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Pharmaceutical Policy:

Balancing Innovation, Access and Affordability

Design Principles for a Coherent Pharmaceutical System

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More from this series

This is the second of three reports as part of a series commissioned by The Health Foundation on pharmaceutical policy and economics. This report presents design principles for building a coherent pharmaceutical system.

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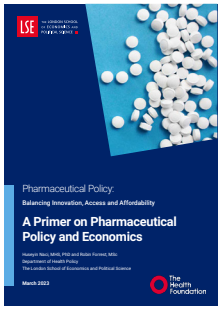

A Primer on Pharmaceutical Policy and Economics

This report describes the process and policy environment surrounding the discovery, development, approval, pricing and adoption of pharmaceuticals.

Pharmaceutical Policy in the UK

The overarching purpose of this report is to describe the pharmaceutical policy landscape in the UK, in the context of global pharmaceutical policy and economics, and design principles for building a coherent pharmaceutical system.

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A note to readers

Objectives of this report

The overarching purpose of this second report is to present design principles for building a coherent pharmaceutical system.

The aims of this report are to:

- Define the objectives of pharmaceutical policy concerning innovation, access and affordability.
- Examine the current policy landscape surrounding pharmaceuticals, and identify its shortcomings.
- Outline the key design principles for building a more coherent pharmaceutical system, which balances both health policy and industrial policy objectives.

Target 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 governments 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.

No prior knowledge of the pharmaceutical industry is required to understand the key concepts of this report. However, readers might find the first report in this series (*A Primer on Pharmaceutical Policy and Economics*) useful to introduce key policy issues and to provide additional context.

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Boxes

Abbreviations and acronyms

COVID-19	Coronavirus disease 2019
EMA	European Medicines Agency
FDA	Food and Drug Administration
GDP	Gross Domestic Product
HTA	Health Technology Assessment
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
QALY	Quality-adjusted life year
R&D	Research and development
RCT	Randomised controlled trial
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
UK	United Kingdom
US	United States

Section 1 Introduction

Pharmaceutical innovation plays an important role in improving health outcomes.[1]

Over the past few decades, many new drugs have provided more effective alternatives over existing treatment options. For example, sofosbuvir (Sovaldi®) has transformed the treatment of hepatitis C, substantially improving patient outcomes, demonstrating high cure rates of more than 80 per cent.[2,3] Another groundbreaking treatment, imatinib (Gleevec®), fundamentally altered chronic myeloid leukaemia treatment, leading to marked improvements in prognosis for patients.[4] Most recently, several highly effective vaccines for coronavirus disease 2019 (COVID-19) were developed at record speed, substantially reducing the risk of severe illness, hospital admissions and mortality associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[5]

Such innovations that yield a step-change improvement on patient outcomes are a testament to the success of the current global pharmaceutical policy landscape, which has effectively incentivised the development and approval of many new therapeutically beneficial medicines.

However, not all new drugs have been transformative innovations. In recent years, innovation pipelines have delivered an increasing number of new drugs that provide much smaller additional health benefits over existing treatments, often at much higher prices.[6] Many new drugs also offer no added therapeutic benefit over existing alternatives.[7] The recent approval in the United States (US) of aducanumab (Aduhelm®) for the treatment of Alzheimer's disease, which occurred despite major concerns over its efficacy, highlights growing uncertainty associated with the clinical benefits of new drugs.[8]

The nature of pharmaceutical innovation has also changed over the past decades. A large proportion of new drugs target increasingly small patient populations.[9] Cancer is now the single largest category of new drug approvals.[10] And many new drugs have extremely high and increasing launch prices.[11] Between 1995 and 2013, the list price per life-year gained for new cancer drugs increased from about £40,000 to approximately £150,000.[12] Therapies with extremely high prices present policymakers with difficult decisions, for which there is little historical precedent.

Adding complexity to these decisions is the evolving political economy of pharmaceutical policy and regulation. Pharmaceutical companies are powerful political actors, with financial ties to policymakers, regulators and other stakeholders in health systems, including patient organisations.[13–17]

In addition, the role of patients (and organisations representing patients' interests) has become central to both regulatory approval and reimbursement decisions in many health systems, advocating alongside industry for faster and broader access to new treatments.[18] Increasingly, regulators and payers are coming under growing pressure to approve and reimburse new drugs quickly in greater budgetary-constrained health systems than ever before.[19]

Report overview

In this report, we examine the current pharmaceutical policy landscape. We first define the overarching objectives of pharmaceutical policy concerning innovation, access and affordability. We then review the health system and industrial sector goals of pharmaceutical policy. Following this, we look at current approaches to incentivising pharmaceutical innovation, achieving timely patient access and ensuring affordability, identifying the shortcomings of the current landscape for each of these three areas. Finally, we outline four key design principles for building a more coherent pharmaceutical system that better balances the innovation, access and affordability aims of pharmaceutical policies.

Section 2 Objectives of pharmaceutical policy

Pharmaceutical policy aims to ensure timely access to new drugs at affordable prices, while providing a fertile environment for innovation (**Box 1**).[20] On innovation, optimal pharmaceutical policy would favour the development of new drugs that are beneficial for society. On access, optimal pharmaceutical policy would ensure timely patient access to new drugs, prioritising those that clearly demonstrate additional clinical and economic benefits to health systems. On affordability, optimal pharmaceutical policy would maximise the (net) benefit of new drugs to patients while providing sufficient incentives for future research and development (R&D).[21] Transparency would be an essential tenet underpinning all three domains of pharmaceutical policy, ensuring that data that support decision-making are publicly available for independent scrutiny.

