity versus cost: a false trade-off

**Clinical trial design is an important driver of clinical trial costs.**<sup>219</sup> Large, well-conducted clinical trials that are randomised, controlled with ‘active’ comparators and use patient-relevant outcome measures are most useful for decision-making but come at a high cost:

- **The underlying factor that drives clinical trial costs is the sample size (the number of patients required to demonstrate a treatment effect).**<sup>70,220</sup> Sample size requirements in clinical trials are highly variable and depend on several factors such as the therapeutic area. If an intervention has a strong therapeutic effect (ie, large magnitude of effect), then a smaller trial is likely to suffice than for a treatment that has a weak therapeutic effect (ie, small magnitude of effect), which is more difficult to discern.
- **Costs are lowest when new drugs are evaluated in single-arm clinical trials.**<sup>219</sup> However, without a control group, these studies have little protection against bias.
- **Randomised trials that adopt placebo control groups are, on average, more than twice as costly as those without any control group.**<sup>221</sup> Head-to-head trials with active comparators increase costs further.
- **The use of a clinical outcome as trial endpoints more than doubles the cost of clinical trials compared with using surrogate endpoints alone.**<sup>221</sup>

**The costs of clinical trials need not be a barrier to conducting well-designed randomised trials that are useful for decision-making.** Sponsors can make trials more efficient by employing adaptive designs and using electronic health care record systems, routinely collected administrative data and clinical registries to identify eligible patients and streamline recruitment and outcome monitoring.<sup>222,223</sup> In parallel, governments can make trial regulations less burdensome.<sup>224</sup> More efficient clinical trials would address both health and industrial policy objectives.

## Health and industrial policy considerations in relation to clinical trials

**From an industrial policy perspective, clinical trials can serve as useful tools to promote economic activity.** In the UK, for example, market research suggests that in the three-year period from 2016 to 2019, clinical research that the (publicly funded) NIHR Clinical Research Network supported generated thousands of skilled jobs for the UK.<sup>225</sup> Also, patient recruitment into industry-sponsored trials can, in theory, generate revenue for health systems.<sup>225</sup>

**Government policies aimed at improving clinical trial and data infrastructure can benefit both industry and patients.** Issues with patient identification, recruitment, retention and outcome measurement are significant contributors to delays in and increased costs of clinical trials.<sup>226</sup> In theory, policies and regulations aimed at promoting, streamlining and diversifying clinical research can increase the number of clinical trials and generate more meaningful clinical data in less time. Such interventions can also help to reduce the logistical barriers to clinical research.

## Clinical trial transparency

**The aspirational goals of clinical trial transparency rest on five pillars:**

- trial registration – all clinical trials are registered before they start
- summary results posting – results are made public shortly after trial completion
- availability of completed trial reports – detailed trial findings are proactively disclosed
- academic publication – trial results are published in scientific journals
- individual participant data sharing – trial data are effectively shared for replication and reanalysis.

**The benefits of clinical trial transparency are broad.** Transparency allows public and expert scrutiny of the trial process to verify (and challenge where appropriate) original analyses and the conclusions of investigators. In addition, it ensures that relevant practices and regulations are adhered to. Transparency also minimises unnecessary research duplication through knowledge sharing.<sup>227</sup>

**Until recently, the methods and results of clinical trials that were documented in study protocols, full clinical study reports and individual participant-level datasets were not widely available.**<sup>228</sup> Vast improvements in the transparency of clinical trials have been made in recent years.<sup>229–233</sup>

**Recent data suggest that most clinical data used in support of regulatory approvals are now made available either proactively or in response to information requests.**<sup>234</sup> Despite these recent advances, there is significant room for improvement, particularly regarding individual participant data sharing.<sup>235,236</sup>

### Box 10 – Without access to clinical trial data, prescribers are unable to choose the best treatments for patients

Rofecoxib was approved in 1999 by the FDA, and shortly after in Europe by the EMA, as an alternative to non-steroidal anti-inflammatory drugs for the treatment of pain associated with osteoarthritis.<sup>237</sup> In 2004, after more than 80 million patients had taken the drug and annual revenues had surpassed \$2.5 billion, the drug was withdrawn from the market due to an increased risk of heart attacks.<sup>238–240</sup> An estimated 88,000 to 139,000 deaths were caused directly by taking rofecoxib in the US alone.<sup>241</sup> These deaths could have been avoided if the results of an earlier clinical trial were not withheld for commercial reasons.<sup>242</sup>

## Mandating clinical trial transparency: considerations for policymakers

Policymakers and drug regulatory agencies consider four main factors when considering clinical trial transparency policies:<sup>243</sup>

- **Protection of personal data.** Transparency measures must be balanced with the protection of personal data and compliance with relevant regional and national laws on data protection.
- **Protection of Commercially Confidential Information (CCI).** CCI consists of information that is not readily available in the public domain and whose publication might jeopardise the commercial interests of individuals or companies to an unreasonable degree.
- **Protection of regulatory decision-making.** Regulators have a legal mandate to evaluate medicines and should be protected against external pressures, so they are able to focus on science in the best interests of patients.
- **Ensuring future investment in pharmaceutical R&D.** Sustained and extensive R&D is a precondition for future improvements in public health. Clinical trial transparency should not negatively impact the incentives to invest in future pharmaceutical R&D.

## Generating evidence in clinical trials – summary

### Box 11 – Summary of key issues and trade-offs relating to clinical trials

- Data obtained in clinical trials are important in order to elicit the benefits and risks of new drugs before and after regulatory approval.
- Clinical trial data are also important in informing pricing, reimbursement and coverage decisions downstream of regulatory approval.
- Not all clinical trials are optimally designed and useful for decision-making.
- Randomisation, the use of clinical endpoints and the use of active comparators increase the validity, reliability and usefulness of data generated in clinical trials but can increase their cost due to the larger sample sizes and longer follow-up durations required.
- Cost should not be a barrier to achieving optimally designed clinical trials. Increased costs stemming from the design features of high-quality clinical trials can be mitigated in several ways to increase efficiency.
- Government policies can transform the data and clinical trial landscape to improve efficiency, benefiting both industry and health systems.
- Clinical trial transparency promotes public health and has improved substantially in recent years.
- The benefits of clinical trial transparency outweigh the risks. Measures are in place to ensure that patient data are anonymised and CCI is kept out of the public domain in a very limited number of cases where this is in the interests of patients and public health.

# Section 4 Regulatory review

## Section overview

Before new drugs are authorised to go on the market, drug regulatory agencies assess their benefits and risks. As gatekeepers to the pharmaceutical market, regulators are tasked with ensuring that the new drugs are safe and efficacious and that there is valid evidence on their benefits and harms. They must also balance this with timely market access to the new drugs. In this section, we describe the primary role of regulatory agencies in ensuring the safety and efficacy of drugs both before and after market entry. We also outline how regulatory agencies meet industry interests by developing programmes aimed at incentivising the development of new drugs, speeding up their review processes and introducing substantial flexibility in evidence standards through expedited pathways.



## The role of drug regulatory agencies

The role of drug regulatory agencies is threefold:

- 1 The primary role of drug regulatory agencies is to ensure that the benefits of drugs outweigh their risks.**<sup>244</sup> Regulatory agencies evaluate the benefit–risk profiles of new drugs based on data generated through mostly industry-sponsored clinical trials.
- 2 Regulatory agencies reduce informational asymmetry between pharmaceutical companies and physicians and patients.**<sup>245</sup> When a new drug enters the market, regulatory ‘labelling’ for prescribers and patients accompanies it, which summarises the essential information about the drug’s benefits and harms.
- 3 A changing role of drug regulatory agencies is to provide additional incentives for drug development.**<sup>246</sup> By the time a drug receives regulatory approval, its *effective* patent life is often reduced due to R&D. Regulatory agencies issue regulatory exclusivity and supplementary patent protection which extends beyond the market protection that patents afford, providing industry with additional incentives to invest in R&D.

### **Information generated in clinical trials is not always optimal for decision-making.**

When assessing new drugs, regulators are faced with a trade-off between rigorous scientific evidence and timely access to the drugs.<sup>247</sup> Confronted with high political pressure to ensure the latter, regulators have become increasingly more flexible in their evidence standards for approval and have introduced ‘expedited pathways’ to speed up approvals.<sup>248</sup> The implications of these measures to speed up the approval of new drugs are discussed in this Section.

## Box 12 – Overview of drug regulatory agencies

### Drug regulation in the US

The origins of modern drug regulation can be traced back to the US. The FDA was the first consumer protection agency that mandated manufacturers to demonstrate that new drugs were safe (1938) and efficacious (1962) before entering the market.<sup>249</sup> The clinical trial evidence requirements, in addition to the FDA's scientific evaluation of drug benefits and risks, formed the basis of modern drug regulation globally, with countries around the world having adopted similar regulations since.<sup>249</sup>

### Drug regulation in Europe

In 1995, the European Medicines Evaluation Agency (EMEA, later renamed the European Medicines Agency, EMA) was created to provide a single regulatory agency for the authorisation and supervision of medicinal products in Europe.<sup>250</sup> The modern drug approval system in Europe is based on a network of around 50 regulatory authorities from the 27 EU member states plus three countries of the European Economic Area (EEA) (Iceland, Liechtenstein and Norway), the European Commission and the EMA.<sup>251</sup>

### Brexit, the MHRA and the EMA

The MHRA is the drug regulatory agency in the UK. Before Brexit, it played an integral part in the EMA's collaborative scientific assessment as one of the leading scientific assessors, accounting for approximately a third of regulatory reviews.<sup>252</sup> Since the end of the transition period (post 31 December 2020), the MHRA has transitioned into an independent regulatory agency.

## Objective 1: Ensuring drug efficacy and safety

**During regulatory assessment of new drugs, it is the role of the manufacturer to provide information on drug efficacy and safety to a regulator for approval.** The manufacturer submits comprehensive information relating not only to clinical trials, but also to how the drug is manufactured, non-clinical data and all other information relating to its benefit–risk profile. International standards (eg, ICH guidelines) and codes of practice (eg, Good Clinical Practice [GCP] and Good Manufacturing Practice [GMP]) govern the technical requirements for approval.

**Drug regulatory agencies assess the evidence that manufacturers submit to ensure drug benefits outweigh known harms.** The statutory mandate of regulatory agencies is to evaluate a drug's benefit–risk balance (often against a placebo) and not its comparative benefits and harms against existing treatments.<sup>215,253,254</sup>

**When assessing new drugs, drug regulatory agencies are faced with a trade-off between requiring rigorous scientific evidence and granting early access to new drugs.** Generating data that reduce uncertainty about the benefits and harms of new drugs at approval can be time-consuming.<sup>255,256</sup>

**Regulators face increasing pressure from industry and some patient organisations to expedite the development, review and approval of new drugs.**<sup>257</sup> As a result, several expedited pathways have emerged over the past few decades, leading to shorter clinical development and review times.<sup>258</sup>

**Regulators have become increasingly more flexible in their evidence standards.**<sup>259</sup> Over the past three decades, evidence from the US shows that the proportion of drug approvals supported by at least two late-stage clinical trials has declined from 81 per cent to 53 per cent.<sup>260</sup> Evidence standards in Europe closely parallel those in the US.<sup>261</sup>

**Evidence standards for new drugs that are approved through 'expedited pathways' result in greater uncertainty about the drugs' benefits.**<sup>262</sup> Expedited drugs enter the market based on fewer, smaller and/or earlier-stage clinical trials than non-expedited drugs.<sup>248,260</sup> Such clinical trials may not be informative for decision-making.

