

POLICY BRIEF 29

# Ensuring access to medicines: How to stimulate innovation to meet patients' needs?

Dimitra Panteli  
Suzanne Edwards

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This policy brief is one of a new series to meet the needs of policy-makers and health system managers. The aim is to develop key messages to support evidence-informed policy-making and the editors will continue to strengthen the series by working with authors to improve the consideration given to policy options and implementation.

### **What is a Policy Brief?**

A policy brief is a short publication specifically designed to provide policy makers with evidence on a policy question or priority. Policy briefs

- Bring together existing evidence and present it in an accessible format
- Use systematic methods and make these transparent so that users can have confidence in the material
- Tailor the way evidence is identified and synthesised to reflect the nature of the policy question and the evidence available
- Are underpinned by a formal and rigorous open peer review process to ensure the independence of the evidence presented.

Each brief has a one page key messages section; a two page executive summary giving a succinct overview of the findings; and a 20 page review setting out the evidence. The idea is to provide instant access to key information and additional detail for those involved in drafting, informing or advising on the policy issue.

Policy briefs provide evidence for policy-makers not policy advice. They do not seek to explain or advocate a policy position but to set out clearly what is known about it. They may outline the evidence on different prospective policy options and on implementation issues, but they do not promote a particular option or act as a manual for implementation.

Ensuring access to medicines: How to stimulate innovation to meet patients' needs?

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## Authors

**Dimitra Panteli**, Research Fellow, Berlin University of Technology and the European Observatory on Health Systems and Policies

**Suzanne Edwards**, Research Affiliate, Berlin University of Technology

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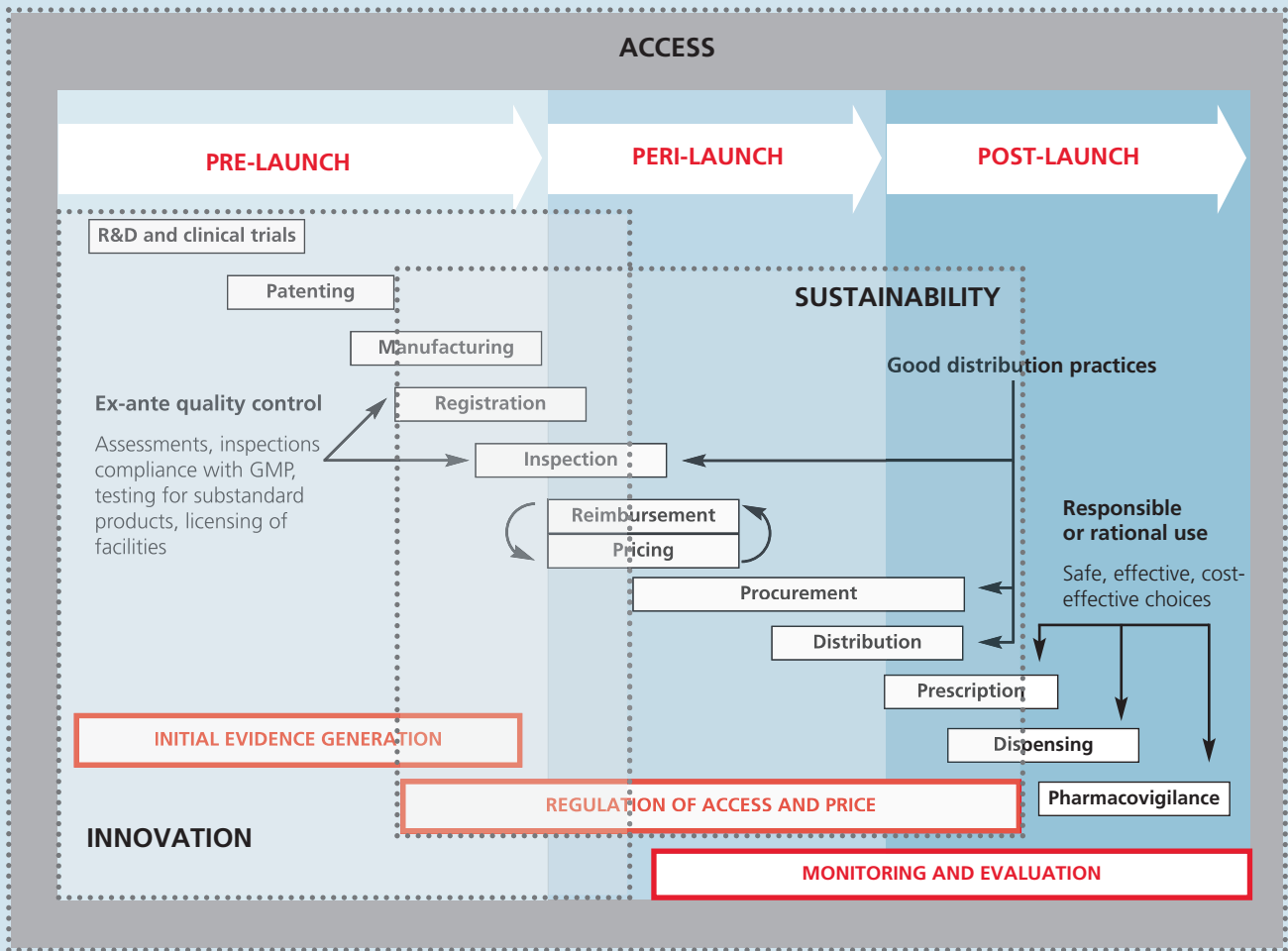
**Box 1: Ensuring access to medicines: How to address policy failures in pharmaceuticals?**