Box 1 – Key objectives of optimal pharmaceutical policy

Innovation

- Pharmaceutical R&D pipelines sustainably deliver new drugs that address unmet medical and therapeutic needs for the long term.

Access

- Safe and effective products enter the market on the basis of robust clinical trial data, without undue delay.
- Patients benefit from timely access to drugs that are proven to be safe, clinically effective and cost-effective.
- Drugs that offer exceptional value are prioritised and adopted in a timely manner.

Affordability

- Drugs are priced according to the benefits they provide, taking into account the opportunity cost of interventions that are displaced across the health system as a result of paying for new medicines, while maintaining incentives for pharmaceutical companies to invest in future innovation.

Section 3 Health system and industrial sector goals

Different stakeholders – governments, industry, regulators, Health Technology Assessment (HTA) bodies, payers, clinicians, patients and citizens – value the innovation, access and affordability objectives of pharmaceutical policies differently.[22] Collectively, all stakeholders strive for better health, but interests may at times diverge, and even conflict. For example, when patients request fast access to new medicines with highly uncertain clinical benefits, this may undermine payers' efforts to achieve high-quality prescribing and to contain prescription drug costs (**Table 1**). Similarly, pharmaceutical companies' profit maximisation conflicts with health systems' and payers' aim to maximise population health given available resources.

Complicating this picture further is governments' ambition to strike a balance between health and industrial policy – policy that aims to attract, sustain and foster a research-based industry that is important to the economy. This balance becomes especially difficult to achieve in countries with a strong life sciences industry, such as the United Kingdom (UK).[22,23] Ultimately, coherent pharmaceutical policy lies at the intersection of health and industrial policy.

Table 1. Overview of key stakeholders in the pharmaceutical system and their objectives

Stakeholder	Objectives	Social and political factors
Industry	• To maximise shareholder value	• Industry is a powerful lobby • Companies pay for regulatory and HTA reviews of their products • Industry sponsors patient organisations • Industry has financial links with clinicians and other health care professionals
Regulatory agencies	• To prevent unsafe and ineffective drugs from reaching the market • To foster innovation	• Regulators are under political pressure to speed up their processes • Regulators compete for 'first-in-the-world' approvals
HTA bodies	• To ensure new drugs provide value for money	• HTA bodies are under political pressure to speed up their assessments • HTA bodies may feel compelled to recommend drugs to avoid controversy
Payers	• To control spending	• Payers may feel compelled to pay for drugs to avoid controversy
Patients	• To have access to new drugs that are safe and effective	• Patients have high expectations about drug benefits • Media coverage on new drugs is overwhelmingly positive • Organisations that lobby on behalf of patients often have financial links with industry
Clinicians	• To provide patients with safe and effective drugs	• Clinicians overestimate the benefits and underestimate the harms of new drugs • Sources of information on new drugs have limitations • Conflicts of interest (financial or otherwise) influence clinicians' perceptions of new drugs

Table 1. Overview of key stakeholders in the pharmaceutical system and their objectives (continued)

Stakeholder	Objectives	Social and political factors
Citizens	• To ensure resources are allocated efficiently and fairly	• Preferences of the general population differ from those of patients • Budgetary constraints for health care services impact population health
Governments	• To improve public health • To control spending • To support industry	• Governments need to balance industrial and health policy • There is political aversion to denying access to new drugs • Pressure to ensure timely access to new drugs can be highly politicised

Section 4 The current pharmaceutical policy landscape

This section outlines current global approaches to promoting innovation, access and affordability in relation to new medicines, along with their shortfalls.

Current approaches to incentivising pharmaceutical innovation

Expected profits – expected revenues net of expected costs (including the cost of capital) – drive industry investment in R&D.[24,25] According to most recent estimates using publicly available data, the median capitalised R&D investment required to bring a single new drug to market is estimated at approximately $1,142 million (£844 million) – both figures relate to 2018, including the cost of failed trials and the cost of capital.[26] Estimates of the cost of drug development are highest in therapeutic areas that have lower regulatory barriers to market entry and those that benefit from higher willingness to pay in health systems.[27] Industry's investment in R&D is greater in such therapeutic areas than in others.[28]

Owing to the size of the US market for pharmaceuticals, US policy has a disproportionately large influence on global pharmaceutical innovation and patterns of R&D (**Box 2**). Without policy intervention, companies would develop drugs that are most likely to maximise profits from large markets, such as the US.[29]

Box 2 – US influence on global pharmaceutical innovation

The US is the largest, and most lucrative, pharmaceutical market in the world, accounting for almost half (£390 billion) of global sales in 2020.[28] In comparison, the UK represented approximately 2 to 3 per cent of global sales in the same year.[28] The US invests considerably more than other countries in pharmaceutical R&D.[30] In addition, lacking comprehensive national-level drug price regulation, the US health care system permits companies to maximise profits by charging payers "what the market will bear".[31] Even recent drug pricing reforms (as recent as 2022) are likely to be narrow in scope.[32] The US health care system therefore signals a considerably higher willingness to pay for new drugs than other systems (as we outline in the first report in this series on pharmaceutical policy, *A Primer on Pharmaceutical Policy and Economics*).