**The role of regulatory agencies in ensuring drug efficacy and safety also extends to the post-approval period:**

- At the time of marketing authorisation, evidence of safety and efficacy is limited to data gained from a small number of clinical trials.<sup>170</sup> Therefore, patient exposure to new drugs around approval is limited to a relatively small selection of patients for a limited length of time.
- Wider and prolonged patient exposure to new drugs in post-approval studies often provides additional information on safety. Approximately a third of new drugs that the FDA approved between 2001 and 2010 were affected by post-approval safety events.<sup>171</sup> Several regulatory mechanisms exist to ensure that any safety signals are detected in a timely manner.<sup>263</sup>
- Regulators may require post-approval studies as a condition of market entry to clarify uncertainty about the effectiveness of new drugs. For example, post-approval studies in the US are sometimes used to address issues including optimal dosing schedules, long-term safety and use in children.<sup>264</sup> However, many of these studies are often delayed or remain incomplete even years after drug approval.<sup>264,265</sup>

### Box 13 – Evidence standards for generic and biosimilar approvals

Generic drugs and biosimilars offer high value for money for health systems. Regulatory agencies in Europe and the US incentivise the development of generics and biosimilars through designated ‘abbreviated’ (US) or ‘abridged’ (EU) regulatory approval pathways.

For generic drugs and biosimilars, regulatory agencies do not require the manufacturer to include pre-clinical or clinical data to establish the safety and efficacy of the products. Instead, manufacturers are able to demonstrate ‘bioequivalence’, or ‘biosimilarity’ (for biosimilars), to a reference (originator) product, demonstrating that there is no clinically meaningful difference in composition. This is intended to lower entry barriers for generic and biosimilar manufactures and facilitates greater market competition post patent expiry.

## Objective 2: Reducing informational asymmetry

**Without access to clinical trial data, prescribers and patients lack the information necessary to determine the benefits and risks of new drugs.** In contrast,

pharmaceutical companies have good knowledge of the benefits and risks from clinical trial data. Regulatory agencies play a key role in reducing this informational asymmetry, allowing prescribers to make the best-informed decisions for patients and to maximise technical efficiency in health care systems by promoting the use of effective new drugs.<sup>245</sup>

**Drug regulatory agencies disclose the scientific conclusions of assessments and the grounds on which regulatory decisions are made.** Public disclosure of information regarding the regulatory assessment procedure helps establish trust in the credibility of the drug evaluation process – and certifies drug quality.<sup>266</sup>

**When a new drug enters the market, it is accompanied by ‘labelling’ for prescribers and patients.** The labelling summarises the therapeutic indications of the drug (ie, the population and use of the drug for which the marketing authorisation is intended), as well as the characteristics and results of clinical trials that form the basis of regulatory decisions.

**After a drug is approved, regulators can also provide information in the form of ‘medicine safety advisories’.** These advisories warn prescribers and the public about the risks of approved prescription drugs.<sup>267</sup>

## Objective 3: Mitigating the unintended consequences of regulation for innovation and access

Historically, requirements to test the safety and efficacy of new drugs in rigorous clinical trials had important consequences for drug R&D:

- The costs of R&D increased because of regulatory evidence requirements for the testing of new drugs in more rigorous clinical trials.
- The duration of clinical development increased, resulting in a reduced *effective* patent term and thus shortening the monopoly period during which companies charge *higher-than-competitive prices*.

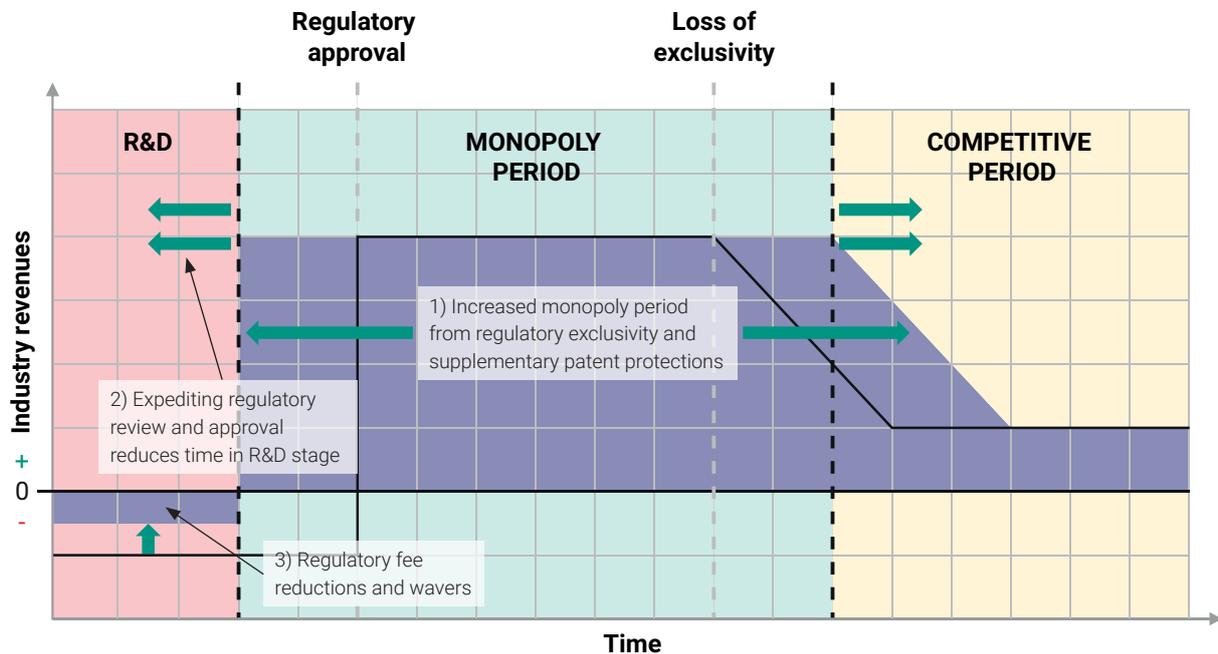
Government intervention and policies have sought to balance more stringent drug regulation with industry's interests in sustaining profitable drug development.

## How do regulatory agencies provide additional incentives for innovation?

To incentivise industry's drug development, policy interventions in recent decades have focused on mitigating the potential adverse consequences of regulation for drug development.<sup>246</sup> These interventions effectively decreased the costs of clinical development and increased the anticipated revenues for pharmaceutical companies in a number of ways (**Figure 6**), by:

- extending the monopoly period to account for the loss in patent protection
- expediting the development, review and approval of new drugs
- introducing reductions or waivers of regulatory fees and assistance with regulatory submissions (eg, early engagement with industry and scientific advice).

**Figure 6 – Influence of regulatory incentives on costs and returns on pharmaceutical R&D**



**Notes:** (1) Drug regulators can issue additional protections and regulatory exclusivities, which increase the duration of the monopoly period. (2) Expediting the development, review and approval of new drugs reduces the time taken to conduct R&D and receive regulatory approval. (3) Reductions or waivers in regulatory fees reduce initial costs.

**Source:** Adapted with permission from Khullar *et al.* (2020)<sup>1</sup>

## Extending the monopoly period

**An overlapping legal framework involving patents, supplementary patent protection and regulatory exclusivity has emerged to restore the patent life lost during the clinical development of new drugs.**<sup>113</sup> Patents and regulatory exclusivity work in similar ways but are governed by different laws, and issued by different bodies.

- **Patents** are an intellectual property protection that a national patent office grants at any time during R&D and can include a wide range of claims. Patents can be issued or expire at any time, regardless of the drug's approval status, and are recognised internationally (see Section 2).
- **Supplementary Protection Certificates (SPCs, EU) or Patent Term Extensions (PTEs, US)** are extensions to the intellectual property rights afforded by patents. Drug regulatory agencies issue them around, or after, the time of approval and they apply only in the country (or countries) within the remit of each regulatory agency.
- **Regulatory exclusivity** refers to protection from competition that drug regulatory agencies grant, which prohibits or delays the regulatory approval and market entry of competitor drugs. The main benefit of regulatory exclusivity is that the protection it provides begins when a new product is approved. Regulatory exclusivities also apply only in the country (or countries) within the remit of each regulatory agency.

**Patents and exclusivity are applied to new drugs in different ways.** Patents are issued during R&D and can expire at any time, regardless of the drug's approval status. In comparison, regulatory exclusivity is awarded upon approval. Patents and regulatory exclusivity may or may not run concurrently and sometimes may or may not cover the same aspects of the drug product.

**Regulatory exclusivity provides drug manufacturers with a defined period of protection from generic (or biosimilar) competition.** In **Box 13**, we outlined how generic manufacturers are required only to demonstrate bioequivalence to originator drugs for regulatory approval. Market exclusivity entitles the pharmaceutical company exclusive rights to the results of pre-clinical tests and clinical trials on its drug. During the period of market exclusivity, generic manufacturers cannot refer to these data for the regulatory approval of their products, preventing generic competition.

**Drug regulatory agencies can issue exclusivity for certain drugs, disease areas, populations or regulatory procedures.** Applications for regulatory exclusivity include exclusivity awarded for the development of novel drugs,<sup>268,269</sup> for rare (orphan) diseases,<sup>270,271</sup> to treat unmet medical needs,<sup>269</sup> for paediatric indications<sup>272</sup> or to incentivise the repurposing and extension of the use of existing drugs in new therapy areas.

**Patents and regulatory exclusivity afford manufacturers of most new drugs around 13 to 14 years of market exclusivity (monopoly) periods, and some even longer.**<sup>273</sup> Dolutegravir (Tivicay®) is an illustrative example. Dolutegravir's patent was first filed in 2006.<sup>274</sup> The drug received EMA approval for the first-line treatment of HIV eight years later, in 2014.<sup>275</sup> This means that the drug could benefit from 12 years of effective patent life post-approval (until 2026). In addition, the manufacturer ViiV Healthcare has obtained additional three-year SPCs in several European countries (eight years until approval minus five years), meaning that total exclusivity afforded by the original patent and SPC accounts for 15 years of exclusivity post-approval, and will last until 2029.