This series of two policy briefs on addressing market and policy failures in the pharmaceutical sector, prepared for the Austrian EU Presidency, revolves around the triple aim that health systems generally pursue:

- Ensuring access: making sure that patients have timely and affordable access to safe and effective medicines;
- Stimulating innovation: providing incentives for research that will lead to innovative medicines that effectively target real therapeutic needs;

- Safeguarding sustainability: developing the mechanisms to purchase these medicines at affordable prices in order to protect the sustainability of pharmaceutical budgets.

These objectives need to take account of the “lifecycle” of a pharmaceutical product and the different regulatory levers and policy interventions that take place over its course (see figure below). The innovation square denotes the focus of this policy brief, while the sustainability square reflects the area covered by the concurrent policy brief [1].



Source: authors' and editors' own, based on [2]

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## List of abbreviations

<b>BARDA</b>	Biomedical Advanced Research and Development Authority
<b>CEPI</b>	Coalition for Epidemic Preparedness Innovations
<b>CTN</b>	clinical trial networks
<b>ECRIN</b>	European Clinical Research Infrastructure Network
<b>EHDN</b>	European Health Data Network
<b>EMA</b>	European Medicines Agency
<b>EORTC</b>	European Organization for Research and Treatment of Cancer
<b>EU</b>	European Union
<b>EUnetHTA</b>	European Network for Health Technology Assessment
<b>FDA</b>	US Food and Drug Administration
<b>HTA</b>	Health Technology Assessment
<b>ICH</b>	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
<b>IMI</b>	Innovative Medicine Initiative
<b>NHI</b>	National Institutes of Health
<b>NME</b>	new medical entities
<b>PPL</b>	Priority Pathogen List
<b>R&amp;D</b>	research and development
<b>RCT</b>	randomized controlled trial
<b>SME</b>	small and medium-sized enterprises
<b>WHO</b>	World Health Organization

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**How do Policy Briefs bring the evidence together?**

There is no one single way of collecting evidence to inform policy-making. Different approaches are appropriate for different policy issues, so the Observatory briefs draw on a mix of methodologies (see Figure A) and explain transparently the different methods used and how these have been combined. This allows users to understand the nature and limits of the evidence.