Predictably, pharmaceutical policy in the US has measurable impacts on global drug development:

- US-based incentives for the development of drugs to treat rare diseases in the 1980s are associated with large increases in R&D spending on clinical trials for and approvals of drugs to treat rare diseases. Health systems' high willingness to pay for rare-disease drugs further sustains these increases.[33]
- Implementation of Medicare Part D in 2006, which provides prescription drug coverage to more than 49 million older Americans, increased drug development activity in therapeutic areas such as cancer that are directly affected by the programme.[24] In Medicare Part D, insurers are legally mandated to pay for all new cancer drugs irrespective of their costs and benefits.[34]
- More recently, the creation of the US Food and Drug Administration (FDA) Breakthrough Therapy Designation in 2012, which introduced additional regulatory flexibility in evidence standards for regulatory approval for so-called 'precision' medicines, led to increased R&D activity in affected treatment categories.[35]

To incentivise industry investment in R&D, governments and policymakers rely on two main mechanisms. First, 'push' incentives are used to subsidise the initial costs of R&D, for example through direct funding of research or tax incentives for private companies.[36] This so-called push funding of R&D accounts for a significant share of early-stage basic and translational drug discovery research.[37] As these public sector investments occur early in the development process, they also have a high contribution to the overall capitalised cost of development after taking account of the cost of capital and the cost of failure. In the US, for example, the National Institutes of Health is the largest single public funder of health research globally, contributing to all new drugs that were approved in the US between 2010 and 2019.[38,39] Public funding of

early-stage research complements and stimulates industry investment in later-stage development.[40,41] Notably, public sector financial support also contributes to late-stage drug development.[42] This public push funding complements industry funding of clinical trials that lead to regulatory approval.[43, 45]

The second mechanism used to incentivise innovation consists of 'pull' mechanisms, which reward industry for the successful development of new drugs.[36] The main forms of pull mechanisms that governments and regulators issue are patents and regulatory exclusivity, respectively. Both forms of monopoly protections are aimed at shielding new drugs from competition for a limited period of time following market entry, during which higher prices than what would be possible in a competitive market can be charged. In recent years, these pull incentives have become a complex system of rewards, not just for developing novel drugs, but also for testing already approved drugs in new areas, expanding the use of existing drugs for paediatric use or for use in rare diseases.[46] Recent analysis shows that the average duration of a drug's market exclusivity (monopoly) period ranges from around 13 to 14 years following market entry, and sometimes even longer.[47]

Shortcomings of the current innovation landscape

The current innovation system delivers large numbers of new drug approvals each year. In 2018, a record number of new drugs were approved in the US.[48] In fact, the average number of new drug approvals over the five-year period between 2016 and 2020 was more than double that of the decade prior.[49] These trends observed in the US can reasonably be used as a proxy for trends elsewhere globally, with similarly large numbers of approvals seen in other regions.[50,51] Of these approvals, cancer treatments dominate, accounting for approximately a third of approvals in 2020.[10] Recent trends also indicate a rapid rise in the number of drugs to treat rare diseases[9], which tend to secure higher prices in health systems.[52]

A growing number of new drug approvals in recent years is not necessarily indicative of therapeutically beneficial innovation. Despite record numbers of prescription drugs entering the market over the past decade, fewer than a third of new drugs provide added therapeutic benefit over existing alternatives.[7,53] Marginal benefits associated with the majority of new cancer therapeutics have been extensively documented.[54–56] Two-thirds of recently approved cancer drugs do not have evidence on their survival or quality-of-life benefits.[55]

Furthermore, recent drug approvals do not directly correspond to unmet medical and therapeutic needs. For example, innovation of new drugs for cardiovascular disease (the leading cause of death globally) is stagnant, and there is still significant unmet need in relation to antibiotics development, rare diseases and neglected tropical diseases.[57]

Box 3 – Tension between health and industrial policy on innovation

In theory, health and industrial policy on innovation is aligned. Pharmaceutical companies' R&D investments can deliver value to both patients and shareholders. Health policy objectives are met if R&D pipelines deliver new drugs that address unmet therapeutic or medical needs. Government industrial policy objectives are met when domestic R&D activity contributes to economic growth. Thus, government industrial policy is often aimed at reducing the duration, complexity and therefore the cost of R&D. This is designed to attract and promote industry investment in R&D.

In practice, however, industrial policy does not consistently align with health policy objectives.[22,23] For example, existing 'push' mechanisms are often designed to prioritise domestic investment in pharmaceutical R&D activity, and create highly skilled jobs. However, the opportunity cost of government investment in promoting domestic pharmaceutical sector jobs is uncertain. Push mechanisms also rarely distinguish between meaningful and duplicative R&D efforts at the global level.

Existing 'pull' mechanisms can also create tensions between industrial and health policy objectives. The current system of government-granted monopolies that intellectual property protections afford (ie, patents and market exclusivities) is the primary reason behind high prices of brand-name drugs. In addition, these mechanisms do not improve – and may even harm – the availability and affordability of new medicines in some resource-constrained health systems.[58]

Current approaches to achieving timely patient access to new drugs

Ensuring that the benefits of new drugs outweigh their harms is time-consuming and resource intensive. Investigational products cannot enter the market before pharmaceutical companies undertake rigorous studies which demonstrate their products' efficacy and safety. Data from clinical studies then undergo scientific assessment, first by regulatory agencies and subsequently by payers or HTA bodies.

Since regulatory evidence standards were established in the US in the 1960s (and implemented shortly after in other settings, including the UK), delays to patient access have been a frequent subject of debate.[59] Critics have argued that requiring companies to conduct lengthy clinical trials will unnecessarily delay access to new drugs, make drug development financially unsustainable and harm innovation.[60] Drugs now spend an average of 8.1 years in clinical testing to meet regulatory evidence standards for clinical efficacy and safety, preceded by several additional years of drug discovery and pre-clinical testing.[27] Similarly, criticism has also been directed towards regulatory and

HTA agencies to speed up their review times.[61,62] Inevitably, the enforcement of more stringent regulatory standards has presented drug regulatory agencies with a trade-off between rigorous evidence standards and timely access to new medicines.