## Expediting the development, review and approval of new drugs

In recent years, drug regulators have developed several ‘expedited’ pathways to speed up the approval of new drugs.<sup>276</sup> These so-called ‘expedited’ programmes utilise three underlying mechanisms to increase access:<sup>277</sup>

- **Speeding up regulatory review processes** – regulators in the US and Europe are now mandated to adhere to strict performance goals for reviewing new drugs within a pre-specified timeframe.
- **Increasing the flexibility of evidence standards** – this is to shorten the duration of clinical development by accepting less complete data than traditionally required to support the approval of drugs targeting unmet medical need in serious, and often life-threatening, conditions.
- **Shifting evidence generation to the post-approval period** – regulators can in some cases require the completion of additional studies during the post-approval period to demonstrate and confirm the hypothesised clinical benefit of new drugs that enter the market on the basis of limited data.

### Box 14 – The pharmaceutical industry pays for regulatory assessment of its products through ‘user fees’

Regulators in the US and Europe now rely on ‘user fees’ from pharmaceutical companies, intended to increase staffing levels and speed up approvals. The pharmaceutical industry now pays 75 per cent of the costs of scientific review in the US.<sup>278</sup> In Europe, industry user fees and charges fund more than 85 per cent of the EMA’s budget. Following the introduction of user fees, regulatory review times declined from more than two-and-a-half years in the 1980s, to approximately a year in most recent years.<sup>248</sup> User fees have become more complex, with discounts or waivers to encourage industry investment in certain disease areas.<sup>279</sup>

Companies developing drugs for certain diseases are eligible for reductions or waivers in regulatory ‘user fees’. Companies in Europe benefit from multiple ‘orphan incentives’ for developing drugs for rare diseases, including reduced fees for protocol assistance, fee reduction grants and other additional incentives for small- and medium-sized enterprises.<sup>271</sup> In the US, companies receive waivers for drug application fees and vouchers for shortened regulatory review times when investing in rare diseases, even with limited evidence of clinical effectiveness.<sup>280,281</sup>

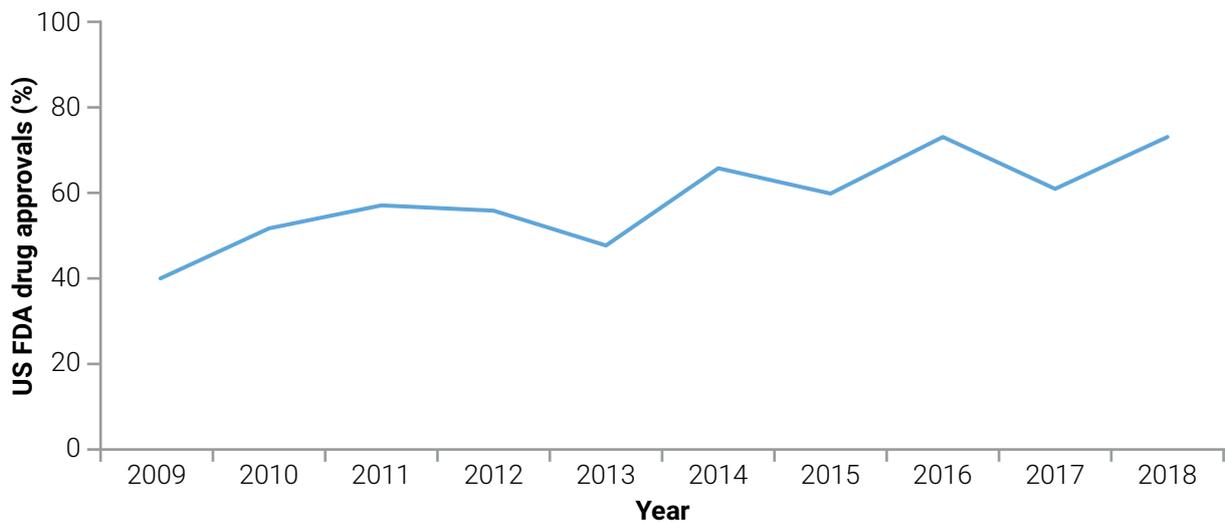
**Several different expedited approval pathways are available, with different aims, eligibilities and associated rewards.** In the US, there are four such expedited programmes: Fast Track Approval (1987), Accelerated Approval (1992), Priority Review (1992) and Breakthrough Therapy Designation (2012).<sup>282</sup> In Europe, the EMA has three such programmes: Accelerated Assessment (2006), Conditional Marketing Authorisation (2006) and PRiority MEDicines (PRIME) Designation (2016) (**Table 1**).<sup>283–285</sup>

**Table 1 – Expedited programmes in the EU**

<b>Accelerated Assessment (2006)</b> <sup>286</sup>	Products that are of “major interest for public health and therapeutic innovation” may be eligible for accelerated assessment, which can reduce the timeframe for approval down to 150 days (the standard centralised procedure takes around 210 days). There is no single definition of what may be considered a ‘major public health interest’.
<b>Conditional Marketing Authorisation (2006)</b> <sup>287</sup>	New drugs may be granted a conditional marketing authorisation on the basis of less comprehensive clinical data than is normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required.  Drugs are eligible if they are intended for treating, preventing or diagnosing seriously debilitating or life-threatening diseases. This includes orphan medicines and those for a public health emergency (eg, during a pandemic). Conditional marketing authorisations have obligations to conduct additional studies, which must be fulfilled within defined timelines.
<b>PRIME Designation (2016)</b>	A PRIME Designation is granted during clinical development for drugs that address an unmet medical need. The scheme promotes confidential, early interaction and dialogue with pharmaceutical companies to support and optimise the generation of robust data on a drug’s benefits and risks.

**Over time, the popularity of expedited development and approval pathways has expanded greatly (Figure 7).** These expedited development, review and approval pathways have also substantially changed the way regulators approve new drugs. As intended, drugs that benefit from these pathways have shorter clinical development times than other drugs.<sup>258</sup>

**Figure 7 – Proportion of US FDA drug approvals in at least one expedited programme, 2009 to 2018**



Source: Naci *et al.* (2020)<sup>215</sup>

**Only a minority of drugs benefiting from expedited pathways offer meaningful therapeutic benefits to patients.**<sup>288</sup> Fewer than a third of all new drugs that the FDA and EMA approved under these expedited regulatory pathways were rated as having ‘high’ therapeutic value (ie, provide moderate or better improvement in patient outcomes than already approved drugs).<sup>289</sup>

**Speeding up the regulatory review process, increasing the flexibility of evidence standards and shifting evidence generation to the post-approval period lower the barriers to market entry.** However, these regulatory incentives may not always be in the best interests of patients (**Box 15**).

### Box 15 – Industry responds strongly to regulatory incentives

Regulatory incentives aim to reduce the cost or risk of clinical development for industry, or increase revenues. As expected, evidence suggests that industry responds strongly to these regulatory incentives:

- ‘Orphan incentives’ have been successful in promoting research in rare diseases.<sup>290</sup>
- In the years 2018 to 2020, more than half of all new drugs were for rare diseases.<sup>291–293</sup>
- Implementation of the ‘Breakthrough Therapy Designation’ in the US, which introduced substantial flexibility in regulatory evidence standards for so-called ‘precision’ medicines, has led to an increased number of new products entering early-stage trials.<sup>294</sup>

## Box 15 – Industry responds strongly to regulatory incentives (continued)

However, there are trade-offs and unintended consequences to be considered when relying on regulatory incentives to foster drug development. There is growing concern regarding the nature of R&D that the current set of regulatory incentives fosters and whether they have led to new treatments that meaningfully benefit patients.<sup>295</sup>

- Companies benefiting from regulatory incentives often avoid conducting robust clinical trials and rely on less-meaningful trial endpoints, raising concerns about the validity of the data supporting the safety and efficacy of new drugs.<sup>262,296,297</sup>
- Pharmaceutical firms are able to obtain an orphan drug designation, and benefit from market exclusivity (and therefore monopoly prices), in several indications for the same drug simultaneously.<sup>298</sup>
- In an earlier review, drugs that received the FDA's Breakthrough Therapy Designation did not outperform other drugs approved during the same period on similar trial endpoints.<sup>299</sup>

**Shifting evidence generation to the post-approval period has not reduced uncertainty following market entry.** Regulatory requirements offer no economic reward for companies to conduct clinical trials during the post-approval period.<sup>300</sup> Consequently, clinical trial obligations often remain unfulfilled several years after initial regulatory approval.<sup>265,301</sup>

## The increasing role of patients in drug regulation

**Over the past few decades, patient advocacy groups have become major political actors in drug regulation.**<sup>302</sup> The EMA defines patient organisations as “not-for-profit organisations which are patient focused”.<sup>303</sup>

**Patients play an integral role in regulatory approval processes.** Organised patient groups represent patient interests and values on management boards, scientific committees, expert groups and working parties of regulatory agencies. Patient groups also campaign effectively for faster access to new drugs, often strengthening the case for the use of expedited drug approval pathways.<sup>257</sup>

**There may be potential conflicts of interest between industry and patient organisations.** Conflicts of interest arise when an organisation's own financial interests or the interests of its senior members pose risks to the integrity of the organisation's primary interests and missions.<sup>304</sup> These conflicts of interest are relevant when advocacy organisations campaign for the approval of drugs that sponsoring companies have developed (**Box 16**).

## Box 16 – Industry funding of patient groups

Industry funding of patient groups is common. A recent study of 104 US-based patient-advocacy organisations with annual revenues of at least \$7.5 million showed that:<sup>305</sup>

- 83 per cent of the largest patient organisations received funding from pharmaceutical, biotechnology or medical device companies
- 39 per cent had a current or former industry executive on their management board, with at least 12 per cent in a leadership position on the board
- only 12 per cent had published policies in place for managing conflicts of interest.

A recent study from the UK identified 4,572 payments worth more than £57 million, between 2012 and 2016, to patient organisations.<sup>306</sup>

- Of all identified patient organisations, 85 per cent of them received these payments.
- The largest 10 pharmaceutical companies provided almost 70 per cent of payments.
- Company payments consistently prioritised patient groups relevant to recently launched, highly priced drugs in the UK (for cancer, diabetes, hepatitis C and HIV/AIDS).

## Regulatory review – summary

### Box 17 – Summary of key issues and trade-offs relating to regulatory review

- Drug regulatory agencies serve three main functions:
  - regulating drug safety and efficacy, pre- and post-approval – the quantity and quality of evidence generated in clinical trials underpin the accurate measurement of the benefit–risk profile of a drug
  - reducing the informational asymmetry between physicians/patients and industry
  - providing additional incentives for industry to foster R&D.
- Regulatory incentives now define the minimum bound of new drugs' competition-free periods following market entry. In some cases, this additional form of protection can last for substantial periods of time post-approval, helping industry maximise revenues during the monopoly protection period.
- Expedited pathways aim to speed up the review process, increase the flexibility of evidence standards and shift evidence generation to the post-approval period. These approaches satisfy industry interests by reducing the cost and risk of drug development but may not always be in the best interests of patients.
- Although expedited pathways achieve shorter clinical development periods and faster review times, many of the qualifying drugs are associated with higher uncertainty.
- Uncertainty of effectiveness complicates decision-making in clinical practice, as well as pricing and reimbursement decisions downstream of regulatory approval.

