# NEW BUSINESS MODELS FOR PHARMACEUTICAL RESEARCH AND DEVELOPMENT AS A GLOBAL PUBLIC GOOD: CONSIDERATIONS FOR THE WHO EUROPEAN REGION

**OSLO MEDICINES INITIATIVE TECHNICAL REPORT**

Suerie Moon, Marcela Vieira, Adrián Alonso Ruiz, Danielle Navarro

## Oslo Medicines Initiative

Established in 2020, the Oslo Medicines Initiative (OMI) is a collaboration between the WHO Regional Office for Europe, the Norwegian Ministry of Health and Care Services and the Norwegian Medicines Agency. The OMI aims to provide a neutral platform for the public and the private sectors to jointly outline a vision for equitable and sustainable access to and affordability of effective, novel and high-priced medicines.

In line with the Regional Office's European Programme of Work 2020–2025 – "United Action for Better Health", equitable and sustainable access to quality medicines is critical for universal health coverage and for achieving the Sustainable Development Goals. The OMI provides a strong focus on equity and on leaving no one behind, and is underpinned by three pillars: solidarity, transparency and sustainability.

The OMI has commissioned a series of technical reports to summarize relevant evidence and to provide policy considerations as a basis for discussion to inform its work. These reports are also in line with the implementation of World Health Assembly resolutions, in particular, resolution WHA72.8 on improving the transparency of markets for medicines, vaccines, and other health products.

# NEW BUSINESS MODELS FOR PHARMACEUTICAL RESEARCH AND DEVELOPMENT AS A GLOBAL PUBLIC GOOD: CONSIDERATIONS FOR THE WHO EUROPEAN REGION

## OSLO MEDICINES INITIATIVE TECHNICAL REPORT

Suerie Moon, Marcela Vieira, Adrián Alonso Ruiz, Danielle Navarro

**Abstract**

Public concern has been increasing about the high prices of novel medicines, limits on availability and access, and the strain on health-care budgets across all countries. Addressing these challenges requires scrutinizing the underlying system of research and development (R&D) that produces these outcomes. Increasing policy attention has turned towards how to make the outputs of the innovation process accessible to all, and what changes to the current innovation model are needed. This report analyses the implications and challenges of transforming medicines – which have to date largely been treated as national private goods – into "global public goods" (GPGs). It describes the current model for pharmaceutical R&D and assesses how well it performs in producing GPGs along three dimensions: generation of pharmaceutical knowledge, its global availability and its global affordability. It then investigates alternative business models, including those implemented for COVID-19, and analyses how well they may be able to produce GPGs, concluding with proposals for consideration by public and private actors in the WHO European Region that could reorient the R&D system towards delivering GPGs.

# Contents

# Acknowledgements

# Abbreviations

| | |
|---|---|
| **AMC** | advance market commitment |
| **BARDA** | United States Biomedical Advanced Research and Development Authority |
| **CEPI** | Coalition for Epidemic Preparedness Innovations |
| **EMA** | European Medicines Agency |
| **EU** | European Union |
| **FDA** | United States Food and Drug Administration |
| **GDP** | gross domestic product |
| **GERD** | gross domestic expenditure on research and development |
| **GPG** | global public good |
| **Health GERD** | gross domestic expenditure on research and development in the health and medical sciences |
| **IP** | intellectual property |
| **MPP** | Medicines Patent Pool |
| **NIH** | United States National Institutes of Health |
| **OECD** | Organisation for Economic Co-operation and Development |
| **OMI** | Oslo Medicines Initiative |
| **PDP** | product development partnership |
| **PRV** | priority review voucher |
| **R&D** | research and development |
| **SMEs** | small and medium enterprises |
| **WIPO** | World Intellectual Property Organization |

# Executive summary

## Background

Public concern has been increasing about the high prices and limited availability of novel medicines (including vaccines, drugs, diagnostics and other health technologies – referred to as "medicines") that can both restrict access and strain budgets across all countries. Addressing such challenges requires focusing not only on the prices themselves, but also on the underlying system of research and development (R&D) that produces these outcomes.

Increasing policy attention has turned towards how to make the outputs of the innovation process global public goods (GPGs). A GPG, in the economic definition, is a good that is non-excludable (no one can be excluded from consuming it) and non-rival (consumption by one person does not reduce the availability of the good for others) in consumption globally. Some scientific information that is fundamental to the development of medicines is already generated as a GPG – in particular, open access basic scientific research. However, a great deal of pharmaceutical-related knowledge – such as knowledge about specific compounds produced by private, public and philanthropic actors – is not routinely made available as a GPG, but could be with intentional policy changes.

## Objectives and approach

This report analyses the implications and challenges of transforming medicines into GPGs. In the current business model, medicines are treated as private goods, and policies have largely focused on making them available (that is, "non-excludable") nationally rather than globally. How can goods that have been *national* and *private* be made more *global* and *public*? Realizing the vision of pharmaceutical R&D as a GPG requires a rethinking of the fundamental purpose and a re-evaluation of the current business model for pharmaceutical R&D. In this report, the term "business model" is used to refer to the way R&D is financed (including push funding and pull incentives), organized, facilitated, regulated and governed.

In practical terms, for pharmaceutical innovation to be a GPG, it must first be generated (for example, the knowledge must be created, and a medicine must be invented and demonstrated to be safe and effective); it must be widely available (for instance, physically available in health systems); and there should be no barriers to access (such as high prices). This paper applies these three criteria to assess the extent to which existing and alternative innovation business models approach the ideal of a GPG.

# Findings and policy considerations

The current R&D business model has evolved from a vertically integrated model (with one firm bringing a product from early development all the way to market as a product demonstrated to be safe and effective) to a "relay race," with various public, non-profit and commercial "runners" involved at different stages, with an increasing role of small- and medium-sized firms along the process. Both public and private actors take on risks and costs throughout the R&D process, but a key question under debate is how fairly benefits are distributed, especially given the lack of transparency and underappreciation for the contribution of the public sector across the entire innovation chain.

The current business model for pharmaceutical R&D has yielded significant technological and therapeutic advances. However, it suffers from several shortcomings that impede the generation, availability and affordability of pharmaceutical knowledge as a GPG:

- Innovation needs are neglected in areas where the market incentive is too small or risky.

- Competition among R&D actors can retard innovation by disincentivizing, impeding or blocking the sharing of knowledge as a GPG, which drives science forward.

- Monopoly rights can limit the manufacture of end-products, generating artificial scarcity and reducing the global availability of medicines.

- High prices are built into the system by design, as they are the main incentive drawing private investment into R&D.

These shortcomings have prompted experimentation with alternative business models for R&D and proposals for further change. Alternative business models have been developed mainly in four disease "niches" – neglected diseases of poverty, rare diseases (including rare paediatric diseases), biosecurity (pathogens of pandemic potential) and antibiotics. The extent to which each model seeks to address the three shortcomings – lack of invention, limited availability or lack of affordability – and their potential for delivering GPGs varies. However, these different approaches to incentivizing and conducting R&D show that it is possible to move beyond the existing model.

Many of the policy tools and approaches identified in these alternative niche models have been used for COVID-19 health technologies. However, while diagnostics, vaccines and some therapeutics have been developed in record time, global access to them remains grossly inadequate. Momentum generated and experience gained during the pandemic relating to funding, development, manufacturing and distribution of novel, high-price medicines should be built on, and merits further analysis for lessons on how to realize such technologies as GPGs.

This analysis of current and alternative R&D models leads to the following conclusions and proposals for consideration by Member States in the WHO European Region:

- invest in strengthening the WHO European Region's contributions to the WHO Global Observatory on Health Research and Development to guide decisions in terms of priorities, investments and policy reform; greater transparency is needed on the drivers of escalating costs of end-products to shape public policies and incentives;

- negotiate binding commitments ensuring that, where there has been public investment in R&D, the resulting data, knowledge and intellectual property will be openly shared. Investments in R&D could be made domestically, regionally or globally; what is critical is to ensure that all knowledge generated rapidly enters the public domain as a GPG;

- create a pooled regional fund to support high-priority/high-risk pharmaceutical R&D that both responds to jointly agreed priorities and ties conditions to its investments to ensure availability and affordability of the end-products;

- create a pooled regional procurement initiative that would increase the negotiating leverage of governments and that would pool various risks, including the risk of R&D failure, and consider pooled procurement options ranging from limited information-sharing across countries to demand pooling (single buyer) to full joint negotiation and procurement of products;

- create mechanisms to enable increased investment in small and medium enterprises (SMEs), tying fair pricing and transparency conditions to funding. Pharmaceutical SMEs, which are broadly distributed across the Region, often rely on external investors to assume the risk and finance their R&D, and the scale of the investment is smaller than for later-stage R&D, therefore, investing in SMEs may be more financially feasible for many individual countries (compared to financing late-stage R&D or multinational firms);

- act as system integrators: by not necessarily only funding projects, but by fostering collaboration and knowledge sharing, and by identifying complementarities between different actors in the Region; and

- invest in manufacturing capacities in the Region, ensuring cross-European coordination to ensure greater availability and resilience of medicines' supplies once the knowledge has been generated.

Entrepreneurial leaders from the pharmaceutical industry could:

- engage productively and proactively with policymakers to test alternative R&D business models that would deliver GPGs.

Vision, creativity and an appetite for risk-taking from the pharmaceutical industry are needed to meet the growing societal expectation that medicines should be available as GPGs.

The current R&D business model functions on the logic of restricting access to knowledge as a means to pay for its creation, rather than on making that knowledge publicly available. Alternative business models with outcomes better aligned with public interests are possible, but they must be purposefully constructed with appropriate investment, organizational arrangements, incentives and underlying laws and policies. While a wide range of alternative business models have been implemented, a unifying theme across them is the fundamental role of governments as stewards of the innovation system. This stewardship role needs to be strengthened both nationally and through intergovernmental cooperation. Generating GPGs also requires investors to put money on the table and to accept risks, and Member States have historically been willing to do so as the "patient investors" that have enabled major technological progress. The risks can be quantified, managed and pooled across countries. Finding ways to share costs and risks across countries is essential to subsequently being able to share the "reward" or benefit of advancing pharmaceutical innovation.

However, current international arrangements are too thin and inadequate to do the necessary coordination. It may be useful to revisit the negotiation of binding international rules to structure cooperation across countries in the Region. Regardless of the specific policies pursued, moving from the national to the regional level and beyond will require strong political leadership to re-orient the R&D system towards delivering the results of the innovation process as GPGs.

1

# Introduction

## 1.1  Background, purpose and overview

Public concern has been increasing about the high prices and limited availability of novel medicines (including vaccines, drugs, diagnostics and other health technologies – referred to as "medicines" in this report for brevity), which can both restrict access and place a strain on health-care budgets across all countries *(1)*. It is increasingly understood that addressing such challenges requires focusing not only on the prices themselves, but also on the underlying system of research and development (R&D) that produces these outcomes.

In mid-2020, as the COVID-19 pandemic gained force, high-level political leaders, including the European Commission President von der Leyen, called for COVID-19 vaccines and other technologies to be considered "global public goods" (GPGs) *(2,3,4,5)*. While this term is not precisely defined, the key concept behind GPGs is that they are freely available to all, worldwide.

Realizing the vision of pharmaceutical R&D as a GPG, however, requires a rethinking of its fundamental purpose. Pharmaceutical R&D has been pursued with various goals: improving individual or population health; advancing science; maximizing profit; providing employment; and strengthening a country's technological capacity and competitive advantage in the global economy. Some of these goals conflict with the aim of making the outputs of pharmaceutical knowledge openly and freely available to all. Doing so, therefore, requires a re-evaluation of the current business model for pharmaceutical R&D, which was not designed to generate GPGs.

While the term "business model" can be used in different ways *(6)*, it is used in this report to refer to the way R&D is financed (including push funding and pull incentives), organized, facilitated, regulated and governed. The concept of a business model is not limited to either the public or the private sector, but encompasses both; it recognizes that public laws, policies and regulations, and private organizations and investment ultimately shape the production of pharmaceutical knowledge. Increasing attention has been paid to whether pharmaceutical R&D can be reconceived and reorganized into new business models to ensure widespread access to the health technologies that result from it.

The WHO European Region is a major source of both innovation and spending on medicines, and plays an influential role in the global pharmaceutical ecosystem. Europe, with its wide range of income levels, innovation and access-to-medicines challenges, is fertile ground for the implementation of new business models.

This report begins with a review of the concept of GPGs and considers how this relates to medicines. It examines how well the current R&D business model is able to deliver medicines as GPGs by summarizing its key features and investigating how it has evolved over the past several decades. It then turns to alternative business models, including those implemented for COVID-19, and analyses how well they may be able to provide pharmaceutical innovation as a GPG. Finally, it offers proposals for consideration by both public and private actors in the WHO European Region to move closer to the ideal of universal accessibility to the end-products of the innovation process.

## 1.2  Methods

This study uses a mixed-methods approach to describe and analyse the pharmaceutical R&D ecosystem and potential changes that may better meet public interests and deliver GPGs. It draws on literature reviews previously conducted by the authors.[1] Original data collected in previous research projects at the Global Health Centre of the Graduate Institute of International and Development Studies are summarized for this report (see, for example, Moon, Vieira & Kimmitt *(7)*). The authors also conducted primary research to collect novel data, especially on initiatives for COVID-19 *(8)*. This report draws on these literature reviews, previous research and new data, as well as on the authors' expert knowledge, to analyse the current pharmaceutical R&D system and to suggest potential alternatives and proposals for change.

---

1   See, for example, literature reviews on the public funding of pharmaceutical R&D *(9)*, the role of SMEs *(10)*, product development partnerships *(11)*, biosecurity R&D *(12)*, R&D costs *(13)*, and time frames and success rates of pharmaceutical R&D *(14)*.

2

# Medicines as GPGs

## 2.1  GPGs: defining the concept

The term "GPG" is sometimes used loosely to denote that which is "good" for the global public. This report uses the technical economic definition, as this offers useful analytical clarity: a GPG is a good that is globally non-excludable and non-rival in consumption *(15,16)*. "Non-excludable" means that no one can be excluded from consuming the good. "Non-rival" means that consumption of the good by one party does not reduce the amount of good that remains for others to consume. The key idea is that a GPG is freely available to everyone.

Textbook examples of public goods include lighthouses, traffic rules and public information – for each of these, consumption by one ship captain, driver or student does not diminish the availability of the good for others; and other captains, drivers and students are generally not excluded from consuming them *(17)*. One example is that once the weather report is published in the morning, an early riser can "consume" it, but no less information remains for late risers who may also wonder what shoes to put on before going outside that day. Examples of important GPGs for health include norms and rules; standards and guidelines; research into the causes and treatment of disease; and comparative evidence and analysis (see Table 1 for further examples).

**Table 1. Examples of GPGs for health**

| Category | Examples |
| --- | --- |
| Norms and rules | • International Health Regulations<br>• International Classification of Diseases<br>• International nonproprietary names |
| Standards and guidelines | • Treatment guidelines<br>• Good manufacturing practices |
| Research and assessments | • Basic scientific research published open access<br>• Target product profiles |
| Comparative evidence and analysis | • Marketing approval from health authorities (such as the EMA or the FDA)<br>• Health technology assessments<br>• WHO prequalification |

EMA: European Medicines Agency; FDA: United States Food and Drug Administration; GPG: global public good.

Some scientific information that is fundamental to the development of medicines is already generated as a GPG – in particular, basic scientific research (such as knowledge of how a disease or the human body works) that is published with open access. A great deal of pharmaceutical-related knowledge – produced not only by private actors, but also by public/philanthropic institutions – is not routinely made available as a GPG, however, but it could be. Furthermore, some goods may best be understood as potential rather than de facto GPGs (Table 2). "Club goods" are potential public goods that have been made excludable – often as a means to finance their production – but their non-excludability trait is not immutable *(17)*. Rather, the degree to which a good is made more or less excludable is frequently the result of social and political choices *(18)*. For example, it is possible either to construct a paywall to charge a fee to access a research article online or to adopt an open access model. Similarly, it is possible to patent a health technology and exclude others from producing or using it, to choose not to apply for a patent or to license the patent freely to others. New financing streams could cover the costs of making a club good non-excludable, such as by paying the fees charged to authors to publish in open access journals or by buying out patents on new medicines so that they may be put in the public domain and immediately produced as generics *(17)*.

**Table 2. Categories of goods and examples**

| Category | Excludable | Non-excludable |
|---|---|---|
| **Rival** | Private goods (such as physical components of a medicine – tablet, syrup or injection) | Common goods/common pool resources (such as efficacy of antibiotics) |
| **Non-rival** | Club goods (such as knowledge protected by exclusive rights – patent or data exclusivity) | Public goods (such as scientific information published with open access) |

In essence, a medicine has two components: the scientific knowledge and a physical product. The crucial pharmaceutical knowledge that allows a product to be used with confidence as a medicine can essentially be set out as: compound X at dose Y has effect Z on the average human body (with adverse effects A with a likelihood of B). Once this valuable information is generated (for example, through preclinical studies and clinical trials), validated (by a regulator) and published, anyone can "consume" it, if it is published with open access and made available in the public domain. Further information on how to manufacture compound X at acceptable levels of quality can also be made public as a GPG.

This knowledge is costly to generate, and is often the most valuable component of a medicine. In contrast, a medicine's physical component (the tablet, syrup or injection) can be produced at relatively low cost. The value of that knowledge is why societies allow a capsule that cost €1 to produce to be sold at €1000 *(19)*. The physical component of a medicine is not a public good according to the technical economic definition: if one person swallows a pill, another person cannot (it is excludable), and there is one less

pill for everyone else (it is rival). Thus, it is a private good. Nevertheless, the knowledge component of that pill can potentially be made a GPG if others are free to make use of that knowledge (for example, if it is published with open access and not protected by patents and/or other data and market exclusivity rights[2]), including to produce more pills.

In essence, for pharmaceutical innovation to be a GPG, it must first be generated (for example, the knowledge must be created, and a medicine must be invented and demonstrated to be safe and effective); it must be widely available (for instance, physically available in health systems); and there should be no barrier to access (such as high prices). These three criteria are applied to assess the extent to which existing and alternative business models of innovation may approach the ideal of a GPG (see sections 3 and 4).

## 2.2  Implications and challenges of pharmaceutical R&D as a GPG

Public goods theory emphasizes two types of challenge that arise. First, public goods are costly to generate; if everyone can consume them without paying, there is little incentive for any private actor to invest in producing them because they cannot charge for their consumption. This is often referred to as the "free-rider" problem, because consumers and competitors can enjoy the investment made by the producer of the public good without paying for it. For this reason, international organizations and national governments (rather than market actors) are often responsible for ensuring adequate provision of public goods, either directly through public entities financed by taxation (which addresses the free-rider problem) or indirectly by establishing the rules and incentives for private actors to provide such goods. Scientific knowledge for medicines is costly to produce and is generated through both direct public investment and indirect incentives to private actors. While institutions for the provision of public goods are relatively well established at the national level, they are weak and underdeveloped at the international level – both regionally and globally *(17,20)*. No arrangements are in place for international taxation, for example, meaning that GPGs must often be financed through ad hoc or voluntary arrangements, such as pools of donor funds.