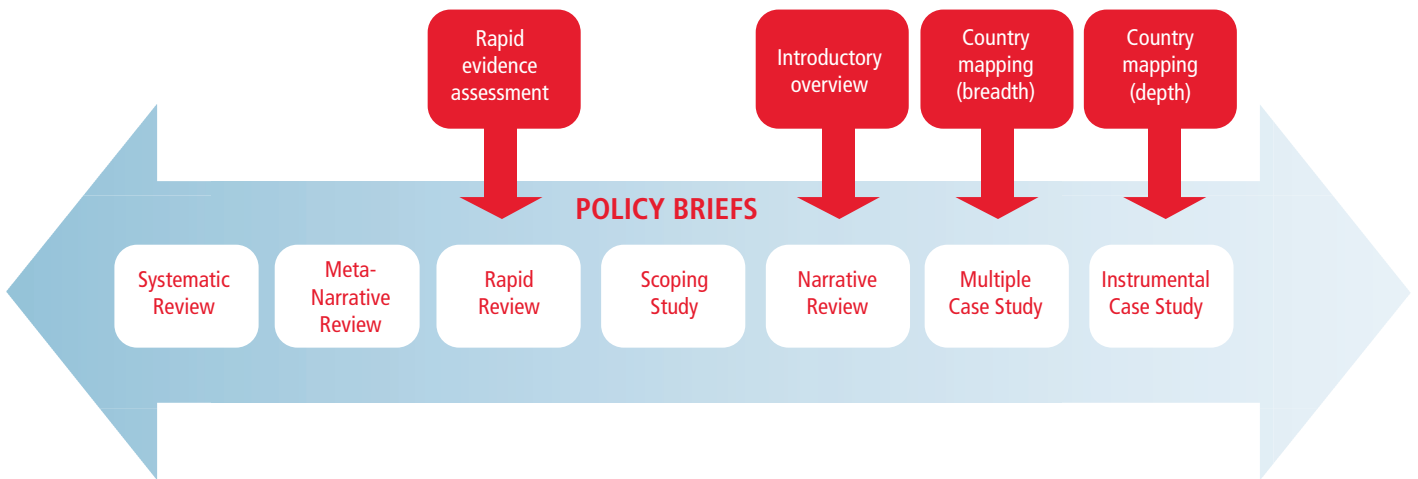
There are two main ‘categories’ of briefs that can be distinguished by method and further ‘sub-sets’ of briefs that can be mapped along a spectrum:

- **A rapid evidence assessment:** This is a targeted review of the available literature and requires authors to define key terms, set out explicit search strategies and be clear about what is excluded.

- **Comparative country mapping:** These use a case study approach and combine document reviews and consultation with appropriate technical and country experts. These fall into two groups depending on whether they prioritize depth or breadth.
- **Introductory overview:** These briefs have a different objective to the rapid evidence assessments but use a similar methodological approach. Literature is targeted and reviewed with the aim of explaining a subject to ‘beginners’.

Most briefs, however, will draw upon a mix of methods and it is for this reason that a ‘methods’ box is included in the introduction to each brief, signalling transparently that methods are explicit, robust and replicable and showing how they are appropriate to the policy question.

**Figure A: The policy brief spectrum**



Source: Erica Richardson

## Key messages

- The development of innovative medicines is essential for making progress in preventing and treating diseases. However, the high price tags put on new medicines do not always reflect the value added for patients. Also, persisting unmet clinical need in the population suggests a misalignment of pharmaceutical research and development efforts.
- There is a growing consensus that existing policies need to be rethought and new approaches need to be found to strike the delicate balance between stimulating true innovation, particularly towards addressing unmet needs, and ensuring both financial sustainability for health systems and accessibility for patients.
- While small and medium-sized enterprises (SMEs), academia and public institutions play a major role in driving innovation and enriching the industry's pipeline, the commercialization of new products is almost exclusively in the hands of large companies, often as a result of mergers and acquisitions. This is a concern for the sustainability of pharmaceutical research and development (R&D) infrastructure.
- The impact of public funding on pharmaceutical innovation cannot be underestimated. A stronger implementation of public interest provisions along the life cycle of pharmaceuticals, including "fair return of investment", is required.
- For public finance of R&D to facilitate better alignment of innovation with unmet clinical needs, more discrimination could be introduced in the reward system. Through limiting the risks, reducing R&D costs and/or increasing the innovation potential, incentives can be created for industry to re-embrace revolutionary – or even disruptive – innovation.
- More can also be done to improve coordination and priority-setting across R&D efforts, ideally globally, but with further refinement from an EU level to reflect regional priorities. In this respect, the creation of an entity to monitor clinical need, in conjunction with inequalities in access to essential medicines, merits consideration.
- Improving the efficiency of evidence generation in clinical research is not only good for driving down the costs of clinical trials, it can also help to remediate some of the related technical and ethical challenges, such as the fragmentation and duplication that unnecessarily expose patients to risk; the lack of comparative effectiveness data; the evidence gaps regarding specific patient groups and therapeutic areas; or the perceived conflicts of interest and related publication bias.
- Raising the bar for market entry by requiring that a new product demonstrate its superiority or equivalence to existing alternatives could encourage manufacturers to focus more on areas with limited treatment options and facilitate increased alignment with specifications applied in post-marketing evaluations for pricing and/or reimbursement (for example, Health Technology Assessment). Increased collaboration and alignment on evidentiary requirements between and within EU Member States are likely to simplify evidence generation for manufacturers as well as increase efficiency on the evaluators' side.
- Only a comprehensive approach that combines initiatives to guarantee funding, optimize evidence generation and align regulatory requirements can effectively tackle innovation deficits. An overall vision with greater policy coherence and backed by strong political commitment and transparency is needed.