# Section 5 Pricing and reimbursement

## Section overview

High drug prices are a key driver of pharmaceutical spending. In this section, we first outline the economic rationale for regulating prices in the pharmaceutical sector. We then discuss the aims of pricing regulation and the tools available to policymakers to meet these aims. We pay particular attention to aligning the price of drugs with the value they provide using Health Technology Assessment.



## Issues in pricing and reimbursement

**High drug prices are a key determinant of pharmaceutical expenditure, which now accounts for about 15 per cent of net health expenditure in OECD countries.** High prices of on-patent drugs, sustained by monopoly protection, account for most of pharmaceutical spending.<sup>115,307,308</sup> In most high-income countries, almost 80 per cent of pharmaceutical spending is on patented drugs, which account for less than 20 per cent of all dispensed prescriptions.<sup>116</sup> High drug prices have become a growing concern for policymakers.<sup>248</sup>

**New drugs are increasingly being priced at high levels.**<sup>31</sup> The past decade has seen an increasing number of highly priced drugs. In 2020, the ‘world’s most expensive drug’, Zolgensma, a gene therapy to treat a rare genetic disorder, was approved in the US with a list price of \$2.1 million (equivalent to £1.7 million in 2020) for a one-off treatment.<sup>309</sup>

**There is growing concern that manufacturer-set prices are not always aligned with drug benefits.**<sup>310–312</sup> Several studies found no association between company-set prices and the clinical benefits of new drugs, even in settings with pricing regulation.<sup>313,314</sup>

**Equitable access to essential medicines has been deemed a fundamental human right.**<sup>315</sup> But achieving access to essential medicines means providing access to new and existing drugs at ‘fair’ prices, while maintaining the financial incentives to ensure that medicines are developed for the future.<sup>316–318</sup> Pricing drugs at the level of production costs would stifle industry’s investment in pharmaceutical R&D. Identifying the optimal price is empirically – and politically – challenging.

## The health opportunity cost of paying high drug prices

**Paying for new highly priced drugs can come at a high health opportunity cost.** In a fixed-budget health system, the health opportunity cost is the health lost as a result of the displacement of existing health care services.<sup>33</sup>

**If drug prices are not commensurate with their benefits, forgone health from displaced interventions may outweigh new drugs’ benefits.**<sup>310,319,320</sup> If this is the case, the reimbursement and coverage of new, high-cost on-patent drugs may be health reducing rather than health enhancing at the population level.<sup>2</sup>

**Benchmarking the costs and benefits of new drugs against other treatments across the health system is required to ensure paying for new drugs represents value for money.** Most high-income countries rely on Health Technology Assessment (HTA) to determine the value of a new drug in the health system. HTA, in theory, helps to align the price of new drugs with their clinical benefit (either directly or indirectly).

## Tension between health system and industry interests in drug pricing

**Pharmaceutical companies have an obligation to shareholders to maximise profits.**

To do so, pharmaceutical companies have an interest in charging higher-than-competitive prices during the monopoly period and, where possible, extending the monopoly period. In contrast, governments seek to contain costs by regulating drug prices (where possible) and/or promoting competition while ensuring incentives are sufficient to sustain investment in R&D.

**From the health system perspective, pricing regulation aims to balance the optimal use of funding on existing drugs and other treatments to minimise the opportunity cost of foregone treatments.** Pharmaceutical companies often argue that lowering drug prices would harm future innovation. However, the relationship between drug price and drug development is complex (**Box 18**).

**Evidence suggests that high drug prices are not necessary to sustain meaningful pharmaceutical innovation that meets medical need.** Although there is a link between drug prices and company revenues, and between revenues and R&D spending, much of the increased R&D spending due to higher revenues is duplicative and targets crowded therapeutic areas, with diminishing health returns.<sup>36,37,87,93,321</sup> There is no evidence to suggest that lower drug prices would reduce the development of drugs that offer major therapeutic benefits over existing alternatives (**Box 18**).

### Box 18 – What is the association between pricing regulation and drug development?

Several studies have shown that pricing regulation reduces pharmaceutical industry revenues.<sup>322–324</sup> This is notable in large markets like the US, which have substantially higher prices than other countries.<sup>74,322</sup>

As we outlined in Section 2, expectations of future profits drive industry R&D practices. Indeed, several studies have shown that growth in market size and potential profits (especially in the US) has a strong impact on R&D activity.<sup>73–80</sup> As expected, evidence also suggests that R&D spending is correlated with drug prices.<sup>325</sup>

However, in the past, increased R&D spending has not always yielded clinically meaningful innovation. Much of the increased spending has been directed at ‘me-too’ drugs and diseases that already have multiple effective treatment options or towards techniques that are not novel.<sup>35–37,93</sup>

## Box 18 – What is the association between pricing regulation and drug development? (continued)

In the future, lower industry revenues due to lower drug prices would likely reduce R&D activity. According to an analysis by the US Congressional Budget Office, a 15 to 25 per cent reduction in expected returns for the highest revenue-earning drugs in the US would reduce the number of new drugs entering the market by approximately 0.5 per cent in the first decade, and by 8 per cent in the third decade.<sup>326</sup> These estimates are broadly aligned with those obtained from a meta-analysis of studies evaluating the relationship between industry revenues and the quantity of drug development.<sup>82</sup>

However, reduced R&D activity need not harm the development of drugs with meaningful clinical benefits for patients. Given that more than two-thirds of new drug approvals do not offer added therapeutic benefits over existing alternatives, a small reduction in the number of new drugs may be an acceptable trade-off.<sup>12,289</sup> Also, any adverse consequences of reduced industry investment in R&D could, in theory, be offset by greater investment in public sector research institutions, which are primarily responsible for early-stage research on drugs that lead to a step-change in patient outcomes.<sup>327</sup>

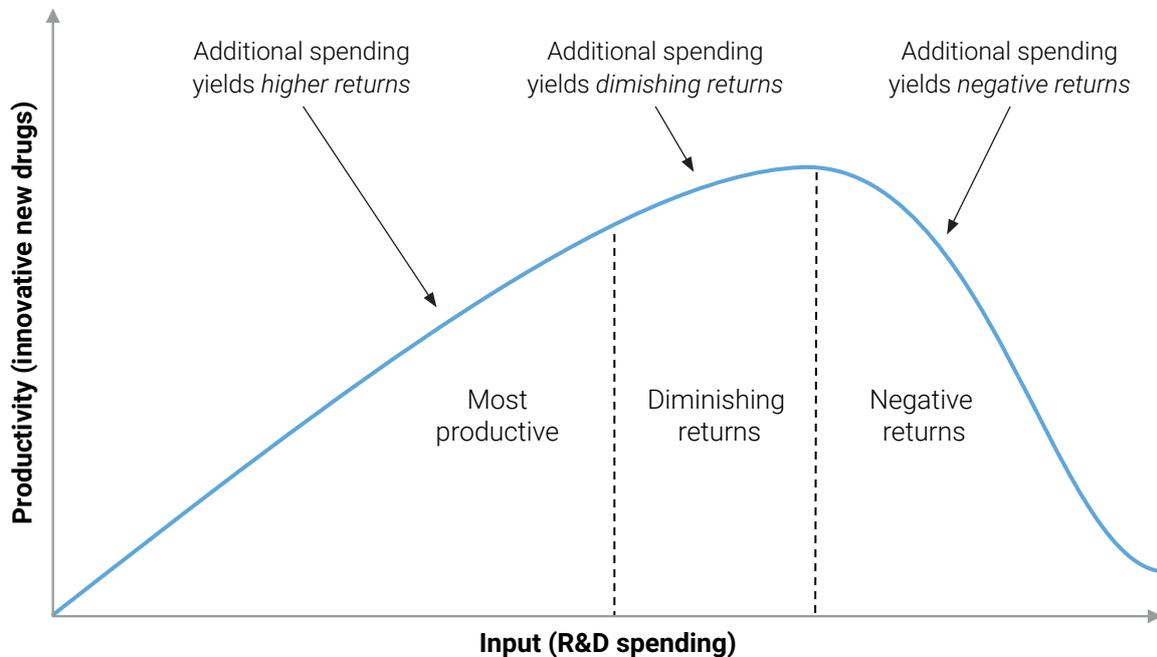
### Diminishing returns on R&D

In economics, as the law of diminishing returns suggests, beyond a certain point, increasing R&D will yield a lower output per incremental unit of input (ie, fewer drugs that offer meaningful therapeutic benefits for patients). At some point, the benefits from additional resources into R&D may no longer justify the cost to society in the form of high prices and money may be better spent elsewhere in the health system (**Figure 8**).<sup>328</sup>

Empirical evidence demonstrates this phenomenon in the market for cancer drugs. A large expansion of prescription drug insurance coverage in the US, which mandated the formulary inclusion of all cancer drugs, was associated with an increase in the number of new cancer drug approvals.<sup>321</sup> However, these newly approved cancer drugs offered fewer clinical benefits over existing alternatives than their predecessors.<sup>321</sup> These findings suggest that there are diminishing returns to health from increased pharmaceutical R&D.

## Box 18 – What is the association between pricing regulation and drug development? (continued)

**Figure 8 – Diminishing returns on pharmaceutical R&D**



### Unintended consequences of pricing regulation

Use of price regulation as a blunt tool for cost containment does not account for the clinical benefit and value of new drugs and may have unintended consequences. For example, companies may cut back on their more novel R&D activity to prioritise areas that generate greater profits. Companies may also increase their sales and marketing spending to fuel demand for their products and maximise revenues in the short term. As we outline in our second report in this series of reports on pharmaceutical policy, *Design Principles for a Coherent Pharmaceutical System*, paying for value, as defined by the system-wide health opportunity cost, would incentivise companies to prioritise meaningful innovation.

## Rationale for regulating prices in the pharmaceutical industry

**As we outlined in Box 1, the market for pharmaceuticals is imperfect in several ways, which, if unregulated, can lead to high drug prices.**

- **Competition usually leads to lower prices.** In the pharmaceutical sector, intellectual property protection and government-granted market exclusivity reduce competition between on-patent drugs. During this period, the availability of multiple similar therapies (eg, from the same product class) does not lower prices.<sup>329–331</sup> High barriers to entry further reduce the number of substitutable products and sellers.
- **Imperfect information on the effectiveness of new drugs at the time of approval can further limit the price-decreasing effects of competition.** This limits the ability of payers and other decision-makers to differentiate between competing products.<sup>332</sup>
- **Third-party payers** (social health insurance, private health insurance or tax-based health system coverage) largely shield patients and physicians from high prices, indirectly incentivising companies to charge higher prices in unregulated markets.

## Price regulation for on-patent pharmaceuticals

**High drug prices are not a necessary precursor to innovation.** Drug price regulation: (1) aims to ensure an optimal allocation of health care resources to existing pharmaceutical products to minimise the opportunity cost of foregone treatments (static efficiency); while (2) ensuring adequate incentives for future innovation (dynamic efficiency).