Over the past few decades, governments and regulators have made several attempts to expedite patient access to new therapies. To speed up regulatory approval, for example, drug regulatory agencies now charge 'user fees' to pharmaceutical companies for their assessments. These charges support greater staffing levels at regulatory agencies, leading to significantly faster review times.[63] The pharmaceutical industry now pays 75 per cent of the costs of scientific review in the US.[64] In Europe, fees and charges that industry pays to fund regulatory review fund more than 85 per cent of the European Medicines Agency's (EMA's) budget.[65]

Governments and drug regulators have also introduced substantial flexibility in their evidence standards by creating 'expedited approval pathways' to speed up the development, review and approval of new drugs.[66-68] These pathways differ in their scope and focus. Some impose strict deadlines on regulatory review times, while others explicitly lower evidentiary standards for market entry to speed up approvals.[68] Between three-quarters and four-fifths of new drug approvals in the US now benefit from these expedited pathways.[9,69] Only a small minority are 'conditional' approvals.[69,70] Drugs that qualify for expedited approval pathways benefit from shorter clinical development durations and regulatory review times, and therefore enter the market faster.[71,72]

Shortcomings of the current access landscape

Regulatory efforts have been successful in speeding up drug approval times. In the US between 1986 and 2018, median FDA drug approval times decreased from 2.8 years to less than a year.[9] Outside of the US, there has also been marked improvements on historic drug review times.[72,73] Although greater regulatory flexibility in evidence standards has also expedited market access to new drugs, efforts to shorten clinical development times (as opposed to regulatory review times) can lead to substantial uncertainty about the drugs' benefits and harms.[68]

To speed up patient access, drugs that qualify for expedited regulatory programmes receive approval based on less comprehensive data than what is traditionally required for approval.[74] Randomised controlled trials (RCTs) are the most appropriate method to determine the benefits and harms of new drugs.[75] However, evidence underpinning the approval of expedited drugs is less likely to come from RCTs than that of non-expedited drugs.[76] Clinical trials of drugs qualifying for expedited programmes also tend to have smaller sample sizes and shorter follow-up durations and are more likely to use 'surrogate' endpoints.[77] Many surrogate endpoints are not valid predictors of clinically meaningful, patient-relevant outcomes such as survival or quality of life.[78-81]

A prevailing misconception is that, in theory, post-approval research can mitigate uncertainties around new drugs.[82,83] However, such research often does not fill the evidence gaps that exist at the time of initial approval.[84] In addition, pharmaceutical companies have little financial incentive to undertake such post-approval studies, [85] meaning post-approval study commitments are often terminated or remain incomplete many years after approval.[86-88] Even when completed, many post-approval studies are found to be inadequately designed to further inform decisions surrounding the drugs' adoption and use.[89] Therefore, in reality, key limitations of evidence available on drugs at the time of regulatory approval often persist during the post-approval period, regardless of whether post-approval studies have been conducted.[90]

In cases where post-approval studies fail to confirm the clinical benefits of new drugs, evidence shows that they nevertheless often remain on the market for long periods of time.[91] Similarly, clinical practice guideline recommendations may not change in a timely manner even when post-approval research finds no evidence of clinical benefit for new drugs.[91]

Regulatory agencies' growing reliance on user fees from industry has led to concerns about the undue influence of pharmaceutical companies on regulatory processes and decisions.[92,93] In the European Union, the Ombudsman recently carried out an inquiry into companies' pre-approval interactions with the EMA and whether these could influence the eventual opinions of EMA committees.[94] In the US, the recent FDA approvals of eteplirsen (Exondys®) and aducanumab (Aduhelm®) against the near-unanimous recommendations of its scientific advisory committees have raised questions about regulatory independence from pharmaceutical companies,[95,96] particularly since drug regulators conventionally adopt the recommendations of their advisory committees.[97]

Box 4 – Tension between health and industrial policy on access

Shortening the duration of clinical development and regulatory/HTA review reduces costs for pharmaceutical companies and can effectively lengthen the monopoly period during which they can charge higher prices. Patients may also derive benefit from faster access to new drugs if they are more effective than existing treatment alternatives.

However, industrial policies aimed at speeding up access by lowering the bar to market entry may be at odds with health policy objectives. Greater uncertainty about drug benefits at the time of regulatory approval complicates decision-making for patients, clinicians, HTA bodies and payers. The absence of necessary data to establish the true comparative benefits, harms and costs of new drugs relative to existing alternatives makes it difficult to determine whether new drugs are more clinically effective than existing alternatives and whether they offer good value for money in health systems.[98]

Current approaches to ensuring affordability

Drug spending is rising across health care systems, driven by both the price and volume of prescription drugs.[31,99] In the countries of the Organisation for Economic Co-operation and Development (OECD), pharmaceutical spending now accounts for between 1 per cent and 2 per cent of Gross Domestic Product (GDP), and roughly 15 per cent of total health spending.[100]

Latest figures from the OECD suggest that spending on drugs prescribed in the community in many high-income countries has remained stable or decreased relative to GDP or health spending during the past 10 to 15 years, primarily due to patent expiry of several commonly used drugs.[101] However, hospital spending on pharmaceuticals has recently increased in many countries, outpacing the growth of overall health expenditures.[102]