Second, fair processes are required to set priorities for which public goods should be generated, since the demand for public goods is potentially infinite. Society could benefit, for example, from more scientific knowledge being generated on all causes and consequences of human and animal diseases. With finite resources, however, priorities must be set to determine which public goods are the most important and how much investment they should receive. Setting such priorities is both technically complicated and necessarily a political process, given that some groups will benefit more than others. Many national innovation systems also value "blue sky" research, which is driven by investigators

---

2    Market exclusivity rights can be granted by regulatory agencies after a medicine has been approved, during which time no other producer is allowed to sell the drug, whether or not it is protected by a patent. Patent rights and market exclusivity periods usually, but do not always, overlap. For example, the EMA grants a 10-year period of market exclusivity after the marketing authorization of a rare (or "orphan") medicine. The FDA grants several types of market exclusivities, including a 5-year period for new chemical entities and for novel antibiotics. Data exclusivity can be granted over the results of tests necessary to obtain regulatory approval, during which time another applicant cannot rely on the data to support obtaining market authorization. In Europe, the general period of data exclusivity is 8 years, which can be extended for 2 years in the case of additional new therapeutic indications of significant clinical benefit (Article 14(11) of Regulation (EC) No 726/2004).

rather than societal priorities or needs. Political processes to decide on priorities are often more clearly established at the national rather than the international level.

In addition to these, there is a third challenge for medicines, which is that knowledge must be translated into a physical product that is delivered to a patient in order to produce health effects. That is, the potential public good (knowledge) must be converted into a private good (such as a tablet, an injection or a device) that is both excludable and rival in consumption. Demonstrating that the product meets regulatory standards – that it is of high quality, safe and effective – and applying appropriate risk management and pharmacovigilance are essential for realizing pharmaceutical innovation as a GPG. These are complex processes with legal and ethical responsibilities and, apart from a few cases, are generally undertaken by the private for-profit sector, requiring significant investment with a rate of return to make them an attractive investment option for private actors. Note that the production and quality assurance phases fall largely outside the scope of this report, so they are addressed only briefly.

These three challenges of public goods provision are relevant across the WHO European Region and globally. Countries could agree to approach pharmaceutical R&D as a public good that is regional or global, so that the benefits of new scientific knowledge would be openly available to all. Realizing this vision, however, requires agreement on how to share the financing of R&D among countries and how to set priorities. Important precedents for this type of regional collaboration include the European Organization for Nuclear Research, which is jointly financed and governed by 23 countries, or the European Union (EU) Framework Programmes for Research, which are funded by contributions of EU member states. No region-wide funds for pharmaceutical R&D or priority-setting processes to guide public investment in medicine innovation are in place, however. At the EU level, the Innovative Medicines Initiative *(21)* and the European & Developing Countries Clinical Trials Partnership *(22)* have allocated significant public resources to medicine R&D, although not necessarily with the goal of the final products being GPGs. Specific arrangements for funding pharmaceutical R&D across the Region may be needed to realize the goal of generating this knowledge as a public good – regional or global (see also section 6 on proposals). Current investments and incentives could also be redirected and reoriented for that purpose.

3

# Current business model for R&D: description and critique

For medicines to meet the technical definition of a GPG, they must be generated and be available and accessible to all globally. The current business model for pharmaceutical R&D was neither conceived nor built for this purpose. To improve understanding of how to reorient the system towards producing GPGs, this report examines how the current business model works and assesses how well it delivers GPGs.

## 3.1  Actors and policies in the current R&D business model

The R&D system can be understood as comprising the actors (such as academic and public research organizations; small, medium and large firms; policy-makers; and civil society groups) and the rules (including laws, incentives, regulatory standards and reimbursement policies) and practices that govern their interactions.

Pharmaceutical R&D can be summarized as follows. At the earliest stages, basic scientific research is conducted to understand the functioning of the human body, and to identify the causes, consequences and progression of disease. This stage may last a few years or many decades; it can uncover potential "targets" in the body – for example, pathogens or aspects of the immune system that can be strengthened by the intervention of a medicine. In the "discovery" phase, compounds are identified that may be able to hit those targets to prevent, alleviate or cure a disease. In this phase, a large number of potential compounds are screened; leading candidates are identified; and those leads are optimized for further development. In the next stage of "translation", those leads undergo further testing (preclinical) – for example, in animals – before moving on to initial in-human clinical trials (Phase 1), in which a candidate compound is tested for safety in a small number of human volunteers and doses are optimized. The candidate medicine may progress to Phase 2 trials, in which safety and efficacy are tested in a larger number of human volunteers, in the hope of establishing proof of concept – that the compound has its intended effect on the human body. It may then move into larger-scale Phase 3 trials to verify safety and efficacy by generating data from a larger sample size. Thereafter, an application needs to be submitted for regulatory approval (registration), based on the data generated in these trials. Once approved, a product can be manufactured at scale, priced, distributed and sold, and can reach patients. Legal and ethical post-authorization responsibilities also exist, with financial implications, including risk management and pharmacovigilance.

Traditionally, public and academic laboratories conducted early-stage basic research, while large vertically integrated pharmaceutical firms built on the broad foundation of this publicly available scientific knowledge to develop specific products. Commercial firms largely carried out the later stages of R&D – from preclinical testing to clinical trials, through to registration, manufacturing, marketing and post-marketing surveillance. This vertically integrated model is no longer the only – or even the dominant – one, however.

Over the past several decades, the R&D process has evolved to resemble a relay race, with many different public, non-profit and commercial "runners" potentially involved at different stages (Fig. 1).

### Fig. 1. Vertically integrated and multiplayer R&D models

**Historically integrated pharmaceutical firms supply chain**

| Research | Development | Manufacturing | Marketing & sales |

**Renewed multiplayer pharmaceutical supply chain**

| Research-scouting-licensing | Development-trial-management | Production | MKT access & commercialization |

| Development Stage Companies | Contract Research Organizations | CMOs | Health Services |
| University | Clinical Trial Service Firms | Packagers | |
| Life-sciences Incubators | | Formulators | |
| Laboratories | | API Manufacturers | |
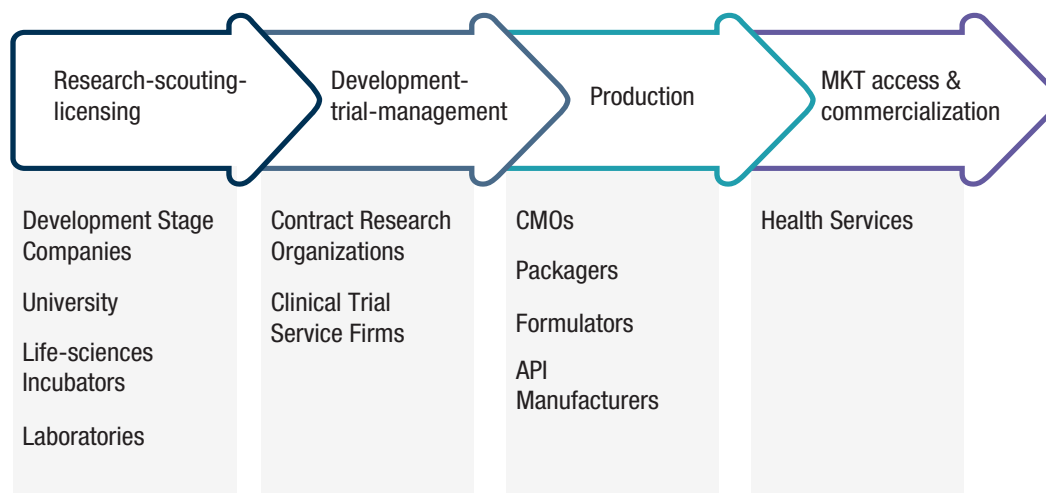
API: active pharmaceutical ingredient; CMO: contract manufacturing organization; MKT: market.
*Source:* Capo, Brunetta & Boccardelli *(23)*.

For example, a discovery of a promising compound made in a publicly funded academic laboratory could be spun off into a start-up commercial firm by the academic researcher. Such spin-offs have been encouraged by public policies, such as the United States of America's Bayh-Dole Act or the Patent and Trademark Amendments Act (Pub. L. 95-517, December 12, 1980) and analogous legislation in other countries. The Bayh-Dole Act sought to translate academic research findings more quickly into products, with mixed effects on innovation and access *(24,25)*. The start-up firm may advance the candidate product a few more steps into preclinical testing before out-licensing it to another developer or being acquired by a mid-size firm. The mid-size firm may further develop the product through Phase 1 and 2 trials, then out-license it again to a large multinational, which may complete Phase 3 trials and apply for registration. Manufacturing may be contracted out to another firm, and marketing and distribution rights sold to different firms in different countries. In reality, the relay race is rarely just a single linear one: multiple runners are often also moving in different directions with a single compound. Intellectual property (IP) rights (such as patents and industrial designs) and other forms of market exclusivity (including regulatory exclusivities, such as those linked to data) enable the seller to charge the highest price the market or price regulator will bear for the medicine. Each time a

runner passes the "baton" to the next – that is, each time partial or full control of the technology changes hands – a transaction occurs that can shape the kind of product that is ultimately developed, how it is priced, who is able to produce it, and where it is made available.

Small and medium enterprises (SMEs) play an increasingly important role in both early- and later-stage R&D *(10)*. Many of the larger firms have reduced in-house R&D investment, by acquiring SMEs or in-licensing their technology at the later – less risky, but costlier – phases of R&D *(26)*. Sources of new medicines have changed in recent years (Fig. 2): 33% of the forecast sales for the 12 biggest pharmaceutical companies derive from acquisitions and not from in-house innovations *(27)*. Recent studies have found that most new medicines obtaining regulatory approval originated from SMEs, and SMEs are increasingly obtaining regulatory approval themselves *(28)*, even if most of the drugs still "change hands" along the development process *(29)*.

An analysis of mergers and acquisitions in the pharmaceutical sector reveals that the baton changes hands at different phases of the development process, with larger pharmaceutical companies mostly coming in at later stages *(30)*. Fig. 3 illustrates the origins and transfers of 55 of 94 new drugs approved by the European Medicines Agency (EMA) from 2010 to 2012 by type of developer, from originating entities to the owners of the marketing authorizations. It has been noted that biotechnology companies and non-industrial institutions (university, hospital and other research centres) have increasingly been leading R&D projects directed at smaller markets *(31)*.

**Fig. 2. Origins and transfers of new medicines, by type of developer**
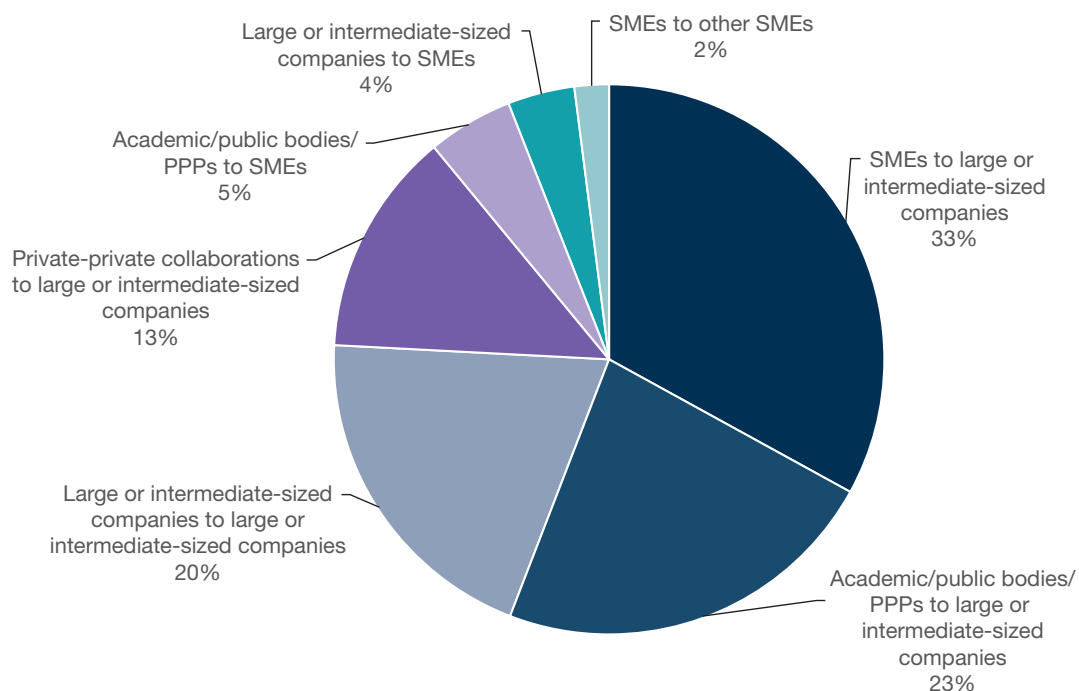


PPPs: public–private partnership; SMEs: small and medium enterprises.
*Source:* Based on data from Lincker et al. *(29)*.

In a vertically integrated model, a single firm would finance R&D from the early stages until a product reached the market successfully and began to generate sales revenue. In a relay race, on the other hand, the flows of financing differ. In the example above, an academic spin-off firm may be financed initially by investors, such as venture capital funds with relatively higher risk appetites. Notably, early-stage investors may also be governments or philanthropic foundations with an interest in seeing a technology developed successfully for a specific problem, such as antimicrobial resistance or a rare disease. As an SME further advances the development of its candidate, knowledge accumulates and risk falls; the candidate technology may eventually carry a high enough potential reward to be acquired by a larger firm with adequate financial resources to develop it. When a firm in-licenses the technology of – or acquires – an SME, the payment flowing to the SME's investors of this asset provides a financial reward. In this way, rewards for investment and risk can be realized at each stage of the R&D process, and not only through the successful sales of an end-product. This staged approach can both break up risk into smaller chunks and shorten the timescale for any particular funder to profit from their investments, reducing the cost of capital (Fig. 3). It can also, however, inflate the total financial investment in a product before it reaches the market – much of which is not an R&D cost, but rather a mid-stream profit for investors – and, consequently, drive up the price of the final medicine.

Each time a runner in the relay race passes the baton to the next runner, a contract with terms and provisions usually shapes the price, supply and characteristics of the final product. These agreements are generally confidential, however, with little information publicly available about their contents. Significant efforts have been made to increase the understanding of such contracts by collecting clauses from model and executed agreements (see, for example, GHIAA *(32)*) and using government freedom-of-information policies to obtain redacted contracts involving government entities (see, for example, KEI *(33)*). These efforts have yielded new knowledge and insights, but they do not replace the need for more systematic disclosure and widespread transparency in order to understand the drivers of the escalating costs of end-products and to shape public policies and incentives.

**Fig. 3. Staged rewards of investment in a simplified, linear relay race R&D model**
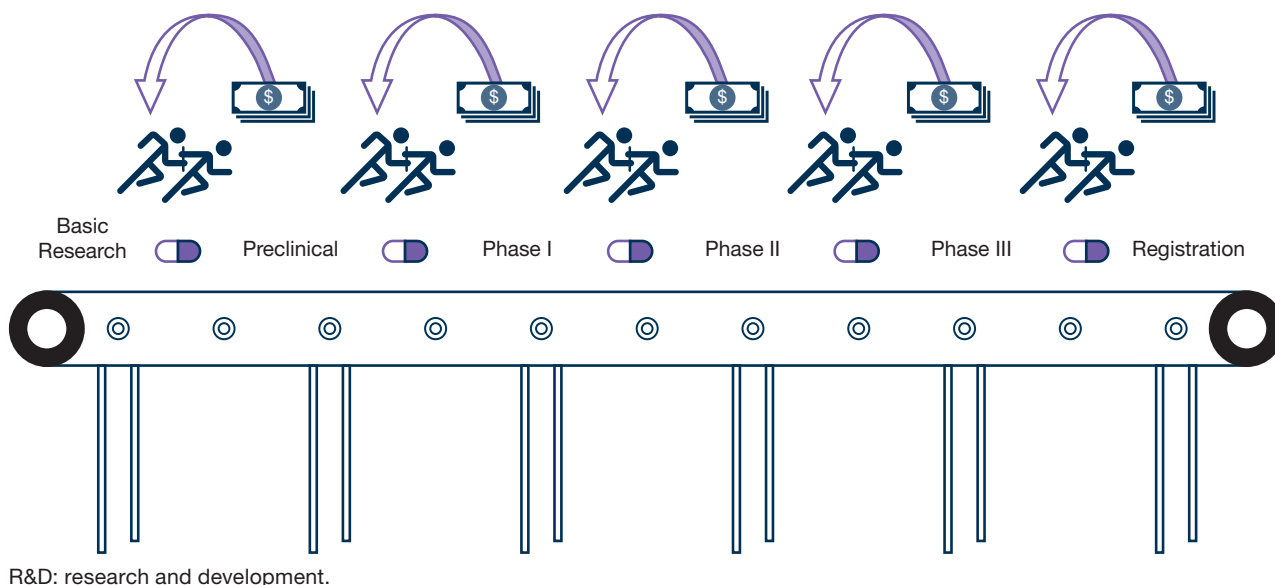


R&D: research and development.

Furthermore, studies have found that the contribution of public (government and philanthropic) investment in R&D has been underappreciated, especially for medicines of public importance. Nor are public and private sector roles clearly divided, as some private firms also engage in early-stage research, and the contribution of the public sector to late-stage R&D is greater than is generally perceived. Growing discussion of the role of the public sector in innovation and evidence shows that public funding is strongly present across the entire innovation chain, not only in basic research. Mazzucato & Semieniuk *(34)* have argued that public actors take an "entrepreneurial and lead investor role" and are "willing and able to take on extreme risks", including in funding early-stage start-ups. They question the perception that it is private venture capital that takes most of the risk. In the health sector, they discuss evidence related to United States National Institutes of Health (NIH) funding for health R&D and examine how it has facilitated the biotechnology revolution and the development of most of the innovative drugs approved by the United States Food and Drug Administration (FDA) over the years.

The public sector also invests significantly in infrastructure for research. For example, the United Kingdom Clinical Research Collaboration *(35)* provided an overview of health research activity across all areas of health and disease funded by the largest government and philanthropic health-related research funders. This shows that, in 2014, 64 public and philanthropic funding organizations spent £3 billion (£2 billion directly on research projects and £1 billion on infrastructure) of an estimated total of £8.5 billion spent on health R&D in the United Kingdom. Another study provided information on funding programmes issued by the Netherlands Organization for Health Research and Development, amounting to an average of €215 million annually *(36)*. This highlighted that the allocation of public funds is targeted to areas where new knowledge or products are needed, especially when these areas are not considered profitable for the private sector. Public investment also spurs private investment. For example, one study estimated the effect of government and philanthropic biomedical and health research expenditure in the United Kingdom on subsequent private pharmaceutical sector R&D expenditure *(37)*. It found that a 1% increase in public sector expenditure is associated with a 0.81% increase in private sector expenditure.

Several studies have provided evidence on the contribution of public funding to drug development. Most of those identified by the authors focused their analysis on the United States and the United Kingdom *(12)*. Using patent data, Sampat & Lichtenberg *(38)* found that of 478 medicines approved by the FDA from 1988 to 2005, half had benefited from publicly financed research, but this proportion increased to about two thirds for the subset of medicines selected for priority review. Of 26 medicines rated as "transformational" by expert physicians, many had been developed through public–private collaborations, whereas some were invented primarily by public or private actors *(39,40)*. In a study using bibliometric data, Galkina Cleary et al. *(41)* found that of 210 medicines approved by the FDA from 2010 to 2016, all had benefited from NIH publicly funded basic biomedical research. Another study *(42)* analysed government spending on health R&D in the United Kingdom and its contribution to the development of many medicines: such as abiraterone (an effective drug for treating advanced prostate cancer) and the whole class of monoclonal antibodies, including alemtuzumab, adalimumab and infliximab. The authors argued that

the public is paying twice: first, through the substantial government funding of health R&D, which amounted to £2.3 billion in 2015; and, second, through the purchase of the medicines by the public health system, which spent more than £1 billion in 2016 alone on medicines developed with significant reliance on national public research funding.