**The oft-cited dichotomy between static and dynamic efficiency is more nuanced than what is often portrayed in policy debates.** Industry asserts that regulation aimed at lowering drug prices would stifle pharmaceutical innovation. However, the trade-off between static and dynamic efficiency does not mean that patients and health systems need to forgo health benefits today, to potentially benefit from treatments in years to come. Indeed, pricing regulation aims to identify the optimal price that strikes a balance between the efficient allocation of resources today and incentivising R&D for the future. It is also important to note that, as we outlined previously in Sections 2 and 4, a number of additional effective incentives – beyond pricing – exist to sustain pharmaceutical innovation.

**Variation exists in the prices paid for prescription drugs and how these prices are achieved between countries.**<sup>333</sup> One recent study shows that in 2018, US drug 'list' prices were 256 per cent of those in 32 comparison countries combined.<sup>334</sup> List prices for 20 top-selling drugs were on average three times higher in the US compared with the UK, although these may not reflect the actual prices that health systems paid for them.<sup>335</sup> These vast differences in pricing are the result of a lack of coordinated pricing regulation in the US, among other factors (**Box 19**).

### **Box 19 – Market structure and a lack of drug pricing regulation in the US lead to high drug prices**

Almost half of pharmaceutical expenditure in the US is for the most expensive drugs, which correspond to only 2 per cent of prescriptions.<sup>116</sup>

Drug prices are high in the US due to a number of factors:

- protection from competition (afforded by patents and regulatory exclusivity)
- a fragmented payer landscape, with limited ability to collectively negotiate drug prices
- market failures associated with a private insurance-based health system
- legislation limiting some of the largest public payers to effectively negotiate drug prices, resulting in a system-level high willingness to pay for new drugs.<sup>115</sup>

In the US, pharmaceutical companies can set their own prices and charge 'what the market will bear' for new drugs.<sup>115,336,337</sup> A fragmented health insurance landscape leads to several different payers for drugs (individual insurance exchanges, private insurers and government-funded insurance programmes).<sup>333</sup> This decentralised process for drug coverage, and in addition, coverage mandates, reduce the ability of payers to leverage their collective purchasing power and negotiate lower drug prices. The latest pricing reforms due to be implemented as part of the Inflation Reduction Act 2022 are narrow in scope, as they allow Medicare, the single largest purchaser of drugs in the US, to directly negotiate prices for a relatively small number of highly priced drugs.<sup>338</sup>

Outside of the US, payers employ several different strategies to assess the clinical and economic value of new drugs and regulate on-patent drug prices (**Table 2**).

**Payers' willingness to pay more for drugs in selected therapeutic areas can affect industry R&D investment.** Cancer is now the single largest category of drugs in development. This partly reflects payers' willingness to pay higher prices for cancer drugs. For example, federal legislation in the US stipulates mandatory insurance coverage of many new highly priced cancer drugs.<sup>339</sup> In the UK, the Cancer Drugs Fund was originally set up in 2010 as a 'special fund' for cancer drugs that were yet to be appraised, were under appraisal or were not recommended by the National Institute for Health and Care Excellence (NICE). As we outline in our third report in this series of reports on pharmaceutical policy, *Pharmaceutical Policy in the UK*, the fund has since been reformed.<sup>340,341</sup>

**Table 2 – Strategies available to payers for regulating expenditure on pharmaceuticals**

<b>1)</b>	<b>Main pricing and reimbursement strategies</b>
	HTA:
	1a) Comparative clinical benefit assessment
	1b) Comparative clinical benefit assessment with economic evaluation
<b>2)</b>	<b>Supplementary pricing and reimbursement strategies</b>
	Internal reference pricing (IRP)
	External reference pricing (ERP)
	Other approaches to contain pharmaceutical expenditure:
	• budgets and expenditure caps

**Note:** Often countries use several of these strategies in combination.

## Health Technology Assessment (value-based approaches)

**An underlying principle of most pricing regulation in recent years is Health Technology Assessment (HTA). Many definitions exist for different forms of HTA.**<sup>342</sup>

In simple terms, HTA is the multidisciplinary evaluation of the clinical effectiveness and/or cost-effectiveness and/or social and ethical impact of a health technology (eg, a new drug) for the lives of patients and the health care system.<sup>343</sup> HTA is often used to influence pricing and reimbursement decisions by considering the clinical and economic evidence to determine which new drugs to reimburse, and at what price.<sup>344,345</sup> In the past two decades, HTA has become a commonly used tool for policymakers.

**In the context of HTA, the 'value' of a pharmaceutical product is multidimensional.**

In addition to assessing the clinical (and sometimes cost-) effectiveness and safety of new drugs, HTA also considers the broader organisational, legal and ethical implications of adopting new health technologies within a health system.<sup>346</sup>

**Key steps of HTA include:**

- 1 A systematic review of the clinical (and often economic) evidence supporting a drug's potential use.
- 2 Scientific assessment of the evidence.
- 3 Independent appraisal of the evidence.
- 4 Evidence-based recommendations.

**Comparative clinical benefit assessment (HTA)**

**Some countries primarily consider the comparative clinical effectiveness of new drugs (eg, France and Germany) (Box 20).**<sup>347</sup> Comparative clinical effectiveness refers to the ability of an intervention to provide the desired clinical outcome(s) in the relevant patient population relative to an alternative treatment.<sup>348</sup> In many cases, it can also be combined with other supplementary pricing techniques such as internal reference pricing (discussed below).

**Box 20 – Use of comparative clinical effectiveness in France**

In France, the *Commission de la Transparence* (Transparency Commission) reviews the comparative clinical benefit of new drugs compared with existing drugs to inform pricing and reimbursement decisions. Comparative clinical effectiveness analysis in France is based on three main principles.<sup>349</sup>

**The medical benefit rendered, or 'service medical rendu' (SMR)**

The SMR represents the clinical value of the medicine and can be in one of four categories (**Table 3**). The SMR takes into account severity of disease, clinical efficacy and safety, aim of the drug (preventative, symptomatic or curative), therapeutic strategy and impact on public health. The SMR is a key driver for the reimbursement rate (coverage).

**The additional medical benefit rendered, or 'amelioration du service medical rendu' (ASMR)**

Additional benefits that the new drug provides over existing alternatives are then ranked in five levels (**Table 3**). Disease severity and other social value judgements are taken into consideration during this appraisal. ASMR forms the *comparative* part of the HTA and is a key driver of prices, which are negotiated between the manufacturer and the *Comité Economique des Produits de Santé* (CEPS) (Economic Committee for Health Products).

## Box 20 – Use of comparative clinical effectiveness in France (continued)

### Internal price referencing to inform pricing and reimbursement

Price negotiations are informed by the cost of existing drugs according to their SMR and ASMR (**Table 3**). This is a form of internal reference pricing, discussed below.

**Table 3 – Commission de la Transparence decision criteria**

Medical benefit rendered ( <i>service medical rendu</i> )	Additional medical benefit rendered ( <i>amelioration du service medical rendu</i> )	Reimbursement rate (coverage/volume)	Internal reference pricing
Insufficient	V: no improvement	None	Lower than comparator
Mild	IV: minor improvement	15%	At comparator price
Moderate	III: moderate improvement	30%	Negotiated, taking into consideration external prices
Important	II: important improvement	65 to 100%	
	I: major improvement		

### Impact of comparative clinical benefit assessment

The vast majority of medicines (eg, 74 per cent in 2016) that the *Commission de la Transparence* assesses have ‘important’ medical benefit. However, more than half of medicines assessed provide ‘no improvement’ over the best alternative existing treatments.<sup>350</sup> The use of HTA and comparative clinical benefit assessment is therefore key to ensuring that prices paid are reflective of the key clinical value of new drugs.

In France, the price of drugs that provide additional clinical benefit is limited to a maximum price charged in a ‘basket’ of other countries. External price referencing is discussed below.

## Comparative clinical benefit assessment with economic evaluation (HTA)

**Other countries consider both the comparative clinical effectiveness and cost-effectiveness of a new intervention (eg, Canada, the Netherlands, Sweden and the UK).** Cost-effectiveness refers to the effectiveness of two or more treatments relative to their costs. The incremental cost per unit of effect can then be calculated and compared between the two interventions to determine which is more cost-effective (**Box 21**).

### Box 21. Fundamentals of comparative clinical effectiveness and cost-effectiveness (economic evaluation)

#### Incremental cost-effectiveness ratio (ICER)

An incremental cost-effectiveness ratio (ICER) is a summary measure representing the economic value of an intervention compared with an alternative (comparator). It is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect), to provide a ratio of 'extra cost per extra unit of health effect'.<sup>351</sup>

$$\text{ICER} = \frac{[\text{Cost (B)} - \text{Cost (A)}]}{[\text{Effect (B)} - \text{Effect (A)}]} \quad \text{Or} \quad \frac{\text{Difference in Costs}}{\text{Difference in Effects}}$$

#### Quality-adjusted life year (QALY)

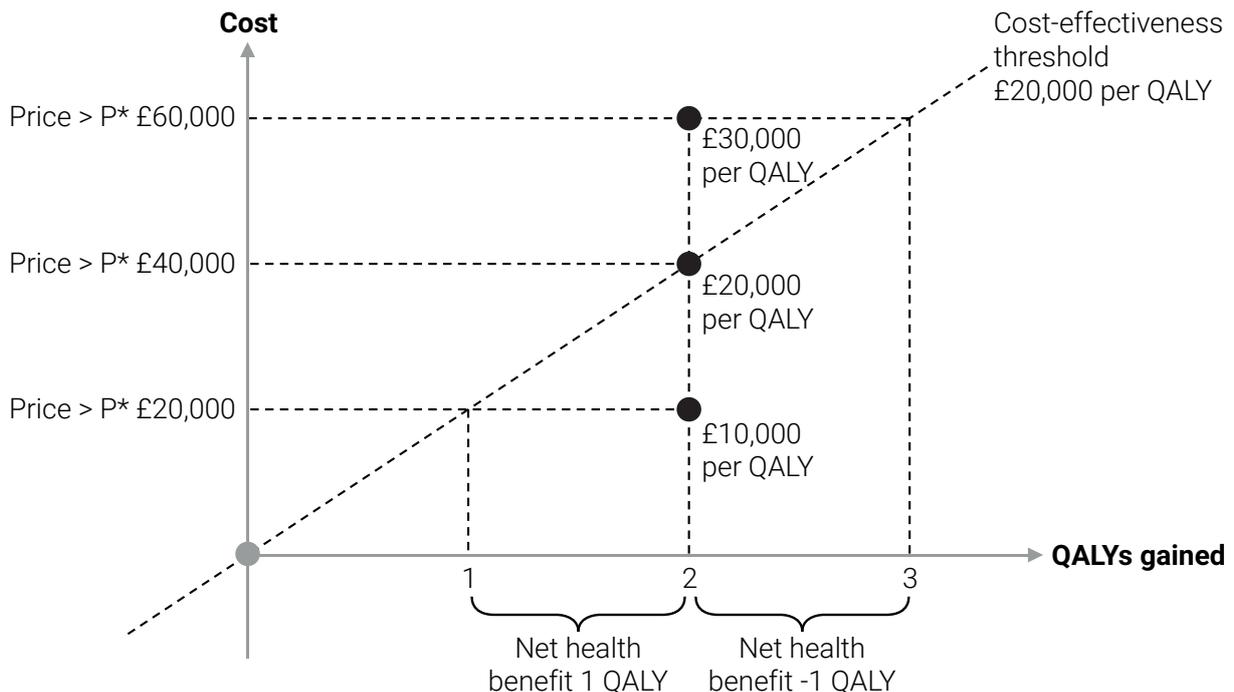
The most common measure of outcomes used in health care economic evaluation is the quality-adjusted life-year (QALY). The QALY combines gains in *quality* of life with the gains in *quantity* of life (life expectancy). Using QALYs allows for direct comparison of outcomes across diseases (eg, between cancer and heart disease) and between different areas of health care (eg, between pharmaceutical interventions and surgical interventions). Incremental QALYs can be calculated to determine the additional health benefits that an intervention provides over another one. Economic evaluation analyses using QALYs as the measure of health effects are called 'cost–utility' analyses.