While recently approved patented drugs typically account for less than 20 per cent of prescriptions in most high-income countries, they are responsible for more than 80 per cent of spending.[103] A considerable proportion of this spending is on highly priced drugs that target relatively rare conditions. In the US, roughly 1 per cent of prescription drugs in public insurance plans account for around 30 per cent of net drug spending.[104]

With the exception of the US, high-income countries have comprehensive pricing regulation to lower prescription drug prices. Most high-income countries rely (at least in part) on HTA to evaluate whether new drugs offer good value for money when compared with existing alternatives.[105] Other common strategies, which are used in combination with HTA, include paying similar amounts for comparable products (internal reference pricing) and anchoring prices in one setting to those in other settings (external reference pricing).[106,107] Predictability in spending is also ensured by requiring companies to pay rebates when spending exceeds a pre-specified budget, as in the case of the UK.[108]

Policymakers have also implemented more targeted mechanisms to improve affordability. For example, NHS England has implemented a 'budget impact test' to phase in the introduction of drugs with a high budget impact (exceeding £20 million in any of the first three years) in England.[109] In the US, public and private payers have embraced utilisation management approaches such as prior authorisations (seeking approval from the payer prior to dispensing certain drugs) to manage high drug costs. In theory, risk-sharing and managed-entry agreements between payers and manufacturers aim to mitigate the risk of uncertainty by creating an opportunity to review prices once more evidence becomes available.[110–112]

Shortcomings of the current affordability landscape

Payers' ability to negotiate with pharmaceutical companies and to say 'no' to highly priced drugs that do not offer good value for money is an effective strategy to lower drug prices and control spending.[20] However, governments and payers have an aversion to denying access to certain treatments,[113] especially if those treatments are available to patients in other settings. As payers are increasingly faced with intense public and political pressure to cover new highly priced drugs, affordability has become a pressing problem.[114]

List prices of new drugs during the monopoly period typically do not reflect the products' clinical benefits. For example, recent studies found no association between company-set prices for new cancer drugs and their therapeutic benefits.[115-118] HTA has had mixed success in better aligning drug prices with their clinical benefits.[119] While drugs that offer added therapeutic benefit over alternatives have higher prices in some countries (eg, Germany [120]), the association between price and benefit is weak in others (eg, France [121] and Italy [122]). There is also growing concern that increased drug spending yields diminishing health benefits at the population level. In fact, drug spending during the monopoly period may be displacing other cost-effective services and treatments and may even be harmful to population health (**Box 5**).

Box 5 – Opportunity costs of drug spending

It is important to consider the opportunity costs of allocating resources to new drugs. Economists define opportunity costs as "benefits foregone by particular use of resources".[123] Under fixed (and often limited) health care budgets, allocating resources to new interventions (including drugs) will displace other existing health care services. The opportunity cost in relation to health is therefore defined as "the health lost as a result of the displacement of activities to fund the selected intervention".[124]

In the context of drug spending, when a new drug that benefits a particular group of patients is funded in a health system, this funding decision may impose costs on other patient populations in terms of foregone benefits.[125]

This may be an acceptable trade-off if the health benefits derived from a new drug are equivalent to, or better than, those derived from treatments or services foregone. However, when a new drug costs more to generate a health outcome than the health care it displaces, the opportunity cost exceeds health benefits and overall population health declines.[126]

It is difficult to identify the precise health opportunity cost due to limitations of available data in health systems, making decisions surrounding these trade-offs challenging. According to recent empirical evaluations, the point at which opportunity costs outweigh treatment benefits may be substantially lower than the current levels of willingness to pay in health systems.[127-129]

Risk-sharing and managed-entry agreements between payers and manufacturers have been counterproductive, as they have put the onus on payers to address gaps in evidence and determine value.[130] Such agreements are designed to facilitate the market entry of new drugs while managing uncertainty around their performance. Payers find risk-sharing agreements administratively complex and costly.[130] Experience to date suggests that they have not produced meaningful evidence to reduce uncertainties post-approval.[111] Risk-sharing and managed-entry agreements may even lead to an increase in manufacturer-set list prices, as companies may charge higher prices to reduce revenue loss associated with anticipated discounts.[131]

Box 6 – Tension between health and industrial policy on affordability

Health and industrial policy objectives in relation to affordability are broadly aligned over the long term. Health policy aims to maximise population health while incentivising future pharmaceutical innovation. Industrial policy aims to support the pharmaceutical sector to promote the development of therapeutic advances. However, objectives diverge in the short term. The health system objective of containing prescription drug expenditures is directly at odds with the industrial policy objective of promoting industry's interests in maximising profits.[22,23,132] This divergence in the short term makes setting a coherent pharmaceutical policy on affordability particularly challenging.