In some cases, public and non-profit actors have also become more directly involved in later-stage R&D. For example, a recent study found that in the United States, of 248 new chemical entities, 25% had either key late-stage research contributions from public sector research institutions (19%) or spin-off companies from one of these institutions (6%) *(43)*. In addition, the NIH National Center for Advancing Translational Sciences initiative is involved in preclinical, clinical and post-licensing research on products *(44)*. The United States Biomedical Advanced Research and Development Authority (BARDA) pays for biosecurity R&D through regulatory approval and stockpiling *(45,46)*. In the area of neglected diseases of poverty, non-profit product development partnerships generally bring a product all the way through Phase 3 trials, registration and marketing, often with an industrial partner *(47,48,49)*. Aside from direct funding, governments globally also provide significant indirect support to encourage private R&D efforts, such as tax-related incentives for research and clinical trial expenditure *(50)*.

This broad set of public, academic and private actors is steered by a range of public policies for the development of health technologies, generally categorized as "push" or "pull". Push policies aim to incentivize actors to engage in product development by reducing costs and risks at different stages of the process. They include grants, subsidies, tax credits and technical support. In contrast, pull incentives provide rewards after the product is developed or a milestone is reached. They include IP rights and other forms of market exclusivity, advance market commitments (AMCs) and prizes (Fig. 4). These mechanisms also build on significant public sector investment in education and infrastructure for R&D *(51)*.

### Fig. 4. Examples of push and pull incentives for pharmaceutical R&D



**REDUCE RISKS & COSTS**

**PUSH MECHANISMS**

Innovation funding / grants
Subsidies for research
Tax credits on R&D
PDPs
Expedited regulatory review
Facilitation mechanisms
Liability protection

**PULL MECHANISMS**

Market guarantees
Purchase funds
Prizes for successful research
Improved market information
Tax credits on sales
Intellectual property incentives
Patent buyouts

**INCREASE REVENUES**

Basic Research → Translational Research → Product Development → Clinical Research → Production Capacity → Regulatory Approval → Delivery & Access

PDPs: product development partnerships; R&D: research and development.
*Source:* DNDi *(52)*.

## 3.2 Outputs, costs and risks in the current business model

Reorienting the current business model requires an understanding of what the system produces, as well as how much risk and cost is involved. On average, about 85 new medicines (of which 35 are new active substances) receive regulatory approval in Europe each year *(53)*. Some are new medicines offering significant therapeutic advances, but many are considered not to have any additional benefit. To illustrate, the German Institute for Quality and Efficiency in Health Care analysed 216 new drugs introduced in the country from 2011 to 2017. It observed that 25% offered a "considerable or major added benefit", 16% offered a "minor" or unquantifiable additional benefit and 58% were not shown to offer an additional benefit based on existing evidence *(54)*. The complex issue of how to assess the value of a medicine for patients and health systems has drawn increased attention given the context of rising prices.

Also of significant interest is the question of how much risk and cost is required for pharmaceutical R&D. It is widely recognized that the process is long, costly and risky, but perhaps less appreciated that such costs and risks vary significantly by therapeutic area and product type, and have been extensively quantified – although with no consensus. Differences in methodology, data sources (many confidential), rates of cost capitalization, types of expenses included as R&D (such as mergers and acquisitions or expenses related to marketing of the product or tax deductions) and other methodological approaches provide a wide range of estimates.

The academic literature on this topic has advanced considerably over the past decade, with new estimates of costs and risks based on larger, more representative datasets than earlier studies (see Vieira & Moon *(13)*). The estimated average cost to develop a new drug varies widely, ranging from US$ 43.4 million to US$ 4.2 billion. Similarly, estimates of development timelines also vary considerably between studies and according to type of technology and indication. For example, for new drugs, the Phase 1 timeline ranges from 5 to 34 months; the Phase 2 from 21 to 38 months; and the Phase 3 from 30 to 45 months. Estimates of success rates – that is, the proportion of projects that entered a particular phase of development and passed to the subsequent phase – show that the overall success rate for the clinical stage (from Phase 1 of clinical trials to successfully ending Phase 3) ranges from 6% to 26% for new drugs, with important variation by therapeutic indication and technology type *(14)*.

Despite this variation, clear overall characteristics of how R&D progresses can be discerned: risk falls as product development advances, while costs rise (Fig. 5).

Fig. 5 illustrates how risk (pictured here as the number of candidates at each phase) falls as product development progresses from discovery through preclinical to Phase 3 trials, while total costs and costs per candidate increase. In general, the public and philanthropic sectors are more involved in earlier phases (the left side of the chart) where risks are higher, while the private sector is more involved in later phases (the right side of

## Fig. 5. Risks and costs of the R&D process
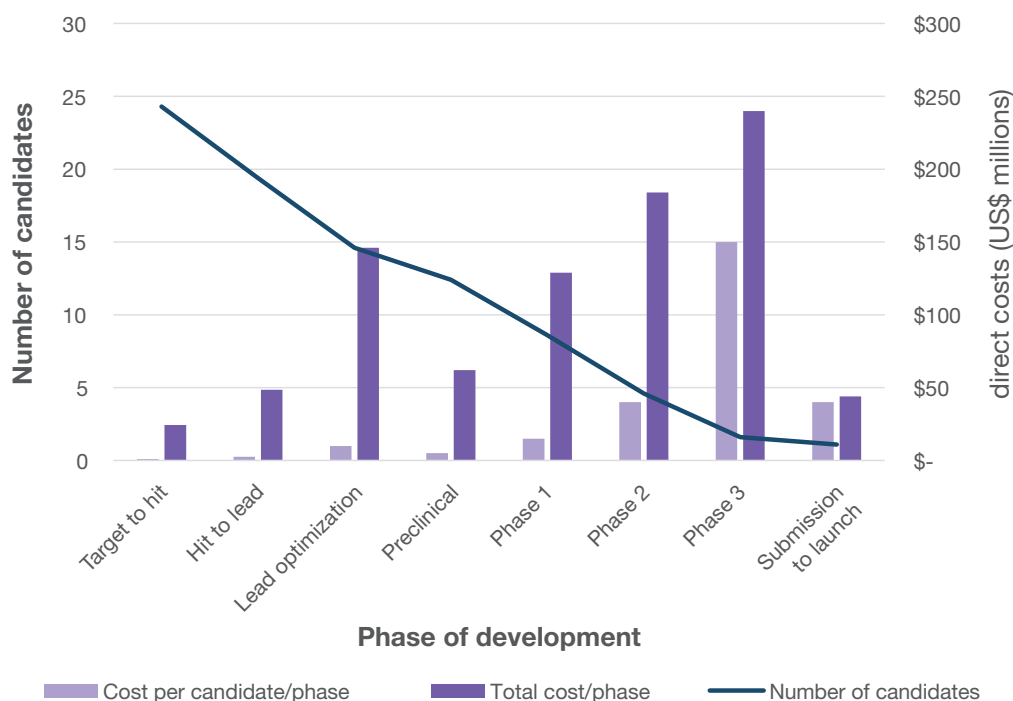


R&D: research and development; US$: United States dollars.
*Source:* Based on data from Paul et al. *(55)*.

the chart) where direct costs are higher. Notably, the emergence of the relay race model of innovation means that the system as a whole may bear the total costs (number of candidates multiplied by cost per candidate), but a single firm may only bear the much lower cost per candidate. This distinction is important because the R&D costs that a single firm must recoup through revenues will be significantly lower in a relay race model than in the alternative of a single, large, vertically integrated firm that internalizes risk and costs from the early stages.

Both public and private actors take on risks and costs throughout the R&D process, including many relay runners, but in the current system financial rewards largely accrue to those who control the last stages – almost always a private firm. While the public benefits from the existence of the invention, how much the public benefits in terms of improved health outcomes depends on how widely affordable and available that medicine becomes. A key question under debate is how fairly benefits are distributed, in light of who takes on various risks and costs.

## 3.3 How well does the current business model deliver GPGs?

The current business model for pharmaceutical R&D has yielded significant technological and therapeutic advances. However, it suffers from several shortcomings that impede the generation, availability and affordability of pharmaceutical knowledge as a GPG. First, innovation needs are neglected in areas where the market incentive is too small or risky, such as for antibiotics, neglected diseases of poverty or outbreak-prone pathogens. Second, competition among R&D actors can retard innovation by disincentivizing, impeding or blocking the sharing of knowledge as a GPG, which drives science forward. Third, monopoly rights – as they allow their holders to control production and commercialization over the protected product *(56)* – can be used to limit the manufacturing of end-products, potentially generating artificial scarcity and reducing the global availability of medicines. Finally, high prices are built into the system by design, as they are the main incentive drawing private investment into R&D. These shortcomings have prompted both real-world experimentation with alternative business models for R&D and proposals for further change *(57)*; these are covered in section 4.

Questions have been raised about the overall efficiency and fairness of the existing system. Rewarding R&D investments through high prices may not be the most efficient way to generate innovation: according to self-reporting, the pharmaceutical industry reinvests 17–22% of its sales revenues into R&D *(58)*. Given the ongoing debate about what should qualify as an R&D cost, and financial incentives to report high levels of reinvestment, the transparency of these figures could be improved. The proportion spent on R&D varies by size and type of firm. A larger proportion on average is spent by smaller biotechnology firms and a smaller proportion by large firms; this trend is particularly pronounced among firms that have adopted a financialized business model *(26,59)*. Scholars have also argued that the distribution of risk and reward is unbalanced *(60)*. Financial rewards are generally reaped at the end of the process by those who control the last stages of R&D – what Mazzucato *(61)* has characterized as "value extraction" – but, as detailed above, a much wider range of firms, public funders and academic researchers have contributed to the knowledge that made the final medicines possible ("value creation").

Debate is growing around the need to attach conditionalities to public funding of pharmaceutical R&D in order to ensure that the end-products are available and affordable, and to achieve a fairer distribution of risk and reward *(9,62)*. Much funding is already subject to conditions, but rarely do these seek to deliver GPGs. For example, recent studies found conditions on the dissemination of research findings in open access publications, but few or none on the availability or affordability of end-products *(42,63,64,65)*. Attaching conditionalities to public funding to promote availability and affordability of medicines has been recommended in several WHO and United Nations reports *(66,67,68,69)*.

## 3.4 Investments and actors in pharmaceutical R&D in the WHO European Region

Actors in the WHO European Region, in both the private and public sectors, have historically been involved in all stages of the pharmaceutical R&D system, and the Region has a large number of organizations conducting pharmaceutical R&D. Over 10 000 "life sciences" companies are based in 14 European countries (Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland and the United Kingdom), conducting R&D activities at different stages of product development and in several disease areas *(70)*.

Countries in the Region invest significant financial resources in health R&D, including pharmaceuticals.[3] Data from the WHO Global Observatory on Health Research and Development *(71)* show that the WHO European Region invests a median of 0.05% of its gross domestic product (GDP) on health R&D (public and private combined); it is the region with the highest investment in R&D *(72)*. In addition to direct funding, European countries provide a diverse mix of indirect policy mechanisms supporting R&D efforts, most of which are applicable to all sectors. The share of tax incentives relative to overall government budget allocations for R&D for all sectors can amount to more than 30% in some EU countries (the highest being France and Portugal at 33% each; Ireland at 32%; and the United Kingdom at 31%). This is the primary public policy for promoting R&D investment *(73)*. Public expenditure on the purchasing of medicines and on reimbursement policies are also incentives that pull and direct pharmaceutical R&D. Many countries in the WHO European Region have public health systems that pay either entirely or in part for medicines.

Increasingly, however, patients in the Region are struggling to access newer medicines and to manage pharmaceutical expenditure within allocated budgets, even when the public sector has invested directly or indirectly in their development. The EU has an important portfolio of health-related R&D initiatives (such as Horizon 2020, the EU Health Programme 2014–2020, Fit for Health 2.0 and the Innovative Medicines Initiative). These are not currently oriented to the development of medicines as GPGs, but they could be reformed by the inclusion of patient access requirements. Overall, its high levels of R&D investment and innovative activity, combined with its strong health-care systems that undertake significant spending on medicines, make the WHO European Region fertile ground for testing alternative business models for R&D that can better meet the public interest and produce GPGs.

---

3   WHO's Global Observatory on Health Research and Development centralizes data sources on health R&D activities, including grants for health research by major funders *(74)* and funding flows for health R&D by country (expressed as gross domestic expenditure on R&D (GERD) and GERD in the health and medical sciences (health GERD)). Health and medical sciences encompass a wide range of R&D activities that go beyond pharmaceutical R&D, including R&D on health sciences (including public health, infectious diseases and health-care sciences), medical biotechnology (cell, tissue or organ manipulation, pharmacogenomics, and genetic therapies and diagnostics) and basic and clinical medicine (such as surgery, anatomy, pharmacology and pharmacy).

4

# Alternative business models

The current business model of pharmaceutical R&D often results in unmet innovative needs where market returns are insufficient, or where there is limited availability and/or high prices. A number of alternative business models have been tested or proposed in recent decades to address one or more of these three shortcomings *(57)*. As noted in the introduction, this report defines business models as the way R&D is financed (including push funding and pull incentives), organized, facilitated, regulated and governed.

Alternative business models have been developed mainly in four disease "niches" – neglected diseases of poverty, rare diseases (including rare paediatric diseases), biosecurity (pathogens of pandemic potential) and antibiotics (described in sections 4.1–4.4). The extent to which each model seeks to address the three shortcomings – lack of invention, limited availability or lack of affordability – and their potential for delivering GPGs is examined (Table 3).

A few notable experiments that are not specific to a disease niche have also been undertaken in alternative approaches to incentivizing (AMCs), facilitating (pooling IP rights and/or technology) and paying for R&D (subscription models). These are summarized in section 4.5. Models that have only been implemented recently, such as social benefit firms, are also described briefly, along with proposals for other models that have not yet (to the authors' knowledge) been implemented. Finally, section 4.6 identifies common themes and approaches across these models.

**Table 3. Summary of current and alternative business models for delivering GPGs**

| Model type | Description | Invention generated | Globally available | Globally affordable |
|---|---|---|---|---|
| Mainstream: current business model | Market-driven large-scale, relay race | Yes, but with gaps | No | No |
| Alternative model: neglected diseases of poverty | Publicly financed, non-profit, needs-driven | Yes, for some | Yes, for PDPs; not necessarily for PRVs | Yes, for PDPs; not necessarily for PRVs |
| Alternative model: rare diseases | Mix of market- and public policy-driven | Yes, for some | No | No |
| Alternative model: biosecurity | Publicly financed, policy-driven | Yes, for some | No (with the possible exception of the CEPI) | No (with the possible exception of the CEPI) |
| Alternative model: antibiotics | Mix of market- and public policy-driven | TBD | TBD | TBD |

CEPI: Coalition for Epidemic Preparedness Innovations; GPGs: global public goods; PDPs: product development partnerships; PRVs: priority review vouchers; TBD: to be determined.

## 4.1 Neglected diseases of poverty[4]

One area that has seen significant experimentation in alternative business models is neglected diseases of poverty (also known as neglected tropical diseases), which predominantly affect people in low- and middle-income countries. It has long been recognized that commercial R&D models did not and would not generate innovative technologies for these diseases because the market incentive is inadequate to do so *(75)*. Approximately two dozen public–private product development partnerships (PDPs) were founded around the turn of the millennium to spur R&D into medicines for neglected diseases, and a sizable body of evidence to assess their effectiveness is now available *(11)*. PDPs as a group have demonstrated that it is possible to develop medicines through alternative business models, as evidenced by significant increases in funding for neglected diseases R&D, a renewed pipeline and a number of new medicines now reaching patients *(76)*.

While there is significant variation in how they operate, a PDP is usually a non-profit organization that acts as a "system integrator" to advance R&D by bringing together academic, government, industry and philanthropic actors to jointly develop new health technologies directed at unmet health needs *(49)*. PDPs are generally funded by public and philanthropic contributions; this allows R&D to focus on health rather than on market outcomes. PDPs play an important role in the coordination of an R&D portfolio across multiple organizations, which allows better candidates to move forward in the development pipeline, minimizing risks and reducing costs *(76)*. Depending on the policies they adopt, the knowledge PDPs produce can be made available as GPGs *(19)*.

Over 50 products developed by PDPs have been put on the market in the past two decades for diseases such as tuberculosis, malaria, HIV/AIDS, leishmaniasis, Chagas disease, sleeping sickness, cholera and Ebola, among others *(76)*. The features of these products are also an important aspect of the PDP model: affordability and accessibility concerns are built into the early R&D process. PDPs seek to develop products that offer significant therapeutic advances – with features that make them suitable for use in resource-poor health systems – and are affordable *(49)*. Most PDPs have a set of access policies and IP and data management plans to ensure that ownership of knowledge does not become a matter of conflict between their mission to provide accessible products and other partners' interests. A recent study comparing non-commercial R&D initiatives – mostly PDPs – with commercial ones found that their direct costs and timelines (per candidate per phase) are comparable *(77)*. While further research is required, these findings suggest that PDPs may be as efficient as purely commercial R&D, while delivering innovation as a GPG.

The PDP model has generated inventions for the treatment of several diseases that previously lacked adequate health technologies, and has made them available and affordable in countries where they are most needed. PDPs have demonstrated the feasibility of developing new medicines through non-commercial approaches for neglected diseases, but the extent to which this model could be expanded to diseases with higher commercial interest remains to be explored *(76)*.

---

4  Excerpts adapted from Navarro & Moon *(11)* and Vieira et al. *(76)*.

Another incentive for the development of health technologies for neglected diseases – priority review vouchers (PRVs) – was also created as a way to generate revenue for product developers *(78)*. PRVs expedite the process of obtaining regulatory approval and, subsequently, reduce the time for a medicine to enter the market. They can either be used to expedite the regulatory review process of another medicine by the same developer or be sold on to another firm. By selling a PRV, developers can earn a financial reward for their R&D investment *(79)*. PRVs were originally granted for medicines for neglected diseases in 2007 in the United States; they were subsequently expanded to include rare paediatric diseases in 2012 and medical countermeasures[5] in 2016 *(80)*. As of 2019, 31 PRVs had been granted by the FDA – 10 for neglected diseases, 19 for rare paediatric diseases and 2 for medical countermeasures. Of these 31 PRVs, 17 were sold: the identified sale values ranged from US$ 67.5 million to US$ 350 million *(81)*.

Studies analysing PRVs for neglected diseases concluded that the results do not indicate that the PRV programme incentivizes early R&D efforts in this field *(82)*. They also highlighted some potential misuse of the PRV programme (such as rewarding drugs already approved in other countries) and unfair distribution of the reward between the different actors involved in the development of the medicine *(83,84)*. For example, one company received a PRV for the approval of a drug to treat leishmaniasis, which was largely funded by public and philanthropic investments. Another limitation of PRVs is that they do not have any affordability requirements: the awarded technologies were often highly priced both in the United States and in other countries *(84)*.

## 4.2 Rare diseases and paediatric diseases and formulations

Rare diseases (or "orphans") are another niche that is not sufficiently attractive to the private sector for R&D investment. Investing in them is associated with high risk and the market for them is considered small, since they affect a relatively low number of potential patients. The models used to address this market failure were designed mainly to increase market size and to decrease risk, to attract investment from private companies.