### Use of thresholds in HTA

**Cost-effectiveness analysis alone cannot help determine whether a new drug offers good value for money. To aid decision-making, a cost-effectiveness or willingness-to-pay 'threshold' can be used.** This threshold refers to the maximum amount payers are willing to pay for health benefits. The threshold can be expressed as the maximum cost per unit of additional health benefit deemed to be acceptable and can be used to help determine whether a new drug offers value for money.

**Based on a pre-defined 'threshold' or willingness to pay, if an intervention is not cost-effective at the 'list' (manufacturer-set) price, a discounted price may be used to make it meet the threshold.** Through this mechanism, economic evaluation can be used to negotiate prices with pharmaceutical companies and inform reimbursement decisions in the context of the maximum price a health system can afford to pay (**Figure 9**). Companies often price their products at the higher end of the explicit threshold.<sup>352</sup>

**Figure 9 – Threshold and health gain example from NICE**



Source: Reproduced with permission from McCabe *et al.* (2008)<sup>353</sup>

**Setting the cost-effectiveness threshold at the empirically derived health opportunity cost would ensure that resources are allocated efficiently to interventions that provide best value for money.**<sup>354</sup> When used with a generic measure of health gain such as a QALY, such a threshold can be used as a benchmark to determine whether the health gain by one intervention exceeds the health forgone by other displaced services or interventions in the health system. Use of such a threshold raises key issues:

#### How is the cost-effectiveness threshold determined?

- In England, NICE typically uses a threshold range of £20,000 to £30,000 per QALY gained. Between 2009 and 2022, NICE had a higher threshold of £50,000 per QALY for treatments for end-of-life care (recently replaced with a 'severity modifier'). Some treatments in England that target very rare conditions are evaluated using an up to 10-times higher threshold of £300,000 per QALY.<sup>355,356</sup>

- However, the empirical basis for these thresholds is limited.<sup>357</sup> A 2015 analysis produced a figure of £12,936 per QALY based on health opportunity costs. This analysis measured the marginal productivity of the National Health Service (NHS), in other words, how much it costs to produce a QALY in the health system. It therefore demonstrated the mortality and morbidity attributable to individuals losing access to services and treatments due to higher expenditures on new drugs.<sup>354</sup> Acceptance of this threshold would suggest that anything less cost-effective does not promote the efficient use of NHS resources, rather that it would, in terms of the overall health system, have health-reducing effects.<sup>2,320</sup>

**The use of QALYs as a yardstick for comparing the health benefits of different interventions is often criticised.**<sup>352</sup> In the US in particular, public payers are explicitly prohibited from using cost-per-QALY thresholds to guide coverage decisions.<sup>358</sup> Other countries, including France, Germany, Italy and Spain, have also avoided use of cost-per-QALY thresholds, opting for alternative methods. Criticisms of the QALY include the following:

- QALYs may be misinterpreted as a method to put a value on a person's life, which can be seen as ethically and morally challenging.<sup>359</sup>
- QALYs may not adequately capture all relevant attributes of health care. QALYs combine quality and quantity of life but do not include other dimensions such as the increased convenience of different treatments.
- QALYs may not reflect social values if individuals differ in how they value QALYs gained by different populations (eg, members of a vulnerable population or younger individuals).<sup>163,360</sup> These concerns can, in theory, be addressed through the use of equity weights.

### Uncertainty in economic evaluation

**At the time of approval, there is often little or no data about a new drug's effectiveness outside of the clinical trials used in regulatory approval.** It is therefore common for HTA agencies undertaking economic evaluation to use clinical studies as the main basis or 'vehicle' for modelling the long-term cost-effectiveness of the drug.<sup>319</sup> In doing so, uncertainty of clinical effectiveness around the time of approval may be exacerbated in the model. As we outlined in Section 3, sources of uncertainty in clinical trials include: the validity and generalisability of outcomes in trial populations,<sup>361–363</sup> the use of unvalidated surrogate endpoints,<sup>206</sup> a lack of follow-up data and poor choice (or lack) of comparators for decision-making.<sup>364,365</sup>

## Box 22 – Role of patients in HTA and reimbursement

As we outlined in Section 4, patient organisations have recently emerged as major political actors in drug regulation. Similarly, patient organisations have become integral to HTA processes. NICE in England, for example, routinely involves members of patient organisations in its appraisals of new drugs. A recent study in the UK showed that almost all NICE appraisals between 2015 and 2016 contained contributions from at least one patient organisation, with many organisations contributing to multiple appraisals.<sup>366</sup>

Patients play an integral role in HTA by ensuring that the scientific scrutiny of clinical and economic data is patient-centric and reflects the values and preferences of those affected by the health condition in question. However, patient organisations' involvement in HTA can also result in conflicts of interest.

More than two-thirds of patient organisations involved in NICE appraisals between 2015 and 2016 had accepted funding from the manufacturer of the products or a competitor within the same year of contributing to the technology appraisal.<sup>366</sup> These payments were not routinely disclosed.

The extent of industry sponsorship of patient organisations has led to concerns, particularly when industry-funded patient advocacy groups campaign for recommending drugs for coverage despite questionable clinical effectiveness or cost-effectiveness.<sup>366–368</sup>

## Supplementary pricing strategies

HTA is often used in combination with other 'supplementary' pricing strategies, which may also be used as standalone approaches.

### Internal reference pricing

Internal reference pricing (IRP) groups drugs with similar characteristics together in a reference price group. Use of IRP infers that a payer (eg, an insurance fund or government) is only willing to pay a certain price for a drug with similar clinical benefits.

- In some countries, IRP is explicitly used to group drugs according to their comparative clinical benefit. Drugs that do not offer meaningful improvement over existing products are placed at or below the reference price of existing treatments.
- IRP may rely on a system such as HTA to determine the comparative effects of new versus existing drugs.

## External reference pricing

External reference pricing (ERP) (also known as international reference pricing) indexes the domestic price of a new drug with prices in other market(s) so that it is equivalent (or similar) to the price of the same drug in a 'basket' of other countries.<sup>369</sup>

- ERP uses the minimum, average or median prices paid for drugs in other countries. Prices are also sometimes adjusted for market factors such as market size and purchasing power parity. In some cases, a 'most-favoured nation' approach may be adopted, which demands the lowest price charged to any country in a selected 'basket' of countries. In Europe, the 'basket' of countries referenced varies greatly, with the UK being one of the most-commonly referenced countries.<sup>370–372</sup>
- ERP places downward pressure on national drug prices and may contain pharmaceutical expenditures in the short term.<sup>373</sup> But ERP in one country has important spillover effects on other countries. In countries that are commonly referenced in ERP or are unable to pay the common reference price, a firm may prefer to delay the launch of a new drug or not launch it at all.<sup>374</sup>
- Most countries implementing ERP resort to using publicly disclosed list prices in their reference countries due to a lack of transparency over discounts and rebates negotiated between payers and manufacturers. This results in countries paying substantially higher prices than intended.<sup>375</sup>

## Budgets and expenditure caps

Budgets and expenditure caps set a pre-determined limit for pharmaceutical spending. Spending above this level is recuperated through rebates, future price controls or other means.

- In France, if pharmaceutical expenditure exceeds an agreed annual growth rate, each pharmaceutical firm must repay between 50 per cent and 70 per cent of sales revenue above the cap.<sup>376</sup> As spending increases, this percentage of 'clawbacks' also increases.<sup>377</sup>
- In the UK, a Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) requires pharmaceutical companies to pay the government rebates if actual pharmaceutical spending exceeds the '*global*' pharmaceutical budget.<sup>378</sup> This mechanism is used to control total growth in spending on branded (on-patent) medicines but has important exemptions, including for new drugs during the first three years after market entry.

## Price regulation for off-patent pharmaceuticals

**Generic drugs provide the same clinical benefits as their on-patent counterparts, at a fraction of the cost.** Once patents and other market protections on new drugs have expired, generics therefore provide a significant opportunity to increase the efficiency of pharmaceutical spending.

**Generic uptake varies substantially from country to country.** In the OECD countries, for example, generic drugs account for between 11 per cent (Luxemburg) and 85 per cent (UK) of total market share by volume.<sup>20</sup> These variations in generic drug use are due to differences in generic policies (discussed in Section 6).

**Generic manufacturers can benefit from the R&D of on-patent drug manufacturers and submit 'abbreviated' drug applications for approval, without incurring the costs of clinical trials.** Generic manufacturers also incur fewer marketing costs since the marketing and promotion of on-patent products have (in theory) already established a market for generics since patent expiry. These reduced barriers to the entry of new drugs since patent expiry help to facilitate generic entry and market penetration.

**As seen in other competitive markets, generic drug prices generally continue to fall as additional products enter the market.**<sup>379,380</sup> This occurs until there are several interchangeable and readily available generics on the market, when prices stabilise around the marginal cost of production.<sup>381,382</sup>

**Effective competition is responsible for substantial reductions in generic drug prices relative to their on-patent counterparts.**<sup>383</sup> Governments and payers may also implement several supply- and demand-side policies to enhance the reduction in price of generics and increase their uptake:<sup>384</sup>

- **IRP** – this establishes a single price for a group of interchangeable drugs.<sup>385</sup>
- **Linking the generic price to the price of the originator** – some countries regulate price reductions on generics based on a percentage of the originator price.
- **Tendering and pooled procurement** – this reverses the roles of the payer and the seller, by allowing manufacturers to compete for a 'tender' or 'contract' based on price, with the lowest price typically awarded the contract. Tendering can therefore lead to lower prices. A main disadvantage of this approach is that fierce price competition and repeated awards of the tender to a single manufacturer can drive competitors out of the market, creating the potential for future price increases.