Historically, health policies on affordability have sent mixed signals to industry. On the one hand, health systems have demonstrated a willingness to pay more for drugs in certain therapeutic areas (eg, oncology) regardless of their clinical benefit or cost. In the US, there are several laws and regulations mandating insurance coverage for new cancer drugs.[34] Under intense public and political pressure, the UK government established a special Cancer Drugs Fund in 2010 to give cancer patients access to drugs that the National Institute for Health and Care Excellence (NICE) did not deem cost-effective (this fund has since been reformed).[133] Inadvertently, such dedicated schemes that guarantee coverage and reimbursement indirectly encourage companies to charge ever-increasing prices for affected products.[134] These schemes also distort R&D practices, favouring disease areas that are more likely to produce substantial financial returns for the industry.[24,25] It is therefore unsurprising that oncology attracts considerably more investment than other therapy areas.[26]

Box 6 – Tension between health and industrial policy on affordability (continued)

On the other hand, payers have used blunt cost-containment tools to reduce the budget impact of certain drugs shown to offer good value for money.[135] Some payer strategies to tackle affordability have disproportionately disadvantaged drugs targeting prevalent conditions due to their high budget impact. Such budget impact concerns have been particularly acute for one-off treatments. Indeed, recent episodes of delayed or restricted access to expensive but cost-effective therapies such as sofosbuvir have shown health systems' limited ability to reward meaningful innovation in prevalent diseases. In the US, the majority of states considered sofosbuvir a 'non-preferred' drug, severely restricting patient access to it.[136] As some observers have pointed out, the budget impact test in England has explicitly 'slow-tracked' expensive new drugs regardless of their cost-effectiveness.[109]

Section 5 Design principles to build a more coherent pharmaceutical system

Recent proposals aimed at addressing the key challenges in the pharmaceutical sector have ranged from a complete overhaul of the current system (such as nationalising drug development)[137] to more incremental changes (such as more stringent price regulation). Other proposals have recommended replacing the patent-based innovation system with prizes, or paying for clinical trials using public funding instead of industry sponsorship of trials.[138,139] Many of these proposals are aimed at completely transforming the pharmaceutical policy landscape, for which there appears to be little political appetite. Furthermore, their implementation would require international cooperation, the renegotiation of trade agreements, legislation change or initial government funding (although these might ultimately yield substantial savings in the long term).

Short of a major overhaul, there are important opportunities to address the limitations of the current system. Below, we outline four evidence-based design principles for improving the coherence of the pharmaceutical policy landscape.

Principle 1 – Integrating health and industrial policy, prioritising areas of alignment

The degree of alignment between health system and industry interests in relation to the innovation, access and affordability goals of pharmaceutical policies varies. Policymakers should explicitly acknowledge the inherent tensions between health and industrial policy objectives and identify and prioritise areas of alignment.

Innovation

Governments have an opportunity to effectively strike an optimal balance between health and industrial policy on innovation. Government-led mechanisms and public institutions are key drivers of R&D and can stimulate industry investment. Public sector funding is disproportionately important in the development of drugs that generate important health gains.[140,141] For example, fundamental research underpinning the development of drugs with major therapeutic benefits over the past half-century can be traced back to public sector research institutions and academic organisations.[140] Therefore, public sector research funding should be directed at areas of unmet need and used as a catalyst for subsequent industry R&D investment in these areas.[142] Lessons from the COVID-19 pandemic confirm the important role of governments in the R&D effort on therapeutics and vaccines.[143,144] Greater global coordination of public investment can reduce the fragmentation of research efforts and better align pharmaceutical R&D and unmet needs.

Access

There is a trade-off between health and industrial policy objectives in relation to fast market access. Policies aimed at increasing the attractiveness of investment to industry by reducing the barrier to market entry and expediting drug development are associated with increased R&D activity in large markets such as the US.[35] However, these increases come at a cost to health systems. The increased uncertainty associated with expediting drug development and approval has important adverse consequences for patients and physicians.[68] It also dramatically limits health systems' ability to ensure that new drugs offer good value for money. Policies aimed at speeding up access to new drugs should prioritise efforts designed to improve both the quality and the efficiency of clinical trials.[145-147]

Affordability

Finding a balance between health and industrial policy in terms of affordability is even more difficult. Pharmaceutical policies that meet the health system goal of affordability would likely reduce pharmaceutical companies' profitability.[127] Several earlier studies have identified a positive association between company revenues and R&D activity.[148] However, much of R&D activity tends to be duplicative and target already crowded therapeutic areas, rather than scientifically novel pathways.[149] There are also diminishing marginal returns to incentives for pharmaceutical R&D.[150] Although lower prices would likely result in reduced R&D activity over time, there may be an opportunity to shed inefficiencies in R&D and direct industry investments towards areas that would benefit health systems.[151] A more coherent payment policy (as we outline below, Principle 3) would send a strong signal to industry to invest in transformative innovation.

A potential concern for policymakers is that pricing regulation aimed at improving affordability could result in fewer new drug launches and launch delays. Although research from the 1990s found an association between pricing regulation and drug launch,[152] more recent evidence from Germany suggests that pricing regulation has had a limited effect on the availability of new drugs, and almost all drugs with added therapeutic benefits have remained on the German market following pricing negotiation.[153]

Across all three domains of innovation, access and affordability, the discourse on pharmaceutical policy often conflates domestic and global issues. The tension between health and industrial policy is starkest when access and pricing policies are framed as levers to promote private investment in domestic R&D activity. Predictably, access and pricing policies in countries that make a relatively small contribution to industry's global profits have a limited impact on the global R&D spending and investment decisions of pharmaceutical companies. There is also no evidence that links national access and pricing policies to domestic R&D investment decisions in different settings.

Principle 2 – Enforcing meaningful evidence standards for new drugs

Evidence standards that regulatory agencies enforce ultimately determine the quantity and quality of the available evidence on new drugs.[154] This evidence reduces uncertainty surrounding a drug's safety and efficacy, and underpins subsequent pricing and reimbursement decisions. Regulators should ensure that regulatory flexibility aimed at promoting timely patient access does not compromise existing evidence standards.