## Executive summary

**The development of innovative medicines is essential for making progress in preventing and treating diseases, but there is doubt whether the high price tags put on new medicines reflect the real value added for patients.** At the same time, there are questions about the alignment of pharmaceutical research and development (R&D) efforts with actual unmet clinical needs in the population.

While manufacturers continue to argue that high prices and long market exclusivity privileges for new medicines are necessary for recouping R&D costs and ensuring future investment in innovation, governments and public payers are struggling with how to make these products affordable and accessible to their populations. There is a growing consensus among European countries that existing policies need to be rethought and new approaches need to be found to strike the delicate balance between stimulating true innovation, particularly towards addressing unmet needs, and ensuring both financial sustainability for health systems and accessibility for patients.

**This policy brief aims to inform discussions about stimulating more meaningful productivity in terms of R&D.** More specifically, it explores how R&D efforts can be steered to areas of unmet clinical needs and how the efficiency in the R&D process can be increased. It also explicitly considers concrete options for strengthening cooperation between European Union (EU) Member States in this context.

**R&D requires investment, but there is a lack of transparency around the cost of innovation and who pays for it.** The pharmaceutical sector is a major contributor to the European economy, with steadily growing sales figures and high profit margins. It is also one of the driving forces of clinical innovation. While there is general disagreement about the costs of bringing a new medicine to market, with estimates ranging from less than US\$ 1 billion to almost US\$ 3 billion, the impact of public funding of pharmaceutical innovation cannot be underestimated. The bulk of basic research paid with public money, and the share of public R&D spend are especially prominent in certain therapeutic areas. Even if almost half of the approved new medical entities (NMEs) seem to originate from small or medium-sized enterprises (SMEs), non-entrepreneurial institutions (academic/public) or public-private partnerships (for orphan medicines even > 70%), the commercialization of new products is almost exclusively in the hands of large and intermediate-sized companies, often as a result of mergers and acquisitions. This is a concern for the sustainability of the pharmaceutical R&D infrastructure.

**Through limiting the portfolio/project risk, reducing R&D costs and/or increasing the innovation potential, incentives are created for industry to re-embrace revolutionary or even disruptive innovation.** Faced with the paucity in genuine clinical advantage and the perceived disconnect in the type of innovation that is produced versus

that which society needs most, public financing mechanisms are needed that introduce more discrimination in the rewarding system in order to stimulate the most desirable and needed R&D.

**Push mechanisms**, which through direct or indirect funding aim to mitigate risk for potential investors, are frequently used by governments nationally or transnationally but rarely directly result in a new product being brought to market. As they are mostly implemented nationally, they bear the risk of duplication and fragmentation at global level. On the other hand, **output-based (or pull) models**, which make financial reward subject to achieving results, entail additional complexity in determining the appropriate size for financial rewards and setting the right targets. They also require long-term political commitment, which is usually difficult to achieve.

**Pooling mechanisms** are often narrow in scope and evidence of their effectiveness is sparse so far. Cost-sharing opportunities based on **collaborative partnerships** are developed at national, multilateral and global levels. They not only vary in their level of maturity, but also in the extent to which they share knowledge, costs and/or risks. In addition, there have been calls for **“open source” approaches** in the development of medicines, highlighting advantages such as improved efficiency, quality, relevance of research as well as increased engagement from scientific and patient communities. Beyond successful applications in malaria, this methodology needs further testing and evaluation before it can become mainstream.

Finally, more could still be done to improve **coordination and priority-setting across R&D**. Policy-makers often perceive the area of ongoing research as a “black hole”, due to a lack of information and transparency. Although such an effort would be best led at a global level, like with the R&D Observatory of the World Health Organization (WHO), the EU could refine/adapt relevant tools to reflect regional priorities. In this respect, the creation of an entity to monitor clinical need, in conjunction with inequalities in access to essential medicines, merits consideration.