The incentives adopted in the United States (the 1983 Orphan Drug Act) and Europe (Regulation (EC) No 141/2000 on orphan medicinal products) include:

- market monopoly periods granted after receiving market authorization for a product with an orphan indication (7 years in the United States and 10 years in the EU);

- grants for conducting clinical trials;

- a 50% tax credit for clinical testing costs in the case of the United States;

- a centralized procedure for registration (valid for 29 countries in Europe); and

- other regulatory and technical benefits and assistance by regulatory agencies, such as fee waivers *(85,86)*.

---

5   This programme is set to expire on 1 October 2023. Medical products and strategies to address biological threats to security are often referred to as "medical countermeasures"; they include drugs, vaccines and devices to diagnose, treat, prevent or mitigate potential health effects of exposure to chemical, biological, radiological and nuclear agents and emerging infectious diseases, such as pandemic influenza.

Adoption of these incentives has increased the development and approval of new medicines for some rare diseases. Between 2000 and 2020, the EMA granted 2382 orphan medicinal product designations *(87)*. A total of 142 orphan medicines were authorized, of which it was estimated that the regulation was directly responsible for the development of about 18–24 medicines *(88)*. In the United States, from 1983 to August 2021, the FDA granted 5824 orphan designations and approved 1003 orphan medicines *(89)*.

However, this trajectory needs to be maintained and to be sustainable for industry and health-care systems; to date only 5% of rare diseases have a treatment option *(90)*. A recent review of the orphan drug incentives adopted by the EU concluded that Regulation (EC) No 141/2000 "has been a strong catalyst for development of orphan medicinal products, but this effect has been stronger in certain areas such as oncology than for other truly rare diseases. There thus continues to be a substantial unmet need for pharmacological treatments for paediatric and orphan diseases" *(91)*.

Orphan medicines have tended to be priced higher than other medicines to offset challenges relating to market size and risk. Their high prices have led to restricted access for patients, therefore resulting in scrutiny about the incentives offered and the risk of the business models for orphan medicines having "unintended effects and created inefficiencies". Examples include orphan designations that were granted to medicines for conditions that had low population prevalence, but that generated "high returns on investment" or that resulted in "overcompensation" with respect to rewarding the sponsors *(88)*. The possibility of applying for several orphan drug designations for one product has also been pointed out as a misuse of the incentives for rare diseases *(91,92)*.

Other analysts have cautioned against extending market monopolies as an R&D incentive, questioning whether they were the main reason for the increase in the number of drugs approved for rare diseases *(85)*. This increase may rather be due to other incentives included in the legislation (such as tax credits and regulatory support), reduced costs of clinical trials and the willingness of health systems to pay high prices for these drugs *(93)*.

It has also been argued that not all successes can be attributed to the private sector and the incentives provided to them through orphan drug legislation. More comprehensive analyses of the cumulative and complex processes that have led to the approval of some orphan drugs found direct support and direct participation of public research institutions and public funds in incentivizing and developing these medicines *(39,94)*. Data on the funding of R&D for rare diseases also show a rise in philanthropic funding in the first decade of the 2000s *(95)*.

As in other therapeutic areas, there are examples of intersections between public, private and/or philanthropic actors in the development of medicines for rare diseases. For example, one type of cancer growth blocker was developed by a pharmaceutical company based on breakthrough basic research conducted at an academic institution that made possible an entire class of drugs currently known as tyrosine kinase inhibitors *(91)*. Other orphan drugs are also the result of multiple actors taking the baton at different stages of product development, where publicly funded research intersects with private and/or philanthropic research and resources *(39,95)*.

Finally, a 2019 study found that R&D costs for orphan drugs are, on average, significantly lower than for non-orphan drugs *(96)*. In contrast, the average annual prices of orphan drugs are 25 times more expensive than those of traditional drugs in the United States *(97)*. High prices for orphan drugs have been justified on the grounds that sales volumes are low; however, one study found that gross profit margins for orphan drugs were over 80%, while the pharmaceutical industry average was 16% *(98)*. Another study found that orphan drugs also generate about a 10% higher return on investment than non-orphan drugs *(99)*. These findings raise further questions about the extent to which high prices of orphan drugs may be justified, and whether alternative R&D models for orphan drugs should be considered to ensure sustainability for industry and health-care systems.

## 4.3 Biosecurity R&D[6]

Another area for alternative business models is biosecurity R&D, which refers to the development of medical products – often referred to as medical countermeasures – and strategies to address biological threats to security. Biosecurity R&D aims to prepare for public health emergencies that affect national security and are typically considered "mission-driven" rather than market-driven *(12)*. Historically, there has been limited development of products for pathogens of pandemic potential, as typically the risk is high and commercial markets are limited until a large-scale outbreak actually occurs *(100)*. This section focuses on R&D not related to COVID-19, which is covered in section 5.

Biosecurity research has historically addressed many infectious diseases. Priorities have been those that have caused outbreaks and threatened military personnel:

- conditions that spread quickly in densely populated areas (respiratory and dysenteric diseases);
- vector-borne diseases (those carried by mosquitoes and other insects);
- sexually transmitted infections (hepatitis, HIV and gonorrhoea); and
- diseases associated with biological warfare *(101,102,103,104)*.

The military contribution to the development of health technologies spans diagnostics, therapeutics, vaccines and vector control. Vaccines for smallpox, yellow fever, tetanus, influenza, viral hepatitis among many others were developed with important contributions from United States military research, for example.

Biosecurity R&D has gradually moved towards health technologies that can be used beyond emergencies and that can be beneficial in general medical care – such as burn care, radiation effects suffered by cancer patients, seizures and so on *(105)*. As the occurrence of biological events is unpredictable, the idea of broad-spectrum technologies (multiplex or multiuse platforms and pathogen-agnostic approaches) that can be adjusted for various pathogens and scaled up easily has begun to be more actively pursued as a

---

6    Excerpts adapted from Sunyoto et al. *(12)*.

goal *(106,107)*. The BARDA developed 51 products from 2007 to 2020, mostly for influenza, but also for anthrax, zika, Ebola and others (see Sunyoto et al. *(12)* for a list).

Most of the literature available on this topic focuses on the role of the United States. Many countries with a colonial history have played similar roles in investing in infectious disease research, however. Examples from Europe include the French Military Biomedical Research Institute, which conducts research – often in partnership with civilian institutions, such as the Institut Pasteur International Network *(108)*. The British military has a long history of involvement in research on infectious and tropical diseases since the 16th century; this fell under the umbrella of the Defence Medical Services for many years *(109,110)*. Many countries maintain biomedical research entities that have historical ties to, or originated from, the military. These include the German Institute of Virology in Marburg and the Russian Federation's S.M. Kirov Military Medical Academy in Saint Petersburg *(111)*.

Several pull and push incentives have been used to promote biosecurity R&D. In the United States, for which more information is publicly available, incentives include government technology transfer, industrial collaboration, grants, prizes (such as the DARPA Grand Challenge, funded by the Defense Advanced Research Projects Agency), exclusive rights and procurement contracts. Each has its strengths and weaknesses *(112)*. Regulatory measures were also established to accelerate biosecurity product development (including the Emergency Use Authorization option and the Animal Efficacy Rule). Another incentive was the addition of the medical countermeasures category to the PRV mechanism in 2016 (see section 4.1).

The number of companies active in developing countermeasures has also reportedly increased: from 133 in 2008 to 303 in 2016. The five countries with the largest numbers of these companies (generally SMEs) are the United States with 159 companies, China with 33, the United Kingdom with 12, and Canada and Switzerland with 10 each *(12)*. SMEs account for 86% of the countermeasures pipeline, although the majority are still in early-stage development *(113,114)*.

Policy Cures Research's G-FINDER project tracks annual investments in R&D for new products and technologies, including for emerging infectious diseases (among which there is considerable overlap with biosecurity targets) *(115)*. Global funding for emerging infectious diseases R&D was very narrowly focused on recent large-scale outbreaks, and the United States Government played a dominant role in both product-specific and early-stage research. From 2014 to 2018, there was an increase in emerging infectious diseases research funding, which reached US$ 886 million in 2018. Overall, this was focused on vaccine R&D (51%), followed by basic research (17%), biologics (9.4%) and drugs (6.7%).

The approach for biosecurity R&D can be summarized as follows. Public authorities identify current and future threats, set priorities for countermeasure development, invest public funds directly in R&D by public and private actors, provide incentives for private investment and engage directly in R&D activity. The purpose, capacity and financing of R&D for biosecurity influences the way such efforts are organized. Biosecurity R&D was built on the historical legacy of military R&D, with sustained investment from the government budget. Involvement of the private sector in biosecurity R&D is heavily shaped by public funding and by legal, regulatory, technological and financial incentives. Overall, increased

awareness of the threat of emerging and re-emerging infectious disease outbreaks seems to determine which countermeasures are a priority and how quickly they progress through the pipeline *(12)*. Biosecurity R&D has traditionally focused on invention, with almost no attention to ensuring global availability or access to the technologies that result. It is thus not intentionally directed to generate medicines as GPGs.

This trend shifted with the creation of the Coalition for Epidemic Preparedness Innovations (CEPI) in 2017 as a global partnership, in which public, philanthropic and civil society organizations aim to accelerate the development of vaccines against emerging infectious diseases and to make them globally accessible during outbreaks. Before the emergence of COVID-19, CEPI included, as priority diseases, Middle East respiratory syndrome, Lassa fever, Nipah virus, Ebola, Rift Valley fever and chikungunya, and invested in platform technologies against unknown pathogens (Disease X). Even before WHO declared COVID-19 a public health emergency of international concern in January 2020, CEPI had announced the initiation of three programmes to develop vaccines against the virus. CEPI works as a system integrator, funnelling resources from public and philanthropic organizations to fund R&D initiatives of research institutions and companies working on its target pathogens. By 2019, CEPI had built a portfolio of 19 vaccine candidates against five priority pathogens, with commitments up to US$ 456 million *(116)*.

Notably, the creation of CEPI aimed not only to accelerate the development of vaccines for certain pathogens, but to make them globally accessible when an outbreak occurred – that is, to make them GPGs. To this end, CEPI developed an access policy shortly after its creation, requiring all contracts to have a baseline of provisions in relation to equitable pricing, management of IP, risk/benefit sharing, and data sharing and transparency. These key requirements were revisited one year later, after an evaluation process in which certain partners expressed concern that the access policy was not flexible enough and, therefore, did not allow CEPI to have a "competitive business model" *(117)*. The revised policy established equitable-access principles, the concrete implementation of which is negotiated individually with each grantee. Further evaluation is needed to determine how effective these policies have been in ensuring global availability and affordability of products developed with CEPI funding (see further discussion of CEPI in section 5).

The COVID-19 pandemic is likely to have profound impacts on national and global approaches to biosecurity R&D (as discussed in section 5). For example, the proposal to create an EU Health Emergency Preparedness and Response Authority (modelled on the BARDA system) was being piloted and actively debated at the EU level in 2021 *(118)*.

## 4.4  Antibiotics: emerging approaches

The rise of strains of bacteria resistant to antibiotics has increasingly been recognized as a global health issue; yet, ensuring adequate R&D for new antibiotics is challenging for many reasons. First, the need to reserve the use of new antibiotics to reduce the risk of resistance means reduced sales for companies. Second, the market size for antibiotics is significantly smaller than for other therapeutic areas (such as oncologic and chronic disease treatments) owing to shorter treatment courses, competition with generic manufacturers, pricing regulations in certain countries and established treatment

paradigms *(119,120)*. This has led to reduced interest in investing in the development of new antibiotics: pharmaceutical companies have reduced their scientific and technical capacities and closed or divested their infectious diseases research units, and investors have reduced their interest in the area.

A large body of literature proposes various models that could help to fix the antibiotic pipeline. Renwick, Brogan & Mossialos *(121)* analysed the antibiotics market and proposed the adoption of several incentives to create an attractive environment for investments, notably:

- improving overall net present value for new antibiotics by creating incentives that increase revenues, decrease costs or lower risks of R&D;

- increasing SME participation by reducing costs through push funding, allowing companies to move through preclinical towards clinical development, bridging what has been called "the valley of death" of antibiotic development;

- increasing large pharmaceutical companies' participation by increasing revenue certainty through AMCs, reduced regulatory pathways and other pull incentives (although incentives for bigger pharmaceutical companies would need to be higher than for smaller companies, at US$ 800 million versus US$ 100–200 million); and

- improving cooperation and synergies by sharing information, resources and expertise among stakeholders, reducing R&D costs, and aligning public and private priorities.

Recognition is growing, however, that relying on incentives to generate market and sales revenues will not be sufficient to stimulate antibiotic R&D, and that new models need to be implemented to create a long-term, stable pipeline of new antibiotic candidates without relying on sales and antibiotic overconsumption *(90,122,123)*. There is a need for "antibiotic stewardship", in which incentives for the development of novel antibiotics are coupled with protection of antibiotic consumption, while also ensuring global access to needed antibiotics *(124,125)*. Models that support stewardship and access by separating rewards from sales volumes – "delinked" models – not only include incentives during R&D, but also propose new ways to reimburse and value antibiotics. Examples of proposed delinked models include the following.

- The Options Market for Antibiotics mechanism *(119)* would allow multinational, nongovernmental or government investors to pay and hold options on promising antibiotics at early stages of development, with the opportunity to purchase the antibiotic if and when it reaches the market at a discounted price (strike price). With this mechanism, R&D investments would be (at least in part) paid for beforehand and the strike price would be closer to the marginal cost of production, partly delinking revenues from sales volumes.

- The service-availability premiums model *(121,123)* sets up parallel insurance premiums, where health systems pay a fee for the long-term availability of new antibiotics instead of paying for volumes of prescribed antibiotics. This model protects companies against low and variable consumption of new antibiotics (by giving them a fixed fee), providing incentives for R&D by ensuring revenue

regardless of volume. It also protects health systems by ensuring availability of new antibiotics. Two pilots are being implemented by Sweden and the United Kingdom, with certain differences in the criteria for payment of rewards: the Swedish pilot sets a baseline premium for companies, which can rise if there is an increase in the volume of antibiotics used; whereas the United Kingdom pilot considers environmental criteria in its model and provides a fully delinked model *(126)*.

Some initiatives that aim to delink revenues from sales volumes at the national level have also been proposed to address global access and, potentially, to generate GPGs. For example, O'Neill's *(125)* proposal to implement a market entry reward as a pull incentive for new antibiotics is conditional on the recipient of the reward making its antibiotic globally accessible and affordable (for example, licensing the knowledge to produce the new antibiotic to the United Nations-backed Medicines Patent Pool (MPP)).

Other initiatives recently created to stimulate antibiotic development include the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), which was created in 2016 by the United States Department of Health and Human Services in response to calls for concerted global efforts to address the growing drug-resistance crisis. It is currently funded by and receives technical support from several governments and philanthropic actors. It was set up as a global, non-profit partnership that aims to develop new health technologies for drug-resistant bacteria. Since 2016, it has invested US$ 303.3 million in 81 projects around the world through the CARB-X Global Accelerator Network, which provides business, scientific and technical expertise and services to CARB-X-funded product developers to support their antibacterial research projects *(127)*.

Also in 2016, the Global Antibiotic Research and Development Partnership was created to address the challenges of antibiotic development, with support from WHO and the Drugs for Neglected Diseases Initiative. It works as a system integrator, mobilizing resources and providing strategic direction to partners from the public and private sectors at different stages of the R&D process, with the aim of delivering 5 new treatments by 2025 with €500 million in funding. It has already "evaluated more than 100 substances for antibacterial activity, resulting in six drug candidates". It is "supporting the late-stage development of a novel, first-in-class treatment for drug-resistant gonorrhoea, and is collaborating on a new treatment for hospital-acquired infections with limited treatment options" *(128)*.

Finally, the AMR Action Fund was created, initially proposed by the International Federation of Pharmaceutical Manufacturers and Associations and the Biopharmaceutical CEOs Roundtable, in collaboration with WHO, the European Investment Bank and the Wellcome Trust. It was set up as a collective fund that aims to invest nearly US$ 1 billion to develop 2–4 new antibiotics by the end of the decade by forging partnerships with institutions and philanthropic organizations to strengthen and accelerate antibiotic development *(129)*.

The extent to which these approaches and incentives for novel antibiotics R&D will be able to generate inventions and make them globally available and affordable is yet to be determined.

## 4.5 Other approaches to alternative business models

In addition to the disease niches described above, several notable experiments have been conducted in alternative approaches to incentivizing, facilitating and paying for R&D. This section describes some of these briefly, with a focus on incentivizing R&D. A separate report will analyse these mechanisms as a way to promote access *(130)*.

Several of these mechanisms have been proposed or adopted with the aim of delinking (at least to some extent) the prices of the end-products from the R&D investments made to develop them. Delinkage policies can move prices towards marginal cost, as R&D investments would be paid for separately and would, therefore, not need to be recouped through high prices, thus relieving health system budgets. They can increase availability of medicines, as the knowledge necessary for their manufacture would ideally be placed in the public domain (with no monopoly/exclusivity rights) or at least made available to a wider range of producers. For countries in which medicines are purchased or reimbursed by third parties (public or private health schemes as opposed to out-of-pocket payments), "these entities could shift budget allocations from paying high prices for patented medicines to funding grants or rewards for innovation, typically at a lower cost" *(131)*.

### 4.5.1  Pooling IP rights and/or technology

This approach to facilitating R&D makes IP, data and knowledge from different actors available to others through a common "pool". The key idea is that doing so makes knowledge more widely accessible, allowing the development of products still in the pipeline to be advanced, promoting the creation of follow-on innovations and facilitating manufacturing of existing and future products *(132)*. Innovation could be rewarded according to the contribution of each actor at different stages of the development process.

In 2010, the pharmaceutical sector created the MPP to increase access to and facilitate the development of life-saving medicines for low- and middle-income countries through an innovative approach to voluntary licensing and patent pooling. The MPP initially focused on medicines for HIV/AIDS, later expanding its mandate to all patented products on the WHO Essential Medicines List and, more recently, to COVID-19. To date, the MPP has signed agreements with 10 patent holders for 13 HIV antiretrovirals, 1 HIV technology platform, 3 hepatitis C direct-acting antivirals and 1 tuberculosis treatment. It has also concluded licences with 22 sublicensees for production of the generic medicines; these have supplied over 14.5 billion doses to 141 countries, saving US$ 1.6 billion in medicines purchases by the international community from 2012 to 2020 *(133)*. While the MPP has achieved its goals of increasing generic manufacturing and access to medicines in many countries, and while licences have been agreed for R&D, the extent to which these will result in successfully developed final products is not yet clear.

Another global initiative to facilitate R&D through technology pooling, created in 2011 and managed by  the World Intellectual Property Organization (WIPO) and BIO Ventures for Global Health, is WIPO Re:Search *(134)*. This initiative builds on the GlaxoSmithKline/ Alnylam Pool for Open Innovation against Neglected Tropical Diseases *(135)*. Through WIPO Re:Search, organizations can share with others, without payment of royalties, their "IP, compounds, expertise, facilities and know-how" relevant to early-stage drug R&D for

neglected tropical diseases, as well as malaria and tuberculosis *(134)*. As of February 2021, it had 154 members – pharmaceutical companies, academic institutions, governmental organizations and non-profit organizations – from 45 countries, classified as a "sponsor", "provider", "supporter" and/or "user" *(134,136,137)*. WIPO Re:Search has facilitated more than 150 collaborations between owners and users of IP (mainly, the screening of library compounds for drug repurposing), with potential impact for medicines development *(138)*. Again, though, the extent to which these will result in final products is not yet clear.