Over the past three decades, the proportion of new drugs entering the market on the basis of at least two pivotal clinical trials has declined, from more than four-fifths in 1995 to 1997 to about a half in 2015 to 2017.[77] A greater share of new drugs now enters the market on the basis of single-arm (uncontrolled) studies.[155] Fewer than half of new drugs are compared against existing drugs.[156] And most new drugs are assessed in clinical trials using surrogate endpoints that are not reliable predictors of clinical outcomes.[76,157,158]

With the ability to intervene before new drugs reach patients, regulatory agencies are uniquely placed to enforce rigorous evidence standards for new drugs. We outline below three important features of clinical studies, which affect the validity and usefulness of evidence for decision-making in health systems. These features may increase clinical trial costs; but these additional costs should be weighed against the health benefits of generating better data and reducing uncertainty.

First is the type of clinical study from which evidence is obtained. RCTs have greater validity than observational studies (or 'real-world evidence') when determining the efficacy and safety of new drugs.[75] Despite recent enthusiasm for using real-world evidence for efficacy and safety assessment,[159] in most cases, only well-designed RCTs can safeguard against known and unknown sources of bias when evaluating new drugs.[160] It is not uncommon for a new RCT to contradict findings of earlier observational studies, leading to 'medical reversal' of or changes in clinical guidance.[161]

Second, clinical studies that collect data on outcomes that matter to patients (eg, longer survival, better symptom relief or improved quality of life) are most informative in clinical practice and health policy.[81] For results of clinical studies to translate into patient outcomes, regulatory agencies should, where possible, strongly favour evidence from clinical endpoints (eg, survival) over surrogate endpoints (eg, tumour shrinkage).[158]

Third, to inform decisions about which new drugs to use and pay for after approval, patients, clinicians, HTA bodies and payers need evidence on the comparative benefits and harms of new drugs versus existing ones. Therefore, drug regulators should incentivise companies to invest in clinical trials that directly compare a new drug to existing treatments (as opposed to a placebo or no control). These trials produce comparative data that are essential for informing reimbursement as well as clinical decisions.[156,162]

Effective enforcement of these three features of clinical studies would considerably reduce uncertainty and improve the data available for decision-making downstream of regulatory approval. Enforcing meaningful evidence standards for new drugs would likely increase the cost of drug development unless such strategies are coupled with efforts to improve the efficiency of clinical trials.[163] However, recent regulatory guidance in the US and Europe to conduct more costly clinical trials in selected therapeutic areas such as diabetes has not hampered drug development.[164] In fact, regulatory guidance has incentivised companies to demonstrate the effects of their drugs on outcomes that matter to patients.[165]

Principle 3 – Paying for value and ensuring affordability

Policymakers and payers strive to achieve the greatest improvement in population health relative to spending on drugs (value for money) while also incentivising future pharmaceutical R&D. To achieve this efficiency goal in both the short and the long term, aligning the price of new drugs with the clinical benefits they provide would ensure that price is commensurate with value and that companies are fairly compensated for their R&D.[166] Crucially, the benefit of aligning drug price with value stretches beyond the individual drug concerned. Doing so would also ensure that prices paid for the health benefits of new drugs are consistent with the amounts paid for generating similar health benefits using already existing treatments in the health care system.

Policymakers in many countries employ economic evaluation to help determine the value of new drugs. Many high-income countries (eg, Australia and England) formally conduct cost-effectiveness analyses as part of their HTA processes.[167] However, such analyses alone are insufficient to determine the value-based price of a new drug.[126] Determining whether a new drug offers value for money requires identifying a threshold – the maximum acceptable additional cost needed to achieve one additional unit of health outcome when using a new drug compared with its alternatives.[126] The cost-effectiveness threshold helps policymakers to ensure that resources are allocated efficiently to maximise population health.

Setting the cost-effectiveness threshold at the health opportunity cost in a given health care system would determine the point at which the cost of a new drug equals its benefits, relative to other treatments across the health system.[168] At this level, the health benefit derived from new drugs would be equivalent to that derived from foregone interventions and services. Pricing new drugs at the health opportunity cost threshold would mean that the net health benefit associated with new drugs would be zero during the monopoly period.[169] Therefore, if new drugs were priced at the health opportunity cost threshold, health systems would only incur positive net health benefits after generic competition drives prices down.[170]

Although some reimbursement systems currently use cost-effectiveness thresholds, they are often not empirically based, and therefore may not reflect value.[171] In England, for example, NICE uses an incremental cost-effectiveness threshold of between £20,000 and 30,000 per quality-adjusted life year (QALY) gained. Yet, the current best estimate of the health opportunity cost in the English National Health Service is around £12,000 per QALY.[127] Implementing thresholds higher than those derived empirically promotes spending on new drugs, which is harmful for population health.[172] Similar principles can be applied to different countries with differing abilities to pay.[128] It is important to note, however, that obtaining an evidence-based estimate of opportunity costs in health systems is not straightforward due to the limited availability of longitudinal data on expenditures as well as mortality and morbidity trends, which are essential for estimating the marginal productivity of the health system.[127]

Cost-effectiveness analyses highlight to policymakers which drugs provide value for money but do not necessarily address affordability. Some cost-effective drugs may still be unaffordable because of their overall impact on spending in a given budgetary period.[173] Recently, some cell and gene therapies had list prices exceeding £500,000 for a one-off treatment. Although these treatments are currently indicated for small numbers of patients, eligibility is expected to broaden in the future, and may require a recalibration of current payment approaches.[174,175] Another illustrative example is that of sofosbuvir (Sovaldi®). Despite providing a cost-effective treatment option, its high list price resulted in the drug costing the US health system more than £5.8 billion in the first year post-approval alone.[176]