## Pricing and reimbursement – summary

### Box 23 – Summary of key issues and trade-offs relating to pricing and reimbursement

- High drug prices are a key determinant of pharmaceutical expenditure.
- Company-set prices are not always commensurate with the clinical benefit provided by these drugs.
- Under fixed health care budgets, paying for highly priced drugs can ultimately result in health lost because of the displacement of existing health care services (health opportunity cost).
- In some cases, resources allocated to highly priced drugs could have a greater impact on overall population health if spent on treatments or services that offer better value for money elsewhere in the health system.
- Pricing regulation aims to maximise population health by allocating limited resources as efficiently as possible and minimising the opportunity costs of foregone treatments.
- Payers can employ several strategies to regulate on-patent drug prices.
- HTA is the main strategy used to align drug prices with their value, helping payers to determine which new drugs to reimburse, and at what price. Other supplementary strategies include reference pricing (internal and external), budgets and expenditure caps.
- As the price per health unit offered by new drugs increases, policymakers are faced with difficult decisions. Setting a willingness-to-pay threshold to determine what constitutes value in a health system is both empirically and politically challenging.
- Limited availability of data supporting new drug approvals compounds the complexity of pricing and reimbursement decisions.

# Section 6 Adoption and use of pharmaceuticals

## Section overview

Physicians' prescribing decisions and patients' preferences for taking and adhering to prescribed medicines have implications for health outcomes and health system efficiency. Both policymakers and the pharmaceutical industry can influence physician and patient demand for prescription drugs, albeit with different intended objectives. This section outlines the need for policies to influence the adoption and use of prescription drugs, the role of the physician as the patient's agent, and methods that governments and industry employ to influence the appropriate use of medicines within the health system.



## Overview of adoption and use

### **The price and volume of drugs prescribed drive net pharmaceutical expenditure.**

Physicians' prescribing choices and patients' ability to take and adhere to prescribed medicines have implications for the efficiency of pharmaceutical expenditure.

Influencing the extent to which new drugs are adopted and used within the health system is critical to policymakers.

### **The demand side of the pharmaceutical sector provides additional scope for policymakers to influence *which* drugs physicians prescribe, pharmacists dispense and patients administer.**

Policy mechanisms discussed in previous sections have focused primarily on the supply side of the pharmaceutical sector.

**Companies developing and marketing drugs also influence the demand for pharmaceuticals.** Pharmaceutical companies benefit financially from increased adoption and use of their medicines. They therefore invest heavily in marketing and promotion efforts to maximise their revenues.

In this section, we:

- discuss the main health system approaches to promoting the appropriate and efficient adoption and use of prescription drugs, including targeting patient demand, physician prescribing and pharmacist dispensing
- outline the main marketing and promotion efforts that industry makes to influence physician prescribing and patient demand.

## Aims of policies that influence the adoption and use of pharmaceuticals

**Several attempts have been made to define 'good' prescribing practices.**<sup>386–390</sup> From a health system perspective, strategies aimed at influencing the adoption and use of pharmaceuticals should aim to:

- consider patient views and preferences in prescribing decisions<sup>391</sup>
- maximise individual health gain by prescribing the safest and most efficacious medicine for a given condition
- maximise improvements in population health and efficiency by considering the health opportunity costs associated with prescribing drugs
- promote evidence-based, rational prescribing of drugs according to clinical and economic evidence.

**Strong evidence generated in well-conducted clinical trials is a prerequisite for 'good prescribing'.** Physicians are inherently faced with uncertainty in prescribing decisions. A strong (ie, valid and trustworthy) and transparent evidence base on drug benefits, harms and costs is fundamental to ensure physicians can make the best evidence-based decisions.

**Limited evidence at the time of new drug approval is common.**<sup>215</sup> Weak evidence about a new drug's benefits, harms and comparative effects increases uncertainty for subsequent decisions in the health care system, and can lead to poor-quality and inefficient prescribing.

**A strong and important link exists between HTA and evidence-based prescribing.** Assessing the value of a medicine through HTA allows physicians to be able to choose which drugs to prescribe over alternatives (their relative effectiveness), which reflect the most cost-effective option for the health system. In Section 5, we outlined the principles of HTA to determine the value of a medicine for the health system.

## Approaches to influence the adoption and use of pharmaceuticals

**Policymakers can influence the extent to which prescription drugs are adopted and used in the health system, in several ways.** These efforts aim to ensure that the adoption and use of prescription drugs are aligned with the goals of good prescribing – prescribing that is in the best interests of the patient, maximises individual and population health under budgetary constraints (ensures allocative efficiency) and is guided by the best available evidence (**Table 4**).

**Table 4 – Health system and industry approaches to influence the adoption and use of pharmaceuticals**

<b>Health system approaches to promote the appropriate and efficient adoption and use of prescription drugs</b>	
Influencing physician prescribing:	<ol style="list-style-type: none"> <li>1 Clinical practice guidelines</li> <li>2 Formulary management</li> <li>3 Financial incentives</li> </ol>
Influencing pharmacist dispensing:	<ol style="list-style-type: none"> <li>4 Generic substitution</li> </ol>
Influencing patient demand:	<ol style="list-style-type: none"> <li>5 Cost-sharing</li> <li>6 Patient adherence and medicines optimisation</li> </ol>
<b>Industry approaches to influence the adoption and use of medicines: marketing and promotion of pharmaceuticals</b>	
Influencing physician prescribing:	<ol style="list-style-type: none"> <li>1 Free samples</li> <li>2 Detailing</li> <li>3 Physician payments</li> </ol>
Influencing patient demand:	<ol style="list-style-type: none"> <li>4 Direct-to-consumer advertising (only explicitly allowed in the US and New Zealand)</li> <li>5 Funding patient organisations</li> </ol>

## Health system approaches to promote the appropriate and efficient adoption and use of medicines

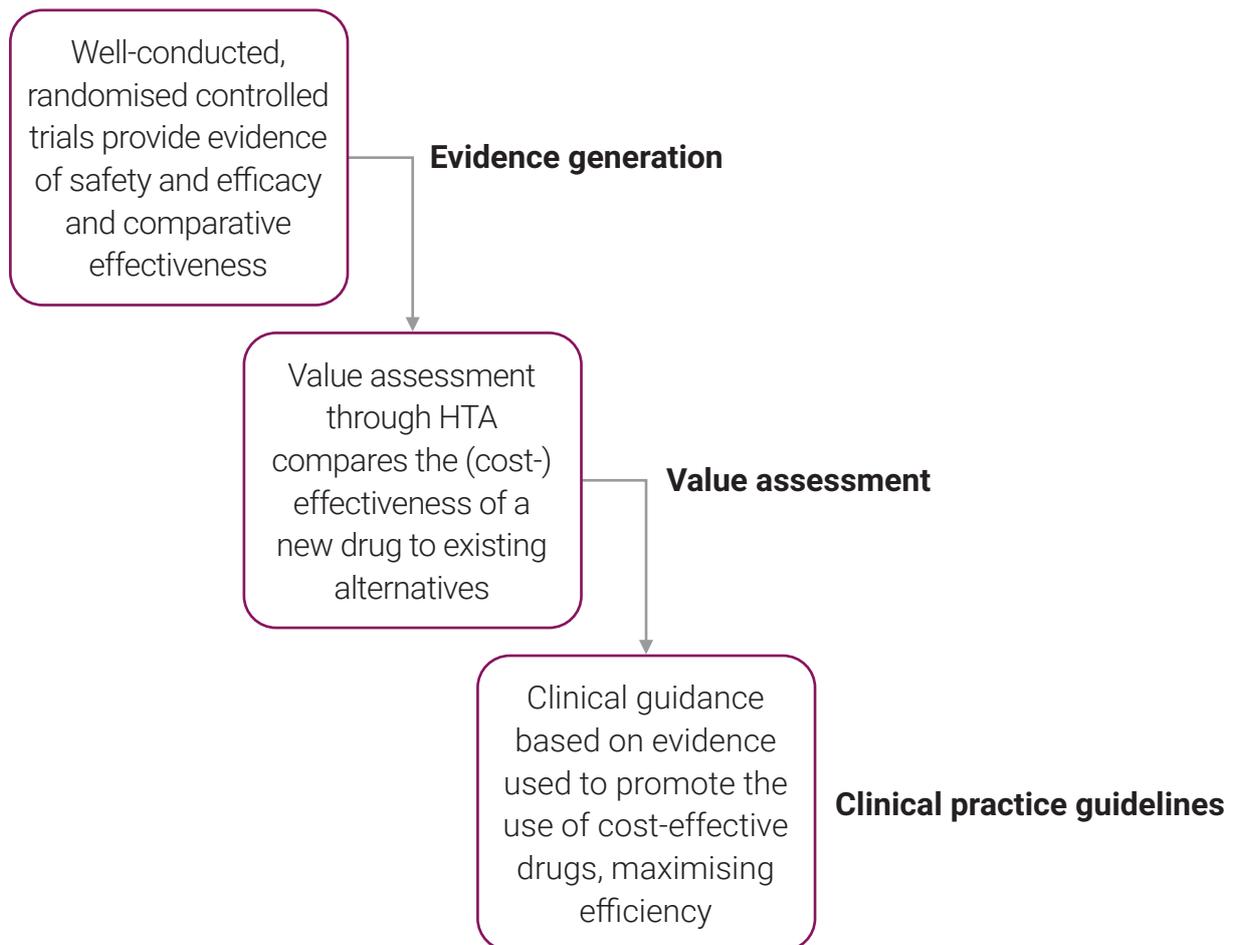
### Clinical practice guidelines

**Clinical practice guidelines are systematically developed statements or guidance which assist physicians and patients in medical decision-making.**<sup>392</sup> These guidelines make recommendations to physicians about which drugs are safe and effective for the treatment of certain conditions and patient populations, how to prescribe or administer the drugs and for how long. In England, NICE is responsible for developing clinical practice guidelines following appraisal of new health interventions, advising the NHS on how they can be most effectively implemented alongside existing treatments.<sup>393</sup>

**Clinical practice guidelines can be used to improve efficiency by reducing outdated practices and ineffective, dangerous and wasteful prescribing.**<sup>394</sup> Clinical practice guidelines also benefit patients by standardising the delivery of care and improving patient outcomes,<sup>395</sup> while improving efficiency and optimising value for money, from a health system perspective.<sup>396</sup>

HTA can be used to develop evidence-based clinical practice guidelines (**Figure 10**).

**Figure 10 – Steps linking evidence generation and value assessment to prescribing**



## Formularies

**A formulary is a list of drugs covered (reimbursed) by a payer or provided in a hospital.** In different settings, a drug formulary may also be known as a drug list or positive list. For example, the British National Formulary (BNF) is the list of drugs prescribed in the UK under the NHS.<sup>397</sup> Private health insurers may also use a formulary to outline the treatments available to patients in different health systems.