A technology pool for COVID-19 has been created by WHO and is discussed in section 5.5.

## 4.5.2 AMCs

AMCs – also known as advance purchase commitments or agreements – have been proposed and adopted as a pull incentive to promote pharmaceutical R&D in specific disease areas lacking a sufficiently sized market *(139)*. An AMC creates a market for producers, providing a guaranteed price for a fixed quantity of a product. Companies can then invest in R&D with the assurance that if their product meets the specified criteria, a certain size of market will be somewhat guaranteed to them (depending on the AMC design).

The largest-scale AMC implemented to date (arguably, excluding COVID-19) is the pilot AMC implemented by GAVI, the Vaccine Alliance, for the pneumococcal vaccine announced in 2009. This had a funding pledge amounting to US$ 1.5 billion for the supply of 200 million doses of pneumococcal vaccine for a period of 10 years. The AMC was intended to address both the lack of R&D for improved pneumococcal vaccines and the problem of low manufacturing volumes and high prices of existing vaccines – both linked to the limited expected market size in developing countries. When the AMC was announced, vaccines against pneumococcal disease were already on the market. The AMC has been credited with securing the production and volume of supply for use in developing countries, but it seems to have had little or no impact in promoting R&D *(140)*.

Another AMC with a value of US$ 5 million was entered into by GAVI, the Vaccine Alliance, and a company providing Ebola virus vaccines in January 2016. Under the AMC, the company was required to seek registration of the vaccine by 2017 and to have a stockpile of 300 000 vaccines for "expanded use clinical trials" or "emergency use" *(141)*. Vaccines from this stockpile were used during the 2018–2020 Ebola outbreaks in the Democratic Republic of the Congo *(142)*. Over 305 000 vaccines under the "expanded access" protocol had been donated by the company since the 2018 outbreak. By 2019, the vaccine had been approved by the EMA and the FDA, and had obtained WHO prequalification *(143)*.

In the context of COVID-19, an AMC was created to make COVID-19 vaccines available to lower-income countries. The EU also used AMCs to purchase COVID-19 vaccines (see section 5.3).

Concerns have been raised about whether implemented AMCs have played a role in the development of novel technologies. For example, the development of the pneumococcal

vaccine was not induced by the creation of the AMC *(140)*. Other issues around AMCs concern whether they have an elevated cost in comparison to the amount required for the R&D *(144)*; the high prices paid for the end-products *(145)*; the provision of subsidies for companies beyond paying for the vaccines *(146)*; their resulting inefficiency to incentivize pharmaceutical R&D *(147)*; and the lack of evidence to back the creation of subsequent AMCs *(140)*. Careful attention to improving the design of AMCs, and comparing them against alternative innovation policies, is needed if they are considered again.

### 4.5.3  Prizes

Another pull incentive that can be used to stimulate innovation is giving cash rewards for the achievement of specified objectives. Prizes can be designed in many ways – they are most commonly set up as "end prizes" once the final target product is developed or "milestone prizes", in which interim results are rewarded. Prizes are results-based: they are only paid if the objectives set by the prize sponsor are met, thereby rewarding only successful innovations. A 2011 assessment of prizes for development of health technologies concluded that milestone prizes were better at attracting different actors to the early stages of development – especially smaller companies or non-industry actors *(148)*. It also noted, however, that it was important to include mechanisms to ensure that candidates are taken all the way to market.

As a pull incentive, prizes require organizations to make investments up front. Milestone prizes reduce the amount of investment necessary before any payment can be received, as opposed to end prizes, in which the investment has to be made all the way through the end of development to obtain a reward. Wilson & Palriwala *(148)* also suggested that the prize design should take accessibility into account, including conditions such as the licensing of IP to all interested manufacturers or including requirements about the final price of the product. Prizes are a way of delinking R&D investments from prices, as the investments are recouped through the prize and not through sales of the end-product *(149)*.

Some innovation prizes have been implemented for the development of health technologies on a small scale. For example, the Prize4Life – dedicated to the discovery of treatments and a cure for amyotrophic lateral sclerosis – gave two US$ 1 million prizes for development of a biomarker to track the development of the disease and for development of a gene therapy approach to treat the disease *(150,151,152)*. The Longitude Prize aims to award £10 million for the development of an affordable, accurate, fast and easy-to-use test for bacterial infections *(153)*. The Life Prize was created to promote development of an affordable, short-course treatment regimen effective against all forms of tuberculosis through a combination of milestone prizes and grants at different stages of product development *(154)*. The XPRIZE Rapid COVID Testing competition offered US$ 6 million for the development of a fast, cheap and easy-to-use test for COVID-19 *(155)*.

The creation of a global prize fund to reward development of health technologies was also one of the main recommendations of the WHO Consultative Expert Working Group on Research and Development. The fund would be part of a global biomedical R&D treaty; it would be financed through public contributions by all countries at a proportion of their

GDP (at least 0.01%). The proposal was that the knowledge required to produce these technologies would be rewarded through this fund and would subsequently be made available in the public domain as GPGs *(67)*. However, neither the fund nor the treaty was created.

Overall, implementation of prizes for development of health technologies has remained relatively small in scale and scope.

## 4.5.4  Patent buyouts

Patent buyouts have been proposed as a way to reward innovation and increase availability and accessibility of products by facilitating manufacturing by a wider range of producers. Governments (or others) can purchase the patent (and other rights) related to a product and place it in the public domain. Patent buyouts could "eliminate monopoly price distortions and incentives for wasteful reverse engineering, while raising private incentives for original research closer to their social value" *(156)*. This model has been used previously – for example, in 1839 the French government purchased the patent on the daguerreotype (photography) process and placed it in the public domain – but not in any significant way in the pharmaceutical sector, to the authors' knowledge.

## 4.5.5  Subscription models

The subscription (or "Netflix®" or "all you can eat") model has been implemented in a few instances in recent years to increase access to patented medicines for hepatitis C. This model is based on the payment of a lump sum in exchange for an unlimited volume of medicines. Under certain conditions, this can remove price as a barrier to access, thereby allowing for universal access to everyone in need *(157)*. It is possible to implement such a model because the production cost of a medicine is often a very small proportion of the monopoly price. The most established use of this approach to date is in Australia, where the government agreed in 2015 to spend about 1 billion Australian dollars (US$ 766 million) over five years in exchange for an unlimited volume of hepatitis C drugs. More recently, the American states of Louisiana and Washington have implemented similar models, but data on the outcomes are not yet available.

This type of model can lead to increased public health benefits by reducing the de facto price of medicines and creating budget certainty, incentivizing early diagnosis and treatment of patients and reducing restrictions on access (for example, those that limit treatment for people with less severe stages of the disease). It can also provide benefits for the seller, including a sizable reward and certainty of revenue. This is an example of delinkage in which the innovation is rewarded separately from the price of the product *(157)*. In the implemented examples of this model, the payments were put in place only after products were available on the market, and focused on access rather than innovation. They operated in a manner analogous to patent buyouts, in that public purchasers paid a lump sum to obtain the medicines at or below the marginal cost of production, even if in these cases the technology was not made available in the public domain. Nevertheless, real-world implementation of relatively large-scale, lump-sum payments (in lieu of per-patient pricing) suggests that such models could be implemented more widely, both for access to other products and as pull incentives for innovation.

### 4.5.6 Non-profit or limited-profit R&D firms

Another proposed or piloted alternative business model is non-profit or limited-profit R&D firms *(158)*. The Institute for OneWorld Health was created in the United States as a "non-profit pharmaceutical company", but was later absorbed into PATH, a large, international PDP *(159)*. Some non-profit firms may, in practice, operate very similarly to PDPs (see section 4.1) or public/academic research institutes.

In contrast, limited-profit firms seem to operate differently from PDPs. Benefit corporations, for example, are for-profit firms with a legal structure that requires them to balance a social mission against earning a return for shareholders *(160)*. Companies can obtain certification as a benefit corporation, granted by the non-profit organization, B Lab, which listed 24 companies in the "pharmaceuticals and supplies" sector as of March 2021 *(161)*. It is possible that benefit corporation status would have an impact on a pharmaceutical company's approach to R&D or pricing, but actual practices are unclear. In addition, some jurisdictions offer other legal forms of limited-profit firms, including "low-profit limited liability companies" in some American states and "community interest companies" in the United Kingdom *(162)*. Further research on limited-profit firms is needed to explore their features and applicability to the pharmaceutical sector.

## 4.6 Common themes and approaches across alternative business models

The overview above underscores the wide range of alternative business models. Nevertheless, several common approaches or themes appear to cut across these models, often working in a complementary way:

- Public or philanthropic funds are used to increase rewards and/or reduce the costs and risks to the product developer through both push mechanisms, such as grants, and pull mechanisms, such as guaranteed markets or faster regulatory review. These are basic policy tools one might expect to use to address market failures.

- A range of additional measures go beyond the economic levers of cost or risk-reduction, however, to shape and support the innovation process proactively *(163)*. For example, public and philanthropic funders set directions for innovative activity by establishing priorities – often by making funding available for specific objectives with mission-driven innovation policies.

- New arrangements are tailor-made to facilitate the R&D process and to help overcome bottlenecks and obstacles, often drawing on the knowledge and resources of a wide range of actors (such as structuring partnerships, providing technical assistance including advice from regulators and health technology assessment agencies, pooling of IP, knowledge hubs, open access data-sharing platforms and other ways to reduce transaction costs).

- A wide range of actors are involved, including public research funders and laboratories, foundations, academic institutions, non-profit organizations, SMEs and large pharmaceutical companies, regulators, payers, reimbursement and procurement agents and patients.

- Novel organizational forms are created to orchestrate these actors, such as PDPs, patent pools, limited-profit firms or targeted funders like BARDA.

- New legislation has often played a foundational role in enabling alternative business models. R&D is not shaped by funding or organizational structures alone: the ground rules of the system are also critical.

Overall, these different approaches to incentivizing and conducting R&D show that it is possible to move beyond the "traditional" model. While a relatively broad range of models have been tested, the overall degree of experimentation is small relative to the global R&D system. Furthermore, each model has pros and cons, but evidence on these is relatively scarce. For some business models (including PDPs for neglected diseases, rare diseases, biosecurity, AMCs, pooling of IP and PRVs), adequate experience is now available to draw at least some conclusions regarding their feasibility, effects, strengths and weaknesses. For others, implementation has been on a limited scale or of a short duration, or they remain only proposals, such that the evidence to date is limited (including antibiotics, patent buyouts, subscription models, prizes and non-profit or limited-profit firms). Ongoing research and analysis are needed,  as is additional analysis of the broader lessons that can be drawn from each model for areas beyond the pharmaceutical sector.

5

# COVID-19 R&D business models

The response to the urgent need to develop safe and effective technologies to diagnose, treat and prevent COVID-19 has demonstrated that it is possible to develop at least some innovative health technologies at unprecedented speed, even if not necessarily with the intention to make them available as GPGs. A key difference between COVID-19 R&D and the traditional R&D model is the extent and intensity of public sector involvement, as detailed below.

Many of the policy tools and approaches identified in section 4 have been used for COVID-19 health technologies. For example, public and philanthropic funders set directions for innovative activity by establishing vaccines as a major priority. Governments reduced the costs and risks of every stage of the process, from R&D to manufacturing to procurement. Various actors sought to facilitate R&D and overcome obstacles, including by coordinating clinical trials for therapeutics (such as solidarity and discovery trials); providing regulatory advice to vaccine developers; forming "match-making" partnerships for manufacturing (as when large firms agree to help manufacture the vaccines of competitor firms); adapting or creating pools for IP, data and knowledge-sharing; and creating other ways to reduce transaction costs.

A wide range of actors have been involved, from public to private to third sector, and from small-scale to multinational. Targeted or new organizational forms have also been created to orchestrate these actors (such as BARDA, the United States Operation Warp Speed, CEPI, and the Access to COVID-19 Tools Accelerator and its component parts, including COVAX).

These features of the business model that have evolved around COVID-19 technologies are described in more detail below, along with initial conclusions that can be drawn from this singular experience.

## 5.1  Push R&D investments: who is investing and how much

Policy Cures Research *(164)* estimated total funding commitments for COVID-19 R&D from public, philanthropic and industry sources at US$ 9.2 billion from January to September 2020. The funds were distributed across basic research (4%), diagnostics (9%), therapeutics (14%), vaccines (59%) and unspecified (14%).

A focus on vaccine R&D offers a clear illustration of the involvement of the public sector. The authors tracked investments to provide a picture of who invested, how much, when and where, to understand better the distribution of risks and potential rewards *(165)*. The research aimed to shed light on how R&D investments may influence who gets access to the vaccines that result, and to inform future approaches to vaccine R&D. Public funding represents the vast majority of the data collected (90.7% of the US$ 6.6 billion tracked).

## Fig. 6. Number and location of recipients, by public funder location



**Funder**

United States
CEPI
Canada
Australia
European Union
United Kingdom
Germany
China
  Hong Kong SAR
  Taiwan, China
France
Japan
India
Indonesia
Singapore

**Recipient**

| | | | |
|---|---|---|---|
| Australia | European Union | Hong Kong SAR | Japan |
| Belgium | France | India | Republic of Korea |
| Canada | France/United Kingdom | Indonesia | United Kingdom |
| China | Germany | Ireland | United States |
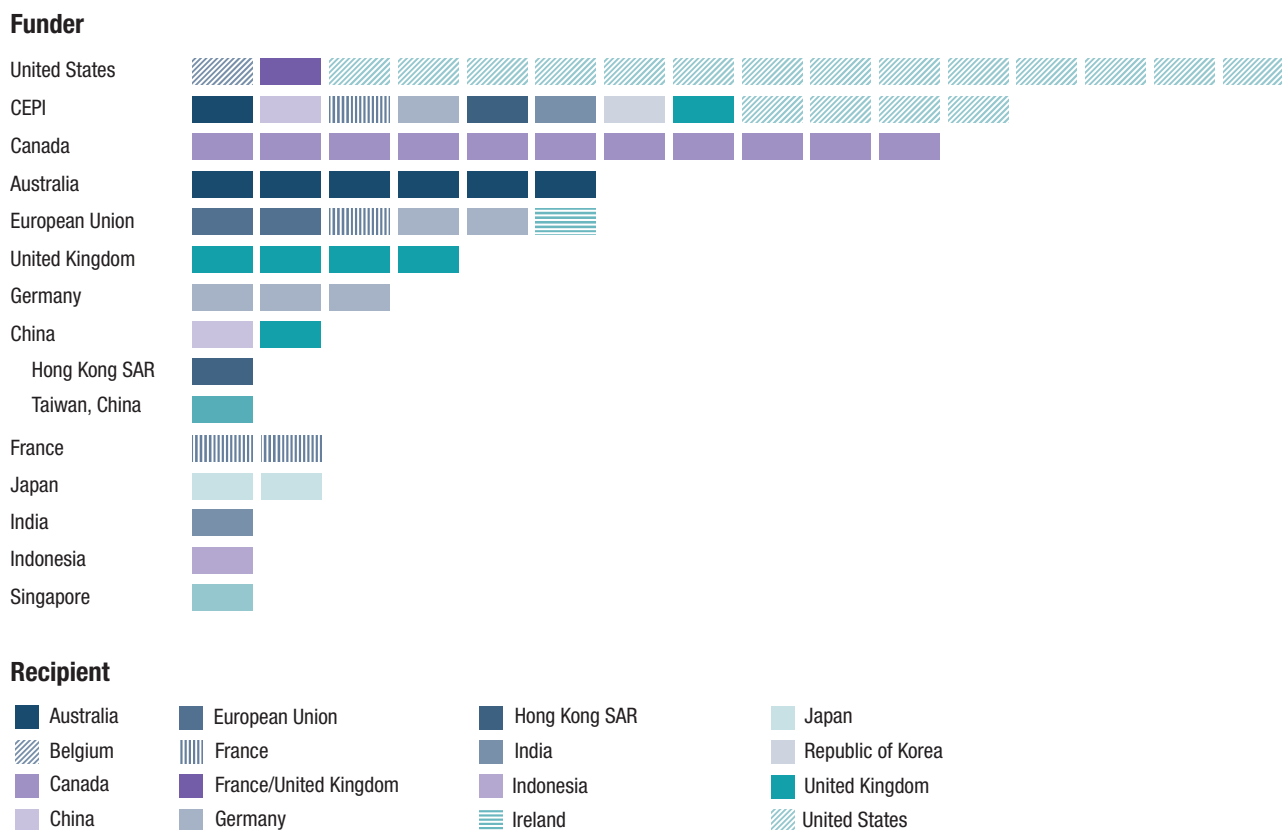
This figure shows the number of recipients and where each recipient is located, per public funder location. The figure only includes direct funding from public sources and the investments made by CEPI (Secondary funding from CEPI). Data represented here might include investments to scale-up manufacturing capacity and does not include purchase agreements (see data limitations). Sources include publicly available information such as news releases and reports, and publicly available data sources such as Policy Cures Research Covid-19 R&D Tracker and ACT-Accelerator funding tracker.

CEPI: Coalition for Epidemic Preparedness Innovations.
*Source:* Global Health Centre *(165).*

The dataset does not include any specific numbers from pharmaceutical companies, which have not disclosed specific figures regarding their R&D investments; private sector investments may be underestimated in this chart, but it is not clear by how much. Hooker & Palumbo *(166)* and Burrell *(167)* provide information concerning private investments for basic research and vaccines, but the underlying data are not available, and those figures are not included in data collected by the Global Health Centre as it is not possible to verify their accuracy.

The United States and Germany are by far the largest investors in vaccine R&D, followed by a relatively small number of other (mostly) high-income countries, China being the (middle-income) exception. Funding includes direct investments in R&D implementers and investments in intermediaries – mainly CEPI (see section 4.3). In an attempt to capture all spending that could be categorized as investment in R&D, the authors included advance purchase agreements (those signed before approval by a regulatory authority): these were made before certainty emerged of the safety and efficacy of the vaccines, so they could be understood as an additional incentive that reduces risk at the R&D stage. When considering advance purchase agreements, the United States and the EU account for the majority of the funding (US$ 41.6 billion of the US$ 52 billion tracked) *(165)*.

Funding went primarily to private companies concentrated in a relatively small number of high-income countries, with western European countries, the United States and Canada accounting for most of the funds received. India, China, Nigeria and Indonesia are important exceptions[7] *(165)*. Most countries invested in companies or research institutions from their own countries (Fig. 6), suggesting broader interest in investing in domestic R&D and industrial capacity, as well as guarding against the risk of export bans. In addition to direct investments to research institutions and pharmaceutical companies, the EU and its member states channelled about a third of their investments through CEPI, whereas the United States did not *(165)*.

## 5.2 Internationally pooled R&D grants with access conditions

CEPI (see section 4.3) has been actively involved in the development of COVID-19 vaccines, supporting 12 research institutes and pharmaceutical companies based in nine different countries with over US$ 1.4 billion in push funding to develop, scale up manufacturing of and supply vaccines and vaccine adjuvants. Most of the contributors to CEPI are European governments: the United Kingdom, Germany and Norway are the largest contributors, followed by Saudi Arabia, the European Commission, Spain and the Netherlands, among others. CEPI's funding has helped to push the development of several of the vaccine candidates that are being rolled out or that are in late-stage clinical development at the time of writing *(165)*.

As noted above, most national and regional funding was directed to organizations from the funders' own country or region. In contrast, CEPI's investments follow a more geographically diverse portfolio, which spread out both scientific and manufacturing risks (see Fig. 6) *(168)*.