**More could be done to improve efficiency in evidence generation.** Although randomized controlled trials are the reference standard for clinical research and have contributed substantially to advances in patient care, they are also quite resource-intensive. Clinical trial costs are the main driver of expenditure within R&D efforts. Policy action to improve the efficiency of evidence generation in clinical research can not only drive down these costs, but could also help to remediate some of the related technical and ethical challenges, such as the fragmentation and duplication that unnecessarily expose patients to risk; the lack of comparative effectiveness data; the evidence gaps regarding specific patient groups and therapeutic areas; or the perceived conflicts of interest and related publication bias.

**Clinical trial networks (CTNs)** can help to streamline the clinical trial infrastructure so that the investigation of new research questions can quickly draw on resources that are already in place. Further public backing for CTNs is



warranted but it is also important that these networks are developed collaboratively, run independently, and subsidized publicly.

**Adaptive clinical trial designs** seek to quickly identify medicines with therapeutic effects and zero in on patient populations who are most likely to derive benefit, promising greater flexibility and efficiency. **Master protocols** are another methodological innovation, which aims to enable the answering of multiple questions more efficiently. To implement these new models more broadly, further experience and clear understanding of their methodological implications are required.

Finally, the **increasing stringency of transparency requirements** observed on both sides of the Atlantic can help to improve the extent and structure of available knowledge on the benefits and harms of (new) medicines. Also, the further harmonization of requirements for the authorization, conduct and reporting of clinical trials at European and international level, can help to reduce both hurdles for developers and overall R&D costs as well as increase transparency.

**One way to address unmet need has been to accelerate approval by lowering evidentiary requirements for relevant medicines.** However, concern is growing that this will become the standard regulatory pathway rather than the exception and that it will outbalance safety over speed of access. Less attention is given to the opposite possibility, namely increasing approval standards. Raising the bar for the market entry of new medicines by requiring that a new product demonstrate its superiority or equivalence over existing alternatives, could indeed encourage manufacturers to focus more on areas with limited treatment options where there are obviously fewer comparators.

This approach could also support the convergence of evidence requirements applied by regulators and payers. In the area of post-marketing evaluations, or **Health Technology Assessment (HTA)**, used for making price and reimbursement decisions, increased collaboration and alignment between EU Member States is likely to contribute towards simplifying evidence generation for manufacturers and increasing efficiency on the evaluators' side. Furthermore, through collaborative horizon-scanning, payers can signal their preferences for pipeline products that match prioritized areas. Also, further integration of scientific advice to manufacturers, both between and within countries, can help to clarify evidentiary requirements, including on the role and usability of real world data.

**Only a comprehensive approach that combines initiatives to guarantee funding, optimize evidence generation and align regulatory requirements can effectively tackle innovation deficits.** None of the individual approaches discussed in this brief can provide an overarching solution. An overall vision with greater policy coherence and backed by strong political commitment and transparency is necessary, as well as a stronger implementation of public interest provisions along the life cycle of pharmaceuticals. All of this cannot be achieved by simply modifying or refining current reward systems. Fragmented national responses also have their limitations, especially when dealing with globally acting partners such as the pharmaceutical industry.

From a European perspective, significant progress might be achieved through enhanced collaboration, for instance in specifying and actively signalling agreed research priorities, identifying promising emerging technologies, ensuring appropriate priority status for approval and coverage decision-making and making available the necessary funding to overcome commercial unattractiveness.

## Policy brief

### Introduction

The development of innovative medicines is essential for continued progress in the prevention and treatment of disease. In the last few years, this was perhaps most clearly highlighted by the emergence of curative treatments for hepatitis C and new developments in immuno-oncology. However, recent trends in pharmaceutical markets also include an increasing number of newly approved substances per year, the proliferation of high-priced specialty and orphan medicines, very high launch prices and steep price increases, as well as mounting concerns about the appropriateness of traditional regulatory levers for tackling these challenges and ensuring sustainable patient access. For several new medicines, it is uncertain whether higher prices reflect added value for patients.