'One-off' treatments such as cell and gene therapies present distinct affordability challenges.[117] Such treatments may cost health systems multiple orders of magnitude more than chronic treatments. Costs associated with chronic treatments are spread over the full lifecycle of the product, with an opportunity for health systems to benefit from post-patent expiry savings. There is no similar opportunity for one-off treatments, as they require payment upfront. This is further exacerbated in therapeutic areas with high prevalence and low incidence, as demand typically declines over time.[178]

To ensure the long-term affordability of one-off treatments, it is possible to explicitly incorporate budget impact considerations into cost-effectiveness analyses for HTA.[179] Payment models that 'de-link' payment from volume, spreading the upfront costs of new drugs (eg, the so-called 'Netflix model'),[180] could also be better alternatives than 'slow-tracking' or restricting access to expensive but cost-effective therapies. Annual payments linked to drugs' performance on measurable and clinically meaningful outcomes may help alleviate the affordability challenges associated with one-off treatments.[177]

Principle 4 – Improving transparency

Transparency is essential for meeting the innovation, access and affordability aims of pharmaceutical policies. Enhanced transparency surrounding clinical trial data would lead to a more reliable evidence base, and facilitate better understanding of the benefits and harms of new drugs at approval.[181] Greater transparency would also improve public health by allowing third parties due scrutiny of trial data and decision-making processes.[182]

Yet, several key aspects of the current pharmaceutical system lack transparency. For example, clinical trials supporting the regulatory approval of new drugs may not be disseminated in a timely manner. Until recently, clinical trials with favourable results were more likely to be published than trials with null or non-favourable findings.[183,184] Combining findings from published and non-published trials can alter a drug's apparent benefit–harm profile.[185,186] Such selective publication can therefore distort decision-making in clinical practice and health policy. Non-publication of completed studies can also contribute to duplication of efforts and research waste.[187]

Over the past two decades, legal mandates to register clinical trials in publicly available repositories in Europe and the US have substantially improved timely reporting of clinical trials, but there remains room for improvement.[188] More recently, several independent initiatives to promote data sharing have also emerged.[189] However, individual participant data from drug trials remain largely unavailable. Further improvements in the transparency of individual patient data are likely to allow independent re-analysis to verify the findings, generate new hypotheses and identify subgroups of patients who may respond differently to the drug in question.[190,191] Sharing individual participant data can help guide evidence-based decisions.[192]

Much of the recent policy attention has been on improving transparency on drug pricing.[193] Pharmaceutical companies often argue that high drug prices are necessary to recoup large R&D investments. Currently, information on the amount that companies spend on R&D to bring a single new drug to market is not publicly available. Even the most credible estimates are based on the small subset of publicly traded US companies, accounting for fewer than a fifth of drug approvals over the past decade.[26] However, greater transparency of pharmaceutical R&D costs may have unintended consequences. Public reporting may inadvertently reduce the efficiency of R&D and increase the cost of drug development. From an economic perspective, it is not desirable to link drug prices to R&D expenditures (as outlined above, Principle 3).

In addition, payers do not disclose any information on negotiated discounts, rebates and similar mechanisms to lower drug prices in other settings.[194] In 2019, member states of the World Health Organization adopted the 'Transparency Resolution' (World Health Assembly resolution 72.8), which aims to improve the public disclosure of net drug prices (including rebates and discounts).[195] Notably, disclosure of confidential discounts may compromise payers' negotiating power and further exacerbate access issues in countries with less ability to pay. Explicit use of empirically derived cost-effectiveness thresholds (based on health systems' marginal productivity) to determine pricing and reimbursement decisions would improve transparency internationally.

Greater transparency on industry payments to and interactions with physicians, health care organisations, patient organisations and other decision-makers is warranted.[196] Until recently, there was limited publicly available information on the extent and nature of industry payments to physicians and health care organisations. In the US, the Physician Payments Sunshine Act 2010 has mandated the public disclosure of all physician payments exceeding $10. In other settings, including the UK, attempts at improving transparency on physician and patient organisation payments have been voluntary.[17] Mandatory disclosure of industry payments in a publicly available database is needed to ensure complete transparency.

Section 6 Conclusions

The current pharmaceutical system presents several opportunities to reconcile the innovation, access and affordability aims of health policies. Although existing 'push' and 'pull' innovation incentives are effective in delivering record numbers of new drug approvals, they do not always prioritise unmet needs or innovations that offer step-change improvements in patient outcomes.

Recent policy interventions also achieve substantially faster access to new drugs but do not effectively incentivise the generation of essential evidence on the benefits and harms of new drugs, leading to uncertainty about their clinical effectiveness and cost-effectiveness. Such uncertainty puts significant pressure on HTA bodies, as well as payers, to appraise and cover drugs on the basis of very limited evidence after approval. Despite uncertain clinical benefits, new drugs invariably demand high prices, which patents and other market exclusivities sustain. To date, policy responses to high prices have been fragmented, with varied success in aligning drug prices with their benefits.

A coherent pharmaceutical system would:

- strike a more optimal balance between population health and industrial policy objectives
- address patients' need for timely access to new drugs
- ensure the efficient use of health care resources
- foster meaningful innovation.

Policymakers can strike this balance by:

- more closely integrating health and industrial policy
- enforcing meaningful evidence standards for new drugs
- explicitly linking drug prices to the value they offer relative to existing treatments (while taking account of the health opportunity cost)
- promoting greater transparency throughout the drug lifecycle.

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