## 5.3 Pull R&D incentives

In order to pool resources to fast-track the development of diagnostics, therapeutics and vaccines, and to create a platform to pool demand and procurement of these technologies, the international community created the Access to COVID-19 Tools Accelerator. The Accelerator was set up to coordinate the work of various organizations to provide end-to-end solutions (development, procurement, supply and health system strengthening) to end the acute phase of the COVID-19 pandemic. It comprises four pillars – diagnostics, therapeutics, vaccines and health systems connector – each of which is managed and coordinated by different agencies *(116)*.

The vaccines pillar of the Accelerator – COVAX – was conceived as a global pooled procurement mechanism to supply COVID-19 vaccines to all countries in the world. It created a platform where countries could commit to pool funds, aggregate demand and incentivize the scale-up of R&D and manufacturing capacity for a wide portfolio of candidates; this was to have pricing principles that aimed to ensure a sustainable return

---

7   However, a significant amount of data is likely to be missing, as specific figures on R&D investments in countries where vaccine candidates are known to have been developed or are in development at the time of writing (such as Cuba, Italy and the Russian Federation) could not be found.

for manufacturers and equitable pricing for countries. COVAX comprises two bodies: the Facility and the AMC. The Facility was intended to be a platform to pool resources from upper middle-income and high-income countries (self-financing countries), while the AMC would pool the demand and supply financed by low-income and lower middle-income countries through official development assistance. Through the combination of these two funding streams, COVAX would be able to invest in the R&D of several promising vaccine candidates. Once any of the vaccines had successfully been proved to be safe and effective, both self-financing and AMC countries would be allocated vaccines at the same rate, proportional to their total population size. Further, as a pooled procurement mechanism, COVAX could drive down prices for all participants *(169)*.

As of mid-2021, however, most of the supplies channelled through COVAX were for AMC countries, while upper middle-income and high-income countries relied primarily on bilateral arrangements with various vaccine producers to secure their own supplies *(170)*. COVAX rollout moved much more slowly than scheduled, and fewer than 4% of the doses administered worldwide at the time of writing have been through the platform. Bilateral purchases locked up most of the global supply, leaving a reduced number of doses to be allocated through COVAX, undermining the initial idea of a global mechanism *(169)*.

## 5.4  Public support for manufacturing and technology transfer

Significant public and philanthropic funding appears to have been dedicated to scaling up the manufacturing of COVID-19 vaccines, to a degree that is atypical in the traditional business model (in which such decisions would be left to private firms). Information on the extent of such investment has been difficult to gather and analyse, however. Many vaccine developers have engaged in bilateral agreements for either contract manufacturing and/ or for technology transfer to independently controlled firms (although the line between these two categories is not always clear). These agreements are mostly confidential, and their terms and conditions are not available in the public domain. The extent to which any manufacturing agreements include access provisions – such as commitments to supply lower-margin low- and middle-income countries or to set the price near the cost of production – is unclear. It would be expected that firms in receipt of significant public R&D subsidies from CEPI would be bound by some kind of access provisions, whereas this is less likely for firms that primarily received funding from national governments.

To provide insight into the information available, the authors tracked arrangements between COVID-19 vaccine developers and manufacturers. The dataset contains 117 arrangements between 16 vaccine developers and 99 manufacturers based in 36 countries (17 high-income, 15 upper middle-income and 4 lower middle-income). Some vaccine developers engaged in several such partnerships *(171)*. Among the manufacturers, 40 are privately held and 44 are publicly traded for-profit companies, 4 are government agencies, 6 are state-owned enterprises and one is a PPP, while the rest are unclear. About one third of the agreements are with manufacturers based in Europe (including the United Kingdom). Vaccine developers based in high-income countries have primarily selected manufacturing partners also based in high-income countries. In contrast, vaccine developers based in China and the Russian Federation have primarily engaged in manufacturing arrangements with other middle-income countries *(171)*.

## 5.5  Pooling technology, IP and data

In addition to push and pull incentives, WHO launched the COVID-19 Technology Access Pool (C-TAP) in May 2020, with the support of the Government of Costa Rica and 40 other Member States *(172)*. The initiative aimed to create a pool of technology, knowledge, data and IP in order to share and accelerate the development of COVID-19 technologies and to scale up manufacturing capacity worldwide.

Companies and research institutions were asked to voluntarily share data and information usually kept secret or protected by IP rights, using existing institutions and platforms, such as the technology access partnership, the MPP, launched by the United Nations Conference on Trade and Development, the United Nations Development Programme, the United Nations Technology Bank and WHO to promote technology transfer and local production *(133)* (see section 4.5.1). Another initiative to facilitate the sharing of technologies is the Open COVID Pledge, an open repository of non-exclusive, royalty-free licences on COVID-19 technologies *(173)*.

C-TAP aims to enable voluntary licensing of information, knowledge and data and, at the same time, it creates incentives for companies and institutions – for example, negotiating royalties for those companies that pool resources in C-TAP. It is still working on the creation of these incentives, however, and at the time of writing no organizations have used C-TAP to share IP, data or technology.

## 5.6  Compulsory licensing and suspension of IP rights

In response to the continued global inequity in vaccine access, proposals have been made to suspend IP and other exclusivity rights entirely for COVID-19-related health technologies. The aim would be to remove potential barriers for other producers and to increase global manufacturing capacity and availability. For example, India and South Africa proposed a "COVID-19 waiver" at the World Trade Organization to exempt member states from certain provisions of the Agreement on Trade-Related Aspects of Intellectual Property Rights "for the prevention, containment and treatment of COVID-19" *(174)*. This proposal initially gained support, mostly from low- and middle-income countries, but faced opposition from many high-income countries *(175)*, as concerns were expressed about manufacturing expertise/capacity and pressures on the availability of component materials. The United States Government changed its position in May 2021 to support a waiver limited to vaccines, whereas the EU tabled a counter-proposal, focusing on compulsory licensing. Negotiations are ongoing at the World Trade Organization, and no decision had been made at the time of writing.

Some countries have also implemented or taken measures to facilitate implementation of existing policy options to remove obstacles to manufacturing generated by IP rights, such as compulsory licences. For examples of measures adopted by different countries, see Global Health Centre *(176)*.

While existing measures have not been enough to remove all the barriers caused by IP rights – especially other rights beyond patents – they are policy instruments readily available to most countries to remove some barriers while more comprehensive options are under negotiation. It shows that governments are less willing to accept "business as usual" in a pandemic and are ready to renegotiate some of the global rules governing the pharmaceutical R&D ecosystem to prioritize availability and accessibility of health technologies.

## 5.7  Conclusions on alternative COVID-19 R&D business models

In-depth evaluations of various approaches to accelerating innovation and ensuring access to COVID-19 technologies are required to draw more robust conclusions, and these are beyond the scope of this report. Instead, this section sets out some initial observations and tentative conclusions from the limited vantage point afforded by mid-2021. The focus is almost exclusively on vaccines as, at the time of writing, the majority of investment, experience and public information had focused on these; further analysis of approaches to therapeutics will be valuable, but needs to be carried out in a time frame beyond the scope of this report.

Public investment, at risk in R&D manufacturing and advanced procurement, seems to have been essential for driving forward innovative activity rapidly, as was public facilitation of R&D through coordination, technical support, regulatory advice, match-making and other measures.

While high-income country governments could either invest up front in R&D and/or commit to large-scale advance purchase agreements to de-risk investments by private firms, these approaches did not seek to ensure wider global access to the health technologies that resulted. Only a few funders – such as CEPI *(177)* and the Bill & Melinda Gates Foundation *(178,179)* – seem to have set global access goals for their R&D funding, and it is too early to assess how effective they were (for example, the effect of the access clauses, licensing and manufacturing strategies adopted). These efforts were also challenged, however, by the inherent risk in R&D, vaccine hoarding and export bans by producing countries. It is clear that equitable access is particularly challenging in a pandemic, and that further arrangements to ensure access beyond the national or subnational level is still needed.

China, Cuba, India and the Russian Federation have developed COVID-19 vaccines and have contributed to global access by exporting vaccines to neighbouring countries and far beyond – a reminder that middle-income countries with pharmaceutical R&D and production capacity are, and will be, important actors in the ecosystem. To date, distribution through COVAX of the vaccines developed in these countries has been limited, and it remains to be seen how the outcomes of bilateral versus multilateral approaches to vaccine supply compare in terms of speed, volume and impact. Further research is needed to understand the ways in which vaccine (and therapeutic) development efforts in these four countries differed from traditional business models.

Countries that invested early through push funding for R&D seem to have been more effective at securing early supplies of COVID-19 vaccines for themselves compared to those who provided advance purchase agreements later in the R&D process, although many other factors are also likely to have played a role. In a similar vein, middle-income countries with manufacturing and/or clinical trial capacity used these resources as leverage to get supply commitments for vaccines.

Regulators played a key role in both supporting clinical trial designs early in the R&D process and in reviewing registration dossiers on a rolling basis and with a far greater degree of information transparency than the norm. At the same time, differences in opinions and approaches of various regulatory authorities around the world became clear, as countries adopted widely varying positions on the same candidate products (largely based on the same data). WHO's role was important since it used national and regional regulatory decisions to give a green light to certain vaccines for wider use under emergency provisions. The process is dependent on an application by a company that has been operating under scrutiny from a regulatory agency with Maturity Level 3 status. Some firms seem to have been slow to submit applications for review by WHO *(180)*. Calls for increased coordination among regulators have highlighted the potential benefits for both innovators and the public *(181)*. Further research is needed to understand how different regulatory approaches affected the innovation process and shaped who was ultimately able to access vaccines quickly.

Global supply is limited and insufficient to meet global demand. As of mid-2021, most producing pharmaceutical companies have not been able to deliver all the doses pre-purchased, heightening the need to strengthen manufacturing production across the globe and to take action that could reduce dependency on imports and donor support. For example, export bans and restrictions that led to shortages of medical devices and protective equipment at the beginning of the pandemic also restricted global access to vaccines, as countries where vaccines are produced inoculated their populations first *(182)*. The development of medicines as GPGs could address constraints in global supply caused by private ownership of knowledge and IP barriers to manufacturing.

This leads to the final observation: that the COVID-19 emergency ushered in both increased public demand for transparency from companies, governments and research funders and – to an important extent – an unprecedented degree of public disclosure of clinical trial protocols, clinical trial data, research funding contracts and public procurement contracts. Much critical information remains undisclosed. Nevertheless, this experience suggests that a far greater degree of transparency could be possible elsewhere in the pharmaceutical R&D system.

6

# Proposals for consideration

This analysis leads to several proposals for consideration. First, limited transparency on the functioning of the pharmaceutical R&D system is an ongoing challenge. Relatively small strategic investments to better organize, analyse and gather new data could yield major benefits. The WHO Global Observatory on Health Research and Development *(71)* was constructed as a component of the WHO Global strategy and plan of action on public health, innovation and IP *(66)*. Investment in strengthening the WHO European Region's contributions to this Observatory and in expanding its capacities could provide policy-makers with the information needed to guide key decisions on priorities, investments and policy reform. Mapping existing capacities in the Region is an important element of these, to identify (among others):

- the actors involved in R&D;

- the area and stage of development of their involvement;

- those with the ability to conduct clinical trials;

- where such trials are held; and

- manufacturing capacity.

Private pharmaceutical companies could disclose a far greater degree of detail to inform policy-making processes. While this would entail a significant shift from current practices, in the longer run firms stand to gain from well-calibrated public innovation policies.

Member States in the WHO European Region could negotiate binding commitments to ensure that, where there has been public investment in R&D, the resulting data, knowledge and IP are openly shared. Investments in R&D could be made domestically, regionally or globally; what is critical is to ensure that all knowledge generated rapidly enters the public domain as a GPG. Similar principles were proposed by the WHO Consultative Expert Working Group on Research and Development in 2012 when it recommended that governments consider negotiating a global biomedical R&D treaty *(183)*. The pharmaceutical industry could benefit from increased access to knowledge generated by other actors; compensation for putting knowledge into the public domain could also be included in these rules, ensuring that companies would earn revenue for their R&D while also sharing it as a GPG.

Member States could create a pooled regional fund to support high-priority/high-risk pharmaceutical R&D that both responds to jointly agreed priorities and ties conditions to its investments to ensure availability and affordability of the end-products. Countries at all income levels across the Region could contribute according to ability to pay. A similar fund at the global level was proposed by the WHO Consultative Expert Working Group on Research and Development, to be financed through public contributions by all countries at a percentage of GDP (at least 0.01%) *(67)*. Countries could take the lead in restarting the proposal for the creation of such a global fund.

CEPI is one example of an international R&D fund that pools resources from contributing funders, reduces risk by subsidizing earlier-stage R&D on pathogens of pandemic potential conducted by firms, ties access provisions to its investments and is also involved in managing production. Notably, countries in the European Region contributed 82% of the approximately US$ 1.5 billion that CEPI invested in COVID-19 vaccines. An in-depth evaluation of these investments is needed to understand what worked well and what did not, but it is beyond the scope of this report.

The EU has begun consultations for an EU-wide pooled R&D fund – the European Health Emergency Preparedness and Response Authority *(118)*, modelled in part on BARDA, with a focus on pathogens of pandemic potential. An analogous entity – or an extension of the Authority – could be considered for other R&D priorities beyond outbreaks and/or in a manner that would include countries beyond the EU. A network of regional funds operating on common principles, such as sharing pharmaceutical knowledge as a GPG, could also be considered in lieu of a single global fund *(168)*. The pharmaceutical industry would benefit from the growing financial resources and knowledge generated by increased public investment in R&D: the majority of CEPI investments, for example, went to private firms.

Countries could also create a pooled regional procurement initiative that would increase the negotiating leverage of governments and pool various risks, including the risk of R&D failure. The European Commission played this role in COVID-19 for EU member states, and one objective was to de-risk R&D and production of vaccines through advance purchase agreements. The Pan American Health Organization's Revolving Fund has demonstrated success in securing the supply of affordably priced vaccines and other medicines for its member states since its creation in the 1970s, although it is not clear whether this has had an impact on innovation *(184,185)*. A range of options for pooled procurement are available, on a spectrum from limited information-sharing across countries to demand pooling (single buyer) to full joint negotiation and procurement of products *(184)*.

Pilot initiatives in Europe, such as the Beneluxa Initiative, can be built upon. Pooling increases negotiating leverage, particularly for smaller and/or less wealthy countries. Health technology assessment can be integrated into pooled procurement to calibrate prices paid for evidence of therapeutic or health system value. Pooled procurement can offer benefits to pharmaceutical companies in the form of increased security of payment and reduced transaction costs.

Countries could individually or jointly increase their investment in SMEs, tying fair pricing and transparency conditions to their funding. While large multinational pharmaceutical firms are highly concentrated in just a few countries, pharmaceutical SMEs are more broadly distributed across the Region. As such firms often rely on external investors to assume risk and finance their R&D, and because the scale of the investment is much smaller than for later-stage R&D, investing in SMEs may be more financially feasible for many individual countries (compared to financing late-stage R&D or multinational firms).

There is also a role for governments as system integrators: not necessarily only by funding projects, but by fostering collaboration and knowledge-sharing, and by identifying complementarities between different actors in the Region. Various public entities discussed throughout this report – including CARB-X, NIH, BARDA and CEPI – have played the role of system integrator, as have non-profit PDPs.

Countries could invest in manufacturing capacities in the Region, reducing dependency on imports and ensuring greater availability of medicines once the knowledge has been generated. The EU's Pharmaceutical Strategy for Europe *(186)*, and its proposal to create a European Health Emergency Preparedness and Response Authority, aim to build up "strategic autonomy in the area of medicines", to diversify production and supply chains, and to foster production and innovation in Europe. Increased public investment and subsidies for manufacturing can benefit private producers.

Entrepreneurial leaders from the pharmaceutical industry can engage productively and proactively with policy-makers to test alternative business models for R&D that would deliver GPGs. Too often, making medicines more widely affordable and available is seen as a threat to profitability and to the existing business model that generates it. Vision, creativity and an appetite for risk-taking from the pharmaceutical industry are needed to meet the growing societal expectation that medicines should be available as GPGs.

Finally, each of these options could be undertaken by the Region as a whole, by a large pre-existing grouping such as the EU or by smaller groups of like-minded countries (such as the Beneluxa Initiative, the European Free Trade Association and the Visegrad Group). Smaller initiatives may have less negotiating leverage or financial clout, but they offer the benefit of lower transaction costs to reach agreement and undertake joint action.

7

# Conclusions

Realizing the vision of the outputs of the pharmaceutical innovation process as GPGs, with the benefits of science and technological advances made openly available to all, requires changes to the current R&D business model. This current model functions on the logic of restricting access to knowledge as a means to pay for its creation, rather than making that knowledge publicly available. Alternative business models with outcomes better aligned with public interests are possible, but they must be purposefully constructed with appropriate investment, organizational arrangements, incentives, and underlying laws and policies.

Further ongoing experimentation with business models is also needed. Thus far, such models have been implemented on a relatively small scale or for relatively short periods of time. Ideas for alternative approaches to R&D are plentiful, but the resources to implement them – mostly coming from public and philanthropic funders – have been scarce relative to need *(187)*.

While a wide range of alternative business models have been implemented, one unifying theme across them is the fundamental role of governments as stewards of the innovation system in order to facilitate greater patient access and align innovation with needs. Views on this potential increased role are diverse and it would require greater national and intergovernmental cooperation. Generating GPGs also requires investors to put money on the table and to accept risk, and countries have historically been willing to do so as the "patient investors" that have enabled major technological progress *(163)*. The risks can be quantified, managed and pooled across countries and sectors. Finding ways to share costs and risks is essential to subsequently being able to share the "reward" or benefit of advancing pharmaceutical innovation.

However, current international arrangements are too thin and inadequate to do the necessary coordination. It may be useful to revisit the negotiation of binding international rules to structure cooperation across countries in the Region in the matter of pharmaceutical R&D *(168,188)*. Regardless of the specific policies pursued, moving from the national to the regional level and beyond will require strong political leadership.

# References[8]

1.  Morgan SG, Bathula HS, Moon S. Pricing of pharmaceuticals is becoming a major challenge for health systems. BMJ. 2020;368:l4627. doi:10.1136/bmj.l4627.

2.  Von der Leyen on coronavirus global response: world stands united against coronavirus and will win. In: European Commission [website]. Brussels: European Commission; 2020 (https://ec.europa.eu/commission/presscorner/detail/en/AC_20_811).

3.  Emmanuel Macron speaks at UN General Assembly (22 September 2020). In: French Foreign Policy [website]. Paris: Ministry for Europe and Foreign Affairs; 2020 (https://www.diplomatie.gouv.fr/en/french-foreign-policy/united-nations/news-and-events/united-nations-general-assembly/unga-s-75th-session/article/emmanuel-macron-speaks-at-un-general-assembly-22-sept-2020).

4.  Describing COVID-19 pandemic as wake-up call, dress rehearsal for future challenges, Secretary-General opens Annual General Assembly debate with vision for solidarity. In: United Nations [website]. New York: United Nations; 2020 (https://www.un.org/press/en/2020/ga12268.doc.htm).

5.  WHO: leaders call COVID-19 vaccines a "global public good." In: TWN/Third World Network [website]. Penang: Third World Network; 2020 (https://www.twn.my/title2/health.info/2020/hi200511.htm).

6.  Ovans A. What is a business model? Boston, MA: Harvard Business Review; 2015 (https://hbr.org/2015/01/what-is-a-business-model).

7.  Moon S, Vieira M, Kimmitt R. Do costs, timeframes and attrition rates differ between non-commercial and commercial biomedical R&D? A study of neglected diseases R&D and the P2I model. Geneva: Global Health Centre at the Graduate Institute; 2020 (https://repository.graduateinstitute.ch/record/298834).

8.  COVID-19 vaccine research and analysis. Geneva: Global Health Centre at the Graduate Institute; 2021 (https://www.knowledgeportalia.org/covid-19).

9.  Vieira M, Moon S. Research synthesis: public funding of pharmaceutical R&D. Geneva: Global Health Centre at the Graduate Institute; 2019 (https://www.knowledgeportalia.org/public-funding-of-r-d).

10. Navarro D, Moon S, Vieira M. Research synthesis: role of small and medium-sized enterprises. Geneva: Global Health Centre at the Graduate Institute; 2019 (https://www.knowledgeportalia.org/small-and-medium-enterprises).

11. Navarro D, Moon S. Research synthesis: product development partnerships. Geneva: Global Health Centre at the Graduate Institute; 2019 (https://www.knowledgeportalia.org/product-development-partnerships).

---

8    All references accessed on 2–18 August 2021.

12. Sunyoto, T, Vieira M, Moon S, Bezruki A. Research synthesis: biosecurity research and development (R&D). Geneva: Global Health Centre at the Graduate Institute; 2020 (https://www.knowledgeportalia.org/biosecurityrd).

13. Vieira M, Moon S. Research synthesis: costs of pharmaceutical R&D. Geneva: Global Health Centre at the Graduate Institute; 2020 (https://www.knowledgeportalia.org/cost-of-r-d).

14. Kimmitt R, Vieira M, Moon S, Bezruki A. Research synthesis: time and success rate of pharmaceutical R&D. Geneva: Global Health Centre at the Graduate Institute; 2020 (https://www.knowledgeportalia.org/r-d-time-success).

15. Samuelson PA. The pure theory of public expenditure. Rev Econ Stat. 1954; 36(4):387–9. doi:10.2307/1925895.

16. Stiglitz J. Knowledge as a global public good. In: Kaul I, Grunberg I, Stern M, editors. Global public goods: international cooperation in the 21st century. New York: Oxford University Press; 1999:308–25.

17. Moon S, Røttingen JA, Frenk J. Global public goods for health: weaknesses and opportunities in the global health system. Health Econ Policy Law. 2017;12(2): 195–205. doi:10.1017/S1744133116000451.

18. Desai M. Public goods: a historical perspective. In: Kaul I, editor. Providing global public goods. Oxford: Oxford University Press; 2003:63–77. https://doi.org/10.1093/0195157400.001.0001.

19. Moon S. Medicines as global public goods: the governance of technological innovation in the new era of global health. Glob Health Govern. 2009;2(2):1–23 (http://www.ghgj.org/moon2.2medecinespublicgood.htm).

20. Soucat A, Kickbusch I. Global common goods for health: towards a new framework for global financing. Glob Policy. 2020;11(5):628–35. doi:10.1111/1758-5899.12875.

21. IMI: Innovative Medicines Initiative [website]. Brussels: European Federation of Pharmaceutical Industries and Associations; 2021 (https://www.imi.europa.eu/).

22. EDCTP: European and Developing Countries Clinical Trials Partnership [website]. The Hague: European and Developing Countries Clinical Trials Partnership; 2021 (https://www.edctp.org/).

23. Capo F, Brunetta F, Boccardelli P. Innovative business models in the pharmaceutical industry: a case on exploiting value networks to stay competitive. Int J Eng Bus Manag. 2014;6:23. doi:10.5772/59155.

24. Hemel DJ, Larrimore Ouellette L. Bayh–Dole beyond borders. J Law Biosci. 2017;4(2):282–310. doi:10.1093/jlb/lsx011.

25. So AD, Sampat BN, Rai AK, Cook-Deegan R, Reichman JH, Weissman R et al. Is Bayh-Dole good for developing countries? Lessons from the US experience. PLoS Biol. 2008;6(10):e262. doi:10.1371/journal.pbio.0060262.

26. Lazonick W, Hopkins M, Jacobson K, Sakinc ME, Tulum Ö. US pharma's financialized business model. SSRN Electronic Journal. 2017. doi:10.2139/ssrn.3035529.

27. Measuring the return from pharmaceutical innovation. In: Deloitte [website]. London: Deloitte; 2019 (https://www2.deloitte.com/uk/en/pages/life-sciences-and-healthcare/articles/ten-years-on-measuring-return.html).

28. Geilinger U, Leo C. HBM new drug approval report: analysis of FDA new drug approvals in 2018 (and multi-year trends). Zug: HBM Partners; 2019 (https://www.hbmpartners.com/media/docs/industry-reports/Analysis-of-FDA-Approvals-2018-and-Previous-Years.pdf).

29. Lincker H, Ziogas C, Carr M, Porta N, Eichler HG. Regulatory watch: where do new medicines originate from in the EU? Nat Rev Drug Discov. 2014;13(2):92–3. doi:10.1038/nrd4232.

30. Bhambra R. Biopharma deals of 2020 break through. Biopharm Deal. November, 2020; d43747-020-01176-z. doi:10.1038/d43747-020-01176-z.

31. Pammolli F, Righetto L, Abrignani S, Pani L, Pelicci PG, Rabosio E. The endless frontier? The recent increase of R&D productivity in pharmaceuticals. J Transl Med. 2020;18(1):162. doi:10.1186/s12967-020-02313-z.

32. Master Alliance Provisions Guide (MAPGuide). In: GHIAA [website]. Research Triangle Park, NC: Global Health Innovation Alliance Accelerator; 2021 (https://ghiaa.org/mapguide-home/).

33. COVID-19 contracts. In: Knowledge Ecology International [website]. Washington DC: Knowledge Ecology International; 2021 (https://www.keionline.org/covid-contracts).

34. Mazzucato M, Semieniuk G Public financing of innovation: new questions. Oxford Rev Econ Policy. 2017;33(1):24–48. doi:10.1093/oxrep/grw036.

35. UK health research analysis 2014. In: UK Clinical Research Collaboration [website]. London: UK Clinical Research Collaboration; 2015 (https://www.ukcrc.org/research-coordination/health-research-analysis/uk-health-research-analysis/).

36. Viergever RF, Hendriks TCC. [Targeted public funding for health research in the Netherlands]. Ned Tijdschr Geneeskd. 2014;159:A8174 [in Dutch].

37. Sussex J, Feng Y, Mestre-Ferrandiz J, Pistollato M, Hafner M, Burridge P et al. Quantifying the economic impact of government and charity funding of medical research on private research and development funding in the United Kingdom. BMC Med. 2016;14(1):32. doi:10.1186/s12916-016-0564-z.

38. Sampat BN, Lichtenberg FR. What are the respective roles of the public and private sectors in pharmaceutical innovation? Health Aff (Millwood). 2011;30(2):332–9. doi:10.1377/hlthaff.2009.0917.

39. Kesselheim AS, Tan YT, Avorn J. The roles of academia, rare diseases, and repurposing in the development of the most transformative drugs. Health Aff (Millwood). 2015;34(2):286–93. doi:10.1377/hlthaff.2014.1038.

40. Chakravarthy R, Cotter K, DiMasi J, Milne CP, Wendel N. Public- and private-sector contributions to the research and development of the most transformational drugs in the past 25 years: from theory to therapy. Ther Innov Regul Sci. 2016;50(6):759–68. doi:10.1177/2168479016648730.

41. Galkina Cleary E, Beierlein JM, Khanuja NS, McNamee LM, Ledley FD. Contribution of NIH funding to new drug approvals 2010–2016. Proc Natl Acad Sci U S A. 2018;115(10):2329–34. doi:10.1073/pnas.1715368115.

42. Pills and profits: how drug companies make a killing out of public research. In: STOPAIDS [website]. London: STOPAIDS; 2017 (https://stopaids.org.uk/resources/pills-and-profits-how-drug-companies-make-a-killing-out-public-research/).

43. Nayak RK, Avorn J, Kesselheim AS. Public sector financial support for late stage discovery of new drugs in the United States: cohort study. BMJ. 2019;367:l5766. doi:10.1136/bmj.l5766.

44. National Center for Advancing Translational Sciences (NCATS) [website]. Bethesda, MD: National Center for Advancing Translational Sciences; 2021 (https://ncats.nih.gov/about).

45. Larsen JC, Disbrow GL. Project BioShield and the Biomedical Advanced Research Development Authority: a 10-year progress report on meeting US preparedness objectives for threat agents. Clin Infect Dis. 2017;64(10):1430–4. doi:10.1093/cid/cix097.

46. The power of partnership: BARDA ushers in 50th FDA-approved product for health security. In: Domestic Preparedness [website]. Biomedical Advanced Research and Development Authority; 2019 (https://www.phe.gov/ASPRBlog/Lists/Posts/Post.aspx?ID=362).

47. Moran M, Ropars AL, Guzman J, Diaz J, Garrison C. In: Medicines for Malaria Venture (MMV) [website]. New landscape of neglected disease drug development. London: Wellcome Trust; 2005 (https://www.mmv.org/newsroom/publications/new-landscape-neglected-disease-drug-development).

48. Moran M. A breakthrough in R&D for neglected diseases: new ways to get the drugs we need. PLoS Med. 2005;2(9):e302. doi:10.1371/journal.pmed.0020302.

49. Munoz V, Visentin F, Foray D, Gaule P. Can medical products be developed on a non-profit basis? Exploring product development partnerships for neglected diseases. Sci Public Policy. 2015;42(3):315–38. doi:10.1093/scipol/scu049.

50. Darrow JJ, Light DW. Beyond the high prices of prescription drugs: a framework to assess costs, resource allocation, and public funding. Health Aff (Millwood). 2021;40(2):281–88. doi:10.1377/hlthaff.2020.00328.

51. Mestre-Ferrandiz J, Shaw B, Chatterjee C, Ding J, Singh P, Hopkins MM. Policy instruments (non-price) for medical innovation. Oslo Medicines Initiative technical report. Copenhagen: WHO Regional Office for Europe; 2022.

52. Financing neglected disease R&D: principles and options. Geneva: Drugs for Neglected Diseases Initiative; 2010 (https://dndi.org/publications/2010/sustainable-funding-resources/).

53. Medicine evaluation figures. Amsterdam: European Medicines Agency; 2021 (https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines/medicine-evaluation-figures#annual-medicines-highlights-(2015-2020)-section).

54. Wieseler B, McGauran N, Kaiser T. New drugs: where did we go wrong and what can we do better? BMJ. 2019;366:l4340. doi:10.1136/bmj.l4340.

55. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR et al. How to improve R&D Productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9(3):203–14. doi:10.1038/nrd3078.

56. Correa CM. Intellectual property: how much room is left for industrial policy? Geneva: United Nations Conference on Trade and Development; 2015 (UNCTAD Discussion Papers No. 223; https://unctad.org/system/files/official-document/osgdp20155_en.pdf).

57. Suleman F, Low M, Moon S, Morgan SG. New business models for research and development with affordability requirements are needed to achieve fair pricing of medicines. BMJ. 2020;368:l4408. doi:10.1136/bmj.l4408.

58. Mikulic M. U.S. pharma industry R&D spending as a percent of total revenues 1990–2020. In: Statista [website]. New York: Statista; 2021 (https://www.statista.com/statistics/265100/us-pharmaceutical-industry-spending-on-research-and-development-since-1990/).

59. Lazonick W, Tulum Ö. US biopharmaceutical finance and the sustainability of the biotech business model. Res Policy. 2011;40(9):1170–87. doi:10.1016/j.respol.2011.05.021.

60. Lazonick W, Mazzucato M. The risk-reward nexus in the innovation-inequality relationship: Who takes the risks? Who gets the rewards? Ind Corp Chang. 2013;22(4):1093–128. doi:10.1093/icc/dtt019.

61. Mazzucato M. The value of everything: making and taking in the global economy. Penguin London, UK: Random House UK; 2018.

62. The people's prescription: re-imagining health innovation to deliver public value. London: UCL Institute for Innovation and Public Purpose; 2018 (IIPP WP 2018-10; https://www.ucl.ac.uk/bartlett/public-purpose/wp2018-10).

63. McElfish PA, Purvis RS, Stewart MK, James L, Kim Yeary KH, Long CR. Health research funding agencies' policies, recommendations, and tools for dissemination. Prog Community Health Partnersh. 2018;12(4):473–82. doi:10.1353/cpr.2018.0072.

64. Tschider CA. Innovation in the public sphere: reimagining law and economics to solve the National Institutes of Health publishing controversy. J Law Biosci. 2014;1(3):281–315. doi:10.1093/jlb/lsu025.

65. Van Hecke M, van Gils B. Médicaments: vous les payez deux fois [Medicines: you pay twice]. Test Santé/Test Gezond. 2019;149:8–11 (https://www.test-aankoop.be/overzichtspagina?type=magazine-articles).

66. Global strategy and plan of action on public health, innovation and intellectual property. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/handle/10665/23552).

67. Research and development to meet health needs in developing countries: strengthening global financing and coordination: report of the consultative expert working group on research and development: financing and coordination. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/handle/10665/254706).

68. Fair pricing forum 2017: meeting report, Amsterdam, the Netherlands, 11 May 2017. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/334340).

69. Report of the United Nations Secretary-General's High-level Panel on Access to Medicines: Promoting innovation and access to health technologies. New York: United Nations; 2016 (http://www.unsgaccessmeds.org/final-report/).

70. Stirling C, Hardesty C, Floor J, Sarson T, Gimenez Stamminger N, Freischem B. Site selection for life sciences companies in Europe, fifth edition. Zurich: KPMG; 2018 (https://home.kpmg/ch/en/home/insights/2015/12/site-selection-for-life-sciences-companies.html).

71. Global Observatory on Health Research and Development. In: World Health Organization [website]. Geneva: World Health Organization; 2021 (https://www.who.int/observatories/global-observatory-on-health-research-and-development).

72. Gross domestic R&D expenditure on health (health GERD) as a % of total GERD. In: World Health Organization [website]. Geneva: World Health Organization; 2020 (https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/gross-domestic-r-d-expenditure-on-health-health-gerd-as-a-of-total-gerd).

73. OECD R&D tax incentives database, 2021 edition. Paris: OECD Publishing; 2021 (https://www.oecd.org/sti/rd-tax-stats-database.pdf).

74. World RePORT [website]. Bethesda, MD: National Institutes of Health; 2021 (https://worldreport.nih.gov/wrapp/#/search?searchId=611ab0b4c9b7924e4ca30a81).

75. Trouiller P, Torreele E, Olliaro P, White N, Foster S, Wirth D et al. Drugs for neglected diseases: a failure of the market and a public health failure? Trop Med Int Health. 2001;6(11):945–51. doi:10.1046/j.1365-3156.2001.00803.x.

76. Vieira M, Kimmitt R, Navarro D, Bezruki A, Moon S. Advancing innovation and access to medicines: the achievements and unrealized potential of product development partnerships. In: Partnership effectiveness. Abingdon: Routledge; in press.

77. Vieira M, Kimmitt R, Moon S. Non-commercial pharmaceutical R&D: what do neglected diseases suggest about costs and efficiency? F1000Research. 2021;10:190. doi:10.12688/f1000research.28281.1.

78. Ridley DB, Grabowski HG, Moe JL. Developing drugs for developing countries. Health Aff (Millwood). 2006;25(2):313–24. doi:10.1377/hlthaff.25.2.313.

79. Navarro D, Moon S. Research synthesis: priority review vouchers. Geneva: Global Health Centre at the Graduate Institute; 2019 (https://www.knowledgeportalia.org/priority-review-vouchers).

80. Mezher M, Brennan Z, Gaffney A. Regulatory explainer: everything you need to know about FDA's priority review vouchers. Rockville, MD: Regulatory Affairs Professionals Society; 2020 (https://www.raps.org/regulatory-focus/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know-about-fdas-priority-review-vouchers).

81. Dicken JE. Drug development: FDA's priority review voucher programs. Washington DC: U.S. Government Accountability Office; 2020 (https://www.gao.gov/products/gao-20-251).

82. Jain N, Hwang T, Franklin JM, Kesselheim AS. Association of the priority review voucher with neglected tropical disease drug and vaccine development. JAMA. 2017;318(4):388–9. doi:10.1001/jama.2017.7467.

83. Sunyoto T, Potet J, Boelaert M. Why miltefosine – a life-saving drug for leishmaniasis – is unavailable to people who need it the most. BMJ Glob Health. 2018;3(3):e000709. doi:10.1136/bmjgh-2018-000709.

84. Kesselheim AS, Maggs LR, Sarpatwari A. Experience with the priority review voucher program for drug development. JAMA. 2015;314(16):1687–8. doi:10.1001/jama.2015.11845.

85. Sarpatwari A, Beall RF, Abdurrob A, He M, Kesselheim AS. Evaluating the impact of the Orphan Drug Act's seven-year market exclusivity period. Health Aff (Millwood). 2018;37(5):732–7. doi:10.1377/hlthaff.2017.1179.

86. COMP, EMA Scientific Secretariat. European regulation on orphan medicinal products: 10 years of experience and future perspectives. Nat Rev Drug Discov. 2011;10(5):341–9. doi:10.1038/nrd3445.

87. Orphan medicines figures 2000–2020. In: European Medicines Agency [website]. Amsterdam: European Medicines Agency; 2021 (https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview).

88. Commission staff working document – evaluation: joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Luxembourg: Publications Office of the European Union; 2020 (https://op.europa.eu/en/publication-detail/-/publication/e9a9fff0-dbd9-11ea-adf7-01aa75ed71a1/language-en).

89. Search orphan drug designations and approvals [online database]. Silver Spring, MD: U.S. Food and Drug Administration; 2021 (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/).

90. Horgan D, Moss B, Boccia S, Genuardi M, Gajewski M, Capurso G et al. Time for change? The why, what and how of promoting innovation to tackle rare diseases – is it time to update the EU's Orphan Regulation? And if so, what should be changed? Biomed Hub. 2020;5(2):1–11. doi:10.1159/000509272.

91. de Jongh T, Radauer A, Bostyn S, Poort J. Effects of supplementary protection mechanisms for pharmaceutical products. Amsterdam: Technopolis Group; 2018 (https://www.technopolis-group.com/report/effects-of-supplementary-protection-mechanisms-for-pharmaceutical-products/).

92. Sarpatwari A, Kesselheim AS. Reforming the orphan drug act for the 21st century. N Engl J Med. 2019;381(2):106–8. doi:10.1056/NEJMp1902943.

93. Luzzatto L, Hollak CEM, Cox TM, Schieppati A, Licht C, Kääriäinen H et al. Rare diseases and effective treatments: are we delivering? Lancet. 2015;385(9970):750–2. doi:10.1016/S0140-6736(15)60297-5.

94. Stevens AJ, Jensen JJ, Wyller K, Kilgore PC, Chatterjee S, Rohrbaugh ML. The role of public-sector research in the discovery of drugs and vaccines. N Engl J Med. 2011;364(6):535–41. doi:10.1056/NEJMsa1008268.

95. Cohen D, Raftery J. Paying twice: questions over high cost of cystic fibrosis drug developed with charitable funding. BMJ. 2014;348:g1445–g1445. doi:10.1136/bmj.g1445.

96. Jayasundara K, Hollis A, Krahn M, Mamdani M, Hoch JS, Grootendorst P. Estimating the clinical cost of drug development for orphan versus non-orphan drugs. Orphanet J Rare Dis. 2019;14(1):12. doi:10.1186/s13023-018-0990-4.

97. The rise of orphan drugs. Washington DC: America's Health Insurance Plans; 2019 (https://www.ahip.org/resources/the-rise-of-orphan-drugs).

98. Phillips MI. Big Pharma's new model in orphan drugs and rare diseases. Expert Opin Orphan Drugs. 2013;1(1):1–3. doi:10.1517/21678707.2013.752128.

99. Hughes DA, Poletti-Hughes J. Profitability and market value of orphan drug companies: a retrospective, propensity-matched case-control study. PLoS One. 2016;11(10):e0164681. doi:10.1371/journal.pone.0164681.

100. Smith B, Inglesby TV, O'Toole . Biodefense R&D: anticipating future threats, establishing a strategic environment. Biosecur Bioterror. 2003;1(3):193–202. doi:10.1089/153871303769201842.

101. Beaumier CM, Gomez-Rubio AM, Hotez PJ, Weina PJ. United States military tropical medicine: extraordinary legacy, uncertain future. PLoS Negl Trop Dis. 2013;7(12):e2448. doi:10.1371/journal.pntd.0002448.

102. Mostofi FK. Contributions of the military to tropical medicine. Bull N Y Acad Med. 1968;44(6):702–20 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1750230/).

103. Quail G. The debt tropical medicine owes to the military. J Mil Veterans' Health. 2015;23(3):18–21 (https://jmvh.org/article/the-debt-tropical-medicine-owes-to-the-military/).

104. Yoeli M. The evolution of tropical medicine: a historical perspective. Bull N Y Acad Med. 1972;48(10):1231–46 (https://pubmed.ncbi.nlm.nih.gov/4565244/).

105. Warfield KL, Aman MJ. Role of small biotechnology companies in the fledgling biodefense vaccine industry. Expert Rev Vaccines. 2016;15(9):1079–82. doi:10.1586/14760584.2016.1168702.

106. Casadevall A, Ehrlich SA, Franz DR, Imperiale MJ, Keim PS. Biodefense research: a win-win challenge. Biosecur Bioterror. 2008;6(4):291–2. doi:10.1089/bsp.2008.1114.

107. DeFrancesco L. Throwing money at biodefense. Nat Biotechnol. 2004;22(4): 375–8. doi:10.1038/nbt0404-375.

108. Binder P. Biomedical research: its mission within the French military medical service. Mil Med. 1999;164(5):341–5. doi:10.1093/milmed/164.5.341.

109. Bailey MS. A brief history of British military experiences with infectious and tropical diseases. J R Army Med Corps. 2013;159(3):150–7. doi:10.1136/jramc-2013-000087.

110. Herron JBT, Dunbar JAT. The British army's contribution to tropical medicine. Clinical Medicine 2018;18(5):380–83. https://doi.org/10.7861/clinmedicine.18-5-380.

111. Shanks GD, Edstein MD, Cheng Q, Frances S, Aaskov J, Lilley K et al. Army Malaria Institute – its evolution and achievements fifth decade: 2006–2015. J Mil Veterans' Health. 2016;24(1):25–44 (https://jmvh.org/article/army-malaria-institute-its-evolution-and-achievements-fifth-decade-2006-2015/).

112. Matheny J, Mair M, Mulcahy A, Smith BT. Incentives for biodefense countermeasure development. Biosecur Bioterror. 2007;5(3):228–38. doi:10.1089/bsp.2007.0030.

113. Milne C, Smith ZP, Chakravarthy R. Landscape for medical countermeasure development. Nat Rev Drug Discov. 2017;16(7):448. doi:10.1038/nrd.2017.80.

114. Milne C. The changing landscape for new drug development: medical countermeasures (MCMs) as a case study. In: Betz U, editor. Curious2018. Cham: Springer; 2019:47–68. doi:10.1007/978-3-030-16061-6_7.

115. Landscape of emerging infectious disease research and development: preventing the next pandemic. Sydney: Policy Cures Research; 2020 (https://s3-ap-southeast-2.amazonaws.com/policy-cures-website-assets/app/uploads/2020/10/30095357/EID_Report.pdf).

116. CEPI annual progress report 2019. Oslo: Coalition for Epidemic Preparedness Innovations; 2019 (https://cepi.net/wp-content/uploads/2020/04/CEPI-Annual-Progress-Report-2019_website.pdf).

117. Huneycutt B, Lurie N, Rotenberg S, Wilder R, Hatchett R. Finding equipoise: CEPI revises its equitable access policy. Vaccine. 2020;38(9):2144–8. doi:10.1016/j.vaccine.2019.12.055.

118. European Health Emergency Preparedness and Response Authority (HERA). In: European Commission [website]. Brussels: European Commission; 2021 (https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12870-European-Health-Emergency-Preparedness-and-Response-Authority-HERA-_en).

119. Brogan DM, Mossialos E. Systems, not pills: the options market for antibiotics seeks to rejuvenate the antibiotic pipeline. Soc Sci Med. 2016;151:167–72. doi:10.1016/j.socscimed.2016.01.005.

120. Aitken M, Kleinrock M. Global medicines use in 2020: outlook and implications. Parsippany, NJ: IMS Institute for Healthcare Informatics; 2015 (https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-medicines-use-in-2020).

121. Renwick MJ, Brogan DM, Mossialos E. A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. J Antibiot (Tokyo). 2016;69(2):73–88. doi:10.1038/ja.2015.98.

122. Outterson K. New business models for sustainable antibiotics. London: Chatham House; 2014 (Working Groups on Antimicrobial Resistance, Paper No.1; https://www.chathamhouse.org/ites/default/files/public/Research/Global%20Health/0214SustainableAntibiotics.pdf).

123. Jaczynska E, Outterson K, Mestre-Ferrandiz J. Business model options for antibiotics learning from other industries. London: Big Innovation Centre; 2015 (https://www.biginnovationcentre.com/wp-content/uploads/2019/07/BIC_BUSINESS-MODEL-OPTIONS-FOR-ANTIBIOTICS-APPENDICES_01.02.2015.pdf).

124. Laxminarayan R, Van Boeckel T, Frost I, Kariuki S, Khan EA, Limmathurotsakul D et al. The Lancet Infectious Diseases Commission on antimicrobial resistance: 6 years later. Lancet Infect Dis. 2020;20(4):e51–60. doi:10.1016/S1473-3099(20)30003-7.

125. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. London: Review on Antimicrobial Resistance; 2016 (https://amr-review.org/Publications.html).

126. Gotham D, Moja L, van der Heijden M, Paulin S, Smith S, Beyer P. Reimbursement models to tackle market failures for antimicrobials: approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. Health Policy. 2021;125(3):296–306. doi:10.1016/j.healthpol.2020.11.015.

127. CARB-X: Combating Antibiotic-Resistant Bacteria [website]. Boston, MA: CARB-X; 2021 (https://carb-x.org).

128. GARDP: Global Antibiotic Research and Development Partnership [website]. Geneva: Global Antibiotic Research and Development Partnership; 2021 (https://www.gardp.org).

129. The AMR Action Fund. In: IFPMA [website]. Geneva: International Federation of Pharmaceutical Manufacturers and Associations; 2021 (https://www.ifpma.org/partners-2/the-amr-action-fund/).

130. Vogler S. Access to information in markets for medicines in the WHO European Region. Oslo Medicines Initiative technical report. Copenhagen: WHO Regional Office for Europe; 2022.

131. Love J. Discussion paper: an economic perspective on delinking the cost of R&D from the price of medicines. Geneva: UNITAID; 2016 (https://unitaid.org/news-blog/unitaid-study-looks-delinking-cost-rd-price-medicines/#en).

132. Navarro D, Moon S. Research synthesis: patent pools. Geneva: Global Health Centre at the Graduate Institute; 2019 (https://www.knowledgeportalia.org/patent-pools).

133. Medicines Patent Pool [website]. Geneva: Medicines Patent Pool; 2021 (https://medicinespatentpool.org).

134. WIPO Re:Search (2021a). About WIPO Re:Search [website]. Seattle, WA: BIO Ventures for Global Health (https://www.wipo.int/research/en/about/).

135. Ziegler N, Gassmann O, Friesike S (2014). Why do firms give away their patents for free? World Pat Inf. 37:19–25. doi:10.1016/j.wpi.2013.12.002.

136. WIPO Re:Search Members [website]. Seattle, WA: BIO Ventures for Global Health; 2021 (https://www.wipo.int/research/en/about/members.html).

137. BVGH Partnership Hub snapshot – March 2021. Seattle, WA: BIO Ventures for Global Health; 2021 (https://bvgh.org/wp-content/uploads/2021/03/2021-March-Snapshot.pdf).

138. Sharafudeen M. WIPO Re:Search: advancing science for neglected tropical diseases, malaria and tuberculosis. Geneva: World Intellectual Property Organization; 2019 (https://www.wipo.int/publications/en/details.jsp?id=4423).

139. Navarro D, Moon S. Research synthesis: advanced market commitments. Geneva: Global Health Centre at the Graduate Institute; 2019 (https://www.knowledgeportalia.org/advanced-market-commitment).

140. Plahte J. Is the pneumococcal vaccine advance market commitment motivating innovation and increasing manufacturing capacity? Some preliminary answers. Vaccine. 2012;30(14):2462–6. doi:10.1016/j.vaccine.2012.01.046.

141. Hirschler B, Kelland K. Vaccines alliance signs $5 million advance deal for Merck's Ebola shot. Toronto: Reuters; 2016 (https://www.reuters.com/article/us-health-ebola-vaccine-idUSKCN0UY0OT).

142. From biodefence to the DRC: how the Ebola vaccine became one of the fastest vaccines to license in history. Geneva: GAVI, the Vaccine Alliance; 2021 (https://www.gavi.org/vaccineswork/biodefence-drc-how-ebola-vaccine-became-one-fastest-vaccines-license-history).

143. Merck confirms agreement with UNICEF to establish the world's first global Ebola vaccine stockpile with ERVEBO. In: Merck [website]. Kenilworth, NJ:

Merck; 2021 (https://www.merck.com/news/merck-confirms-agreement-with-unicef-to-establish-the-worlds-first-global-ebola-vaccine-stockpile-with-ervebo-ebola-zaire-vaccine-live).

144. Light DW. Saving the pneumococcal AMC and GAVI. Hum Vaccin. 2011;7(2): 138–41. doi:10.4161/hv.7.2.14919.

145. Wilson P. Giving developing countries the best shot: an overview of vaccine access and R&D. Nairobi: Oxfam International; 2010 (https://www.oxfam.org/en/research/giving-developing-countries-best-shot).

146. GAVI money welcome but could it be more wisely spent? Geneva: Médecins Sans Frontières; 2011 (https://www.msf.org/gavi-money-welcome-could-it-be-more-wisely-spent).

147. Leoni P. Advance market commitment: some issues and a remedy. Rev Econ Polit. 2019;129(1):1–9. doi:10.3917/redp.291.0001.

148. Hecht R, Wilson P, Manno Reott K, Palriwala A, Rao A. Prizes for global health technologies. Washington DC: Results for Development Institute; 2011 (https://r4d.org/resources/prizes-global-health-technologies/).

149. Love J, Hubbard T. Prizes for innovation of new medicines and vaccines. Ann Health Law. 2009;18(2):155–86.

150. Prize4Life Awards $1M ALS Biomarker Prize! In: Fierce Biotech [website]. New York: Fierce Biotech; 2011 (https://www.fiercebiotech.com/biotech/prize4life-awards-1m-als-biomarker-prize).

151. Prize4Life Announces $1 Million ALS Treatment Prize Winner. In: Cision PRWeb [website]. Beltsville, MD: Cision PRWeb; 2017 (https://www.prweb.com/releases/2017/02/prweb14028039.htm).

152. Avi Kremer, founder of Prize4Life, joins the ALS Association team. Arlington, VA: ALS Association; 2018 (http://web.alsa.org/site/PageNavigator/pr_110118.html).

153. Longitude Prize [website]. London: Nesta; 2021 (https://longitudeprize.org/).

154. The Life Prize: a new approach to TB drug and regimen R&D. Geneva: The Union; 2021 (https://www.newtbdrugs.org/sites/efault/files/meetings/files/12_%20The%20Life%20Prize%20WGND%20meeting%20October%202017.pdf).

155. XPRIZE Rapid COVID Testing [website]. Culver City, CA: XPRIZE ; 2021 (https://www.xprize.org/prizes/covidtesting).

156. Kremer M. Patent buy-outs: a mechanism for encouraging innovation. Cambridge, MA: National Bureau of Economic Research; 1997 (NBER Working Paper No. w6304; https://doi.org/10.3386/w6304).

157. Moon S, Erickson E. Universal medicine access through lump-sum remuneration – Australia's approach to hepatitis C. N Engl J Med. 2019; 380(7):607–10. doi:10.1056/NEJMp1813728.

158. Eiser AR, Field RI. Can benefit corporations redeem the pharmaceutical industry? Am J Med. 2016;129(7):651–2. doi:10.1016/j.amjmed.2016.02.012.

159. Institute for OneWorld Health [website]. Palo Alto, CA: Skoll Foundation; 2021 (https://skoll.org/organization/institute-for-one-world-health/).

160. What's behind the B? Business for Good [website]. Berwyn, PA: B Lab; 2021 (https://usca.bcorporation.net/about-b-corps/).

161. Looking for a B Corp? B Corp directory [website]. Berwyn, PA: B Lab; 2021 (https://bcorporation.net/directory).

162. O'Regan M. B Corp certification won't guarantee companies really care for people, planet and profit. London: The Conversation; 2019 (https://theconversation.com/b-corp-certification-wont-guarantee-companies-really-care-for-people-planet-and-profit-124459).

163. Mazzucato M. The entrepreneurial state. London: Demos; 2011.

164. COVID-19 R&D tracker [website]. Sydney: Policy Cures Research; 2020 (https://www.policycuresresearch.org/covid-19-r-d-tracker).

165. COVID-19 vaccine R&D investments. Geneva: Global Health Centre at the Graduate Institute; 2021 (knowledgeportalia.org/covid19-r-d-funding).

166. Hooker L, Palumbo D. Covid vaccines: will drug companies make bumper profits? BBC News. 18 December 2020 (https://www.bbc.com/news/business-55170756).

167. Burrell S. Should vaccines be patent protected in a pandemic? In: Frontier Economics [website]. London: Frontier Economics; 2021 (http://www.frontier-economics.com/uk/en/news-and-articles/articles/article-i8200-should-vaccines-be-patent-protected-in-a-pandemic/#).

168. Moon S, Alonso Ruiz A, Vieira M. Averting future vaccine injustice. N Engl J Med. 2021;385(3):193–6. doi:10.1056/NEJMp2107528.

169. Usher AD. A beautiful idea: how COVAX has fallen short. Lancet. 2021; 397(10292):2322–5. doi:10.1016/S0140-6736(21)01367-2.

170. COVID-19 vaccine access. Geneva: Global Health Centre at the Graduate Institute; 2021 (www.knowledgeportalia.org/covid19-vaccine-arrangements).

171. COVID-19 vaccine manufacturing. Geneva: Global Health Centre at the Graduate Institute; 2021 (www.knowledgeportalia.org/covid19-vaccine-manufacturing).

172. C-TAP: a concept paper. Operationalising the COVID-19 Technology Access Pool (C-TAP). Geneva: World Health Organization; 2020 (https://www.who.int/publications/m/item/c-tap-a-concept-paper).

173. Open COVID Pledge [website]. Washington DC: American University Washington College of Law; 2021 (https://opencovidpledge.org/).

174. Waiver from certain provisions of the TRIPS Agreement for the prevention, containment and treatment of COVID-19: communication from India and South Africa. Geneva: World Trade Organization (IP/C/W/669; https://docs.wto.org/dol2fe/Pages/SS/directdoc.aspx?filename=q:/IP/C/W669.pdf&Open=True).

175. No patents, no monopolies in a pandemic [website]. Geneva: MSF Access Campaign; 2021 (https://msfaccess.org/no-patents-no-monopolies-pandemic).

176. COVID-19 data resources. Geneva: Global Health Centre at the Graduate Institute; 2021 (https://www.knowledgeportalia.org/covid-19-resources).

177. Equitable access policy. Oslo: Coalition for Epidemic Preparedness Innovations; 2018 (https://cepi.net/wp-content/uploads/2019/01/Equitable-Access-Policy. pdf).

178. Global access [website]. Washington DC: Bill & Melinda Gates Foundation; 2021 (https://globalaccess.gatesfoundation.org/).

179. Open access policy [website]. Washington DC: Bill & Melinda Gates Foundation; 2021 (https://www.gatesfoundation.org/about/policies-and-resources/open-access-policy).

180. WHO Director-General's opening remarks at 148th Session of the Executive Board. In: World Health Organization [website]. Geneva: World Health Organization; 2021 (https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-148th-session-of-the-executive-board).

181. COVID vaccines: the world's medical regulators need access to open data. Nature. 2020;588(7837):195. doi:10.1038/d41586-020-03458-z.

182. Vieira M, Alonso Ruiz A. Covid-19 "vaccine apartheid": why local production must be strengthened. In: Swissinfo.ch [website]. Swissinfo, 26 May 2021 (https://www.swissinfo.ch/eng/covid-19--vaccine-apartheid---why-local-production-must-be-strengthened/46648820).

183. Røttingen JA, Chamas C, Goyal LC, Harb H, Lagrada L, Mawethu Mayosi B. Securing the public good of health research and development for developing countries. Bull World Health Organ. 2012;90(5):398–400. doi:10.2471/BLT.12.105460.

184. Erickson E, Moon S. Research synthesis: pooled procurement. Geneva: Global Health Centre at the Graduate Institute; 2018 (https://www.knowledgeportalia.org/pooled-procurement).

185. PAHO Revolving Fund [website]. Washington DC: Pan American Health Organization; 2021 (https://www.paho.org/en/revolvingfund).

186. A pharmaceutical strategy for Europe. Brussels: European Commission; 2020 (https://ec.europa.eu/health/human-use/strategy_en).

187. Young R, Bekele T, Gunn A, Chapman N, Chowdhary V, Corrigan K et al. (Developing new health technologies for neglected diseases: a pipeline portfolio review and cost model. Gates Open Res. 2018;2:23. doi:10.12688/gatesopenres.12817.2.

188. Hubbard T, Love J. A new trade framework for global health care R&D. PLoS Biol. 2004;2(2):e52. doi:10.1371/journal.pbio.0020052.

**The WHO Regional Office for Europe**

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

**Member States**

| | | |
|---|---|---|
| Albania | Greece | Portugal |
| Andorra | Hungary | Republic of Moldova |
| Armenia | Iceland | Romania |
| Austria | Ireland | Russian Federation |
| Azerbaijan | Israel | San Marino |
| Belarus | Italy | Serbia |
| Belgium | Kazakhstan | Slovakia |
| Bosnia and Herzegovina | Kyrgyzstan | Slovenia |
| Bulgaria | Latvia | Spain |
| Croatia | Lithuania | Sweden |
| Cyprus | Luxembourg | Switzerland |
| Czechia | Malta | Tajikistan |
| Denmark | Monaco | Türkiye |
| Estonia | Montenegro | Turkmenistan |
| Finland | Netherlands | Ukraine |
| France | North Macedonia | United Kingdom |
| Georgia | Norway | Uzbekistan |
| Germany | Poland | |