At the same time, there are questions about the alignment of pharmaceutical R&D efforts with actual unmet clinical need in the population. This problem has long been acknowledged in the developing world (diseases with high or exclusive prevalence in countries with limited ability to pay for R&D and medicines procurement) and for conditions with small target populations (for example, rare conditions or specific patient groups, such as children and pregnant women) or short courses of curative treatment (for example, antibiotics). Following a resurgence in the threat from infectious diseases manifested in recent pandemics and the growing incidence and visibility of multidrug resistance, the issue of lacking pharmaceuticals for certain indications has also been gaining traction in European countries.

The pharmaceutical industry is “high fixed cost, low marginal cost”, meaning that while the process of bringing a new medicine to market entails high costs and risk, the unit production cost for medicines already on the market is often insubstantial. Manufacturers argue that high prices and long market exclusivity privileges are necessary for recouping R&D costs for new medicines and investing in the development of future innovation. At the same time, there is objection that revenues from pharmaceutical sales (at high prices) are not primarily channelled to address unmet clinical needs.

Under the 2016 Dutch EU Presidency, the European Council’s conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States noted that “the pharmaceutical sector in the European Union has the potential to be a major contributor to innovation and the health and life sciences sector, through the development of new medicinal products”, especially for patients with high unmet need [3]. The Council also highlighted that there is “an increasing number of examples of market failures in a number of Member States, where patients’ access to effective and affordable essential medicines is endangered by very high and unsustainable price levels” [3]. These are often attributed to high R&D costs, and “it should be avoided that circumstances are

created that might (...) hamper the emergence of new or generic medicinal products and in this way potentially limit patients’ access to new medicines for unmet medical needs (...)” [3]. It concluded that “both public and private investments are essential for the research and development of innovative medicinal products” and posited that where public investment has played a substantial role in the development of a new medicine, an appropriate return of investment, to be put into further innovative research, should be guaranteed [3].

Following the publication of the Council Conclusions, discussions have often culminated in the realization that a reconsideration of existing policies and the development of new solutions are warranted to hopefully strike the delicate balance of stimulating true innovation, particularly towards addressing unmet needs, while ensuring financial sustainability for health systems. This policy brief aims to inform discussion in this direction, focusing on the issues of steering R&D efforts towards areas of unmet need and increasing efficiency in the R&D process (a separate, concurrent policy brief looks at cost containment in the context of pricing and reimbursement mechanisms [1], see also Box 1). This brief also explicitly considers the concrete options to strengthen cooperation between Member States on pharmaceutical policies and the steps required for creating an adapted EU framework to support it. The following paragraphs provide introductory context for the sections to follow.

### The pharmaceutical industry in numbers

The pharmaceutical industry is a major contributor to the European economy, both in terms of trading power and as an employer. According to industry figures, global pharmaceutical sales have shown continuous growth in recent years [4]. They amounted to approximately €763 billion (US\$ 847 billion) at ex-factory prices in 2016; 21.5% of total sale volume was recorded in Europe, compared with 49% in the United States of America and 8.3% in Japan [5]. The newest iteration of Fortune’s 500 top companies globally (“the global 500”) includes 15 pharmaceutical manufacturers, all with revenues in excess of US\$ 20 billion in 2016. Thirteen of those had profits higher than US\$ 1 billion, ranging from US\$ 1.23 billion for GlaxoSmithKline to US\$ 16.54 billion for Johnson & Johnson (albeit for its entire portfolio of products); Gilead Sciences came in second in terms of profitability with US\$ 13.5 billion [6]. In an analysis of 2015 profit margins in the United States of America, Forbes gave the health care industry in general, and the pharmaceutical industry in particular, the highest ranking among industry sectors [7]. The number of industry employees also demonstrates a steadily growing trend. Pharmaceutical companies employed approximately 750 000 people in Europe in 2016. About 15% of those work in R&D, a share that has diminished slightly in recent years, corresponding to a more or less stable total number of R&D workers since 2010 [5].

## R&D inputs – how much does it cost to bring a new medical entity to market?

Industry expenditure on R&D comprised US\$ 156.7 billion in 2016, a number that is projected to rise to US\$ 181 billion by 2022, corresponding to an annual growth rate of approximately 2.4% (compared with 2.5% compound annual growth rate for the period 2008–2016) [8]. Combining the figures from EvaluatePharma and the European Federation of Pharmaceutical Industries and Associations (the latter estimated European R&D expenditure in 2016 at €35 billion, corresponding to US\$ 38.5 billion based on the European Central Bank's average exchange rate for 2016), European R&D spending accounted for approximately 24.6% of the global total. The 2017 EU Industrial R&D Investment Scoreboard places the pharmaceutical sector among the highest in terms of R&D intensity (R&D as a percentage of net sales), joined by the biotechnology, IT-hardware and software sectors [9].

There is general disagreement about the costs of bringing a new medicine to market. Based on figures provided by the industry, estimates of the average cost of bringing a single new medicine to market in the decade 2005–2015 surpassed US\$ 2.8 billion, reflecting a steep increase compared with past values (US\$ 1.04 billion in the bracket 1990–mid-2000s) [10]. However, the methodology applied to derive these figures has been widely criticized, for example in regard to the selection of surveyed manufacturers, the impossibility of data verification and the omission of mitigating factors such as tax savings [11]. Estimates from leading consulting firms regarding the costs of developing a new compound from discovery to launch range from US\$ 1.5 billion to approximately US\$ 2 billion [12,13]. However, recent work focusing on oncology medicines arrives at a much lower estimate, namely US\$ 648 million [14], less than a quarter of the number calculated by DiMasi et al. [10]. The median cost of individual pharmaceutical clinical trials was recently found to comprise approximately US\$ 3.4 million for Phase I, US\$ 8.6 million for phase II and US\$ 21.4 million for Phase III [15]. Although the average cost for post-marketing (Phase IV) trials has been found to be generally comparable to that of Phase III trials; research shows higher variability of costs depending on the therapeutic area [16].

## R&D inputs – who is paying for innovation?

Public contributions to the financing of R&D efforts in the pharmaceutical sector often comprise a considerable share of total R&D expenditure. Recent evidence shows that National Institutes of Health (NIH) funding for R&D on new medical entities (NMEs) approved between 2010 and 2016 exceeded US\$ 100 billion (approximately 20% of the NIH budget for the same period); among these NMEs, first-in-class products – those that use a new and unique mechanism of action for treating a medical condition – were linked to NIH projects adding up to more than US\$ 64 billion [17]. In the United Kingdom, both public and private spending on medical research have gradually increased over time: public funding more than doubled in the 30 years between 1982 and 2012, while private R&D investment

more than quadrupled. In 2012, public funding amounted to £3.4 billion (€4.2 billion, US\$ 5.4 billion, based on average 2012 exchange rates of the European Central Bank) compared with £4.2 billion (€5.2 billion, US\$ 6.6 billion) in industry R&D spending. The share of funding varied by disease area; for example, public spending surpassed private investment in cancer, whereas research on haematological conditions was mostly privately funded [18].

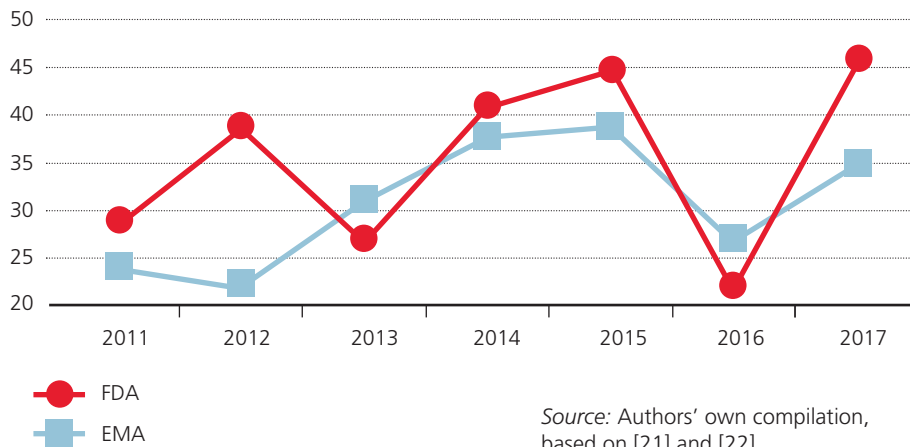
The vast majority of public funding seems to be associated with basic research (most public funding goes into basic research, and the bulk of basic research is funded by public money), suggesting a complementary role between public and private funding in the development of medicines [11,17]. Research looking at the impact of public funding on innovation in the United States of America found that a US\$ 10 million increase in funding by the NIH resulted in an additional 2.3 private patents, but assigning value to individual patents in the form of projected sales is methodologically challenging [19].

## R&D outputs – how much innovation is actually produced and where does it come from?

As previously mentioned, the development of innovative medicines is essential for the continuation of progress in the innovation and treatment of disease. However, since 2000, discussions of whether the pharmaceutical sector is in the midst of an “innovation crisis” have intensified. When the sector's value of productivity is measured by internal rate of return (combining total development expenditure with projected revenues from post-launch sales) a stable declining trend can be discerned since 2010 for major pharmaceutical manufacturers [13]. Annual NME approval rates by the US Food and Drug Administration (FDA) demonstrated a steep downwards trend in the decade 1998–2008 [20]. Despite continued volatility, as of 2013 the trend in number of approvals of NMEs by FDA and the European Medicines Agency (EMA) has been relatively consistent (Fig. 1). A relative low in 2016, which spurred increased debate on the issue, was followed by resurgence in 2017 – the FDA approved the highest number of NMEs in 20 years, not including cell and gene therapies, which were approved under a different category.

Research investigating the provenance of a subset of these NMEs (approved between 2010 and 2012) found that 44% originated from SMEs or academic institutions, public bodies and public–private partnerships. The share rose to 72% for orphan medicines [23]. SMEs were marketing authorization holders for only one fifth of the NMEs for which they were the originators; academic institutions and public bodies were uniformly no longer involved at that point in the process for their discoveries [23]. Furthermore, research on the ownership of NMEs shows that, in 2013, more than two thirds were controlled by 10 large companies, often as a result of mergers and acquisitions [20]. The importance of NME-acquiring organizations with limited internal R&D capabilities is increasing, raising concerns about the sustainability of pharmaceutical R&D infrastructure. Thus, large and intermediate-sized companies are almost exclusively in charge of the commercialization of new products, but SMEs, academia and public institutions play a major role in driving innovation and enrich the industry's pipeline.

**Fig. 1: Number of NMEs approved by the FDA and the EMA**



**R&D outputs – do more new medicines mean more patient benefit?**

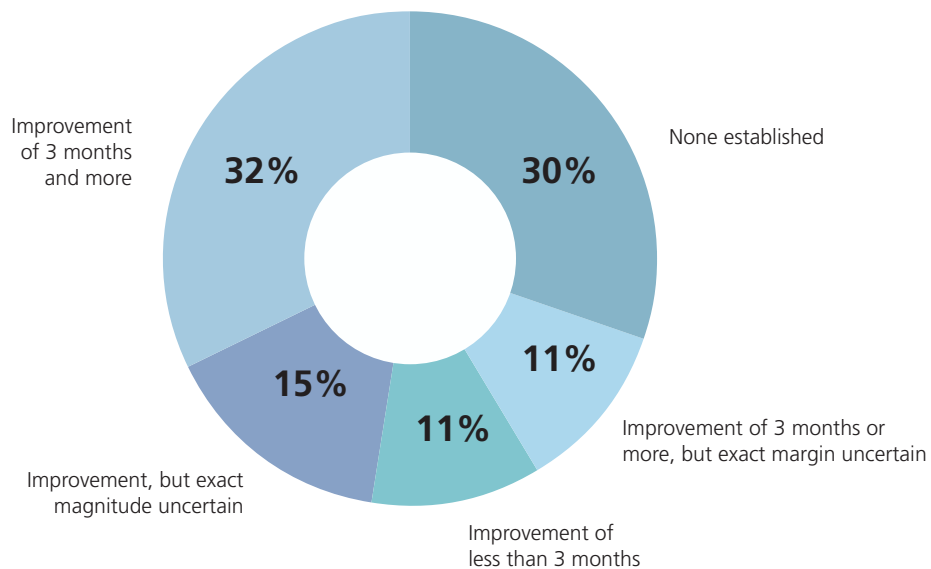
Simply equating the number of approved NMEs with the extent of innovation can be misleading, as these figures often mask a dearth in quality, measured by the therapeutic advance the new medicines offer to patients. New approvals generally represent modest, relatively minor modifications of existing medicines and not therapeutic breakthroughs. There is a growing body of evidence to support the idea that the vast majority of new medicines provide few or no clinical advantages for patients (see Fig. 2) [24–27]. This is often attributed to the fact that comparative effectiveness data on patient relevant outcomes are not required for marketing authorization [24,28]. Recent work on new oncologics found that over the last decade, clinical benefits have not increased in proportion to costs and that costs might be underestimated overall [29].

A related point of criticism with regard to industry practices