### **Formulary design can be used to improve the appropriateness and efficiency of prescribing:**

- Step therapy – this requires physicians to prescribe a less expensive (but clinically equivalent) prescription drug before a more expensive option can be approved.<sup>398</sup>
- Quantity/prescription fill limits – these set the amount of a particular prescription that can be prescribed to one patient within a certain period of time.
- Prior authorisation – this requires a physician to obtain approval from a payer before a drug can be dispensed. Inappropriate use of prior authorisation can create burdensome administrative hurdles for prescribing.<sup>399</sup>

**Formulary design can influence demand for prescription drugs.** Evidence shows that formulary design can increase the use of more cost-effective drugs and contain costs.<sup>400</sup> Step therapy, prescription fill limits and prior authorisation can improve the efficiency and quality of care, and contain prescribing costs without increasing the use of other health services.<sup>398,401,402</sup> Some of these payer strategies may also have important unintended consequences for patients, as they may limit access to essential therapies and create barriers to accessing care.<sup>403,404</sup>

## **Financial incentives**

**In some health systems, policymakers may have scope to directly influence physician prescribing with financial incentives.** These payments may either be direct to the physician or indirectly impact the practice from which they prescribe (eg, a GP surgery). These financial incentives can ‘reward’ physicians for cost savings, or ‘penalise’ them for inefficient prescribing practices.

We briefly outline below two main financial incentive mechanisms used to influence physician prescribing:

- **Prescribing budgets.** These can be set at different levels according to region or therapeutic area or to specific products.<sup>377</sup> Policymakers can impose prescribing budgets upon individual physicians, or groups of physicians, to increase financial responsibility and accountability for the cost of prescribing. Evidence on prescribing budgets is mixed.<sup>405–409</sup>
- **Pay-for-performance (P4P) rewards (or penalises) physicians, or other providers, for attaining targeted service goals, such as meeting health care quality or efficiency standards.**<sup>410</sup> P4P is also known as performance-based funding, payment by results or results-based financing. Financial incentives can be based on quality improvement, ranking of quality compared with other providers (less applicable to physician prescribing) or the attainment of pre-defined quality levels. Evidence of the impact of P4P on prescribing behaviour is also mixed.<sup>411–413</sup>

The impact of physician payment methods on demand for medical services is discussed extensively in the health economic literature.<sup>414,415</sup>

## Encouraging (or mandating) the uptake of generic drugs

**One option for payers to promote generic prescribing is to mandate pharmacist substitution of originator products with generics.** In many countries, pharmacists can substitute the least expensive of the generic drug options according to active substance or international non-proprietary name (INN) rather than a brand name.<sup>416,417</sup> In some countries, generic substitution is not mandatory, but awarded through pay-for-performance schemes or other financial incentives.<sup>416</sup> To receive a more expensive, branded pharmaceutical product, some patients may opt to pay out of pocket.

**The extent of the adoption and use of generic drugs varies considerably between countries.**<sup>417</sup> According to the OECD, in the past decade, policies to encourage or mandate pharmacist-mediated generic substitution have largely been successful in increasing the proportion of generic drugs that are prescribed.<sup>418</sup>

## Influencing patient demand through cost-sharing

**Under increasing budgetary constraints, one option for policymakers is to directly charge patients for their use of prescribed drugs.** Through this mechanism, the cost is shared between the patient and the health system (hence ‘cost-sharing’), with the primary aim of making patients more aware, and more accountable, for prescribing costs, preventing them from consuming additional ‘extra’ or ‘unnecessary’ treatments.<sup>419</sup> Cost-sharing can take several forms:

- **Co-payments** or ‘co-pays’ are fixed flat-rate charges per item or prescription. In England, for example, patients pay an NHS prescription charge of £9.35 (as of November 2022) for each prescribed item, regardless of the total cost.<sup>420</sup>
- **Co-insurance** is based on a fixed percentage of the total cost of a treatment.
- **Deductibles** require users to pay a fixed quantity of the total cost of a prescription, or the cost over a certain time period (eg, a year).

In most instances, cost-sharing is coupled with mechanisms to protect the finances of individuals who are most likely to incur costs (eg, those with chronic conditions or older people) or other vulnerable populations with low incomes. In England, approximately 90 per cent of prescriptions are dispensed free of charge.<sup>421</sup>

### Box 24 – The health costs of cost-sharing

- Cost-sharing reduces demand for ‘low-value’ and ‘high-value’ drugs alike.<sup>422–424</sup>
- Sicker patients who incur costs more regularly are more sensitive to cost-sharing and reduce consumption to a greater extent than healthier patients.<sup>422</sup>
- Cost-sharing worsens adherence to medication and leads to more frequent discontinuation of therapy.<sup>425</sup>
- Patients with a lower socioeconomic status are more sensitive to cost-sharing.<sup>425</sup>
- In some instances, reduced demand for and use of prescription drugs directly translates into worsened patient outcomes.<sup>422</sup>

## Patient adherence and medicines optimisation

**Between 20 per cent and 50 per cent of patients do not take prescription drugs according to the way their physician prescribes them.**<sup>426,427</sup> Reasons for non-adherence to medications are complex, and include patient, physician and health system factors.<sup>428</sup> Such suboptimal adherence can result in poor health outcomes and sometimes increased health care costs due to disease complications.<sup>429</sup> Ensuring patients get the most out of their medicines is therefore an important policy objective.

**Policies that payers implement can influence treatment adherence and discontinuation.**<sup>425</sup> Researchers have tested several strategies to improve adherence, from simple changes made to prescribing recommendations, to complex interventions that address health system barriers and communication between patients and physicians.<sup>430,431</sup>

**There is significant unmet scope for policymakers to influence how patients use their prescribed medications.** According to systematic reviews of the literature, current methods to address patient adherence often fail to make a significant impact on patient outcomes.<sup>432,433</sup>

## Industry approaches to influence the adoption and use of medicines: marketing and promotion of pharmaceuticals

**Health system stakeholders seek to ensure that new drugs are prescribed and used appropriately – from both a clinical and an economic perspective.** In some ways, this health objective is at odds with industry interests to increase demand for its products to maximise revenues.

**According to some accounts, the cost of industry's promotional efforts outweighs the cost of R&D efforts.**<sup>434–436</sup> This observation undermines the industry argument that the high costs of R&D justify high drug prices, as covered in Section 2. The promotion or 'sales and marketing' of pharmaceuticals is frequently a source of media attention and contentious debate.<sup>434,437,438</sup>

**Traditionally, much of promotional spending has been targeted towards physicians.**<sup>439</sup> However, in the past two decades, targets of industry promotional activities have expanded to also include consumers (prospective patients), patient organisations, hospitals and third-party payers.<sup>440,441</sup>

### Free samples

**Free samples are given to prescribers to familiarise them with a new drug, with the expectation that this strategy will increase sales in the long run.** Most free samples are for new and the most-expensive prescription drugs. Free samples can affect physicians' subsequent prescribing patterns and may ultimately raise the cost of prescription drugs, as industry recoups marketing costs through higher prices.<sup>442,443</sup>

### Detailing

**Detailing involves providing physicians and prescribers with information about new products.** It therefore reduces the need for physicians to individually seek out information on new drugs that drug regulators provide, as outlined in Section 4. Detailers often build a strong relationship with prescribers over several years of sustained interactions. Evidence suggests a clear link between industry interactions with physicians and pharmaceutical detailing, with higher frequencies of prescribing, higher prescribing costs and sometimes lower-quality or irrational prescribing of the promoting company's drugs.<sup>444–446</sup>

## Industry payments to physicians and health care organisations

**Industry payments to physicians in the form of cash (eg, for consulting services or invited lectures) and in-kind gifts (eg, meals) are a common strategy that industry employs to promote prescription drugs.**<sup>447</sup> The extent and ubiquitous nature of physician payments have raised questions about the financial interests of physicians.<sup>448,449</sup> Industry payments are associated with increased physician prescribing of the promoted drug.<sup>450</sup>

**Direct industry payments to health care organisations are also common.** In the UK, a total of 4,028 health care organisations received 19,933 payments worth approximately £50 million in 2015 alone.<sup>56,451</sup>

**Industry payments to physicians and health care organisations are becoming more transparent.** Since 2013 in the US, the Open Payments reporting system that the Physician Payments Sunshine Act 2010 created made all payments to physicians and teaching hospitals greater than a value of \$10 public.<sup>452</sup> Since then, industry trade associations have voluntarily implemented similar initiatives in other settings – including Canada, Europe and the UK – to improve the transparency of industry payments.<sup>451,453,454</sup>

## Direct-to-consumer advertising

**In New Zealand and the US, direct-to-consumer advertising (DTCA) is designed directly to influence patient behaviour.** Since 1997, spending on DTCA in the pharmaceutical industry has grown at the fastest rate compared with other marketing efforts, from \$2.1 billion (11.9 per cent) of total spending in 1997 to \$9.6 billion (32.0 per cent) of total spending in 2016.<sup>455</sup>

- **DTCA can induce positive effects through increased public awareness of new drugs.** DTCA is associated with increased prescription of advertised products and increased patient requests for specific drugs.<sup>456</sup>
- **DTCA predictably increases sales revenue and is a common method used to maximise industry revenues.** Although the benefits of DTCA for patients and industry are not mutually exclusive, commercial interests driving DTCA are a source of controversy.<sup>457</sup>
- **New Zealand and the US are the only countries that explicitly permit DTCA that includes product claims (ie, which names a specific product and makes claims regarding its safety and efficacy). DTCA is prohibited in other countries, including in the UK.**

## Funding patient organisations

As we have summarised in previous sections, pharmaceutical company funding of patient organisations is increasingly common.

**Recent studies show that in the UK the prevalence of industry funding ranged from 20 per cent to 83 per cent across different settings.**<sup>54</sup> Industry's top funding priority in the UK is supporting patient organisations' engagement with outside audiences, including "advocacy, campaigning, and disease awareness", "communication" and "policy engagement".<sup>306</sup>

**Patient groups with industry funding are more likely to adopt the sponsoring company's position on controversial issues.**<sup>54</sup> When industry-funded patient groups are involved in decisions surrounding drug approval and reimbursement, this may increase the influence of industry in these decisions.

## Adoption and use of pharmaceuticals – summary

### Box 25 – Summary of key issues and trade-offs relating to the adoption and use of pharmaceuticals

- The price and volume of drugs prescribed, dispensed and used in the health system directly drive net pharmaceutical expenditure. Policymakers can influence expenditure and patient outcomes by ensuring new and existing drugs are used optimally.
- Better knowledge of the benefits and harms of medicines from HTA can lead to better evidence-based clinical guidelines and decreased uncertainty in prescribing, and allows policymakers to prioritise the adoption and use of valuable drugs for the health system.
- Patients, prescribers (physicians and pharmacists), payers and industry influence the demand for pharmaceuticals.
- Health systems should aim to promote the appropriate and efficient adoption and use of prescription drugs by targeting physician prescribing, patient demand and pharmacist dispensing.
- Policymakers can influence: (1) physicians (using clinical practice guidelines, formulary management and financial incentives); (2) pharmacists (using prescribing policies such as generic substitution); and (3) patient demand (through cost-sharing and medicines optimisation).
- Industry can influence physician and patient demand to maximise revenue through marketing and promotion.

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For more information, contact:

Dr. Huseyin Naci

Department of Health Policy

London School of Economics and Political Science

Email: [h.naci@lse.ac.uk](mailto:h.naci@lse.ac.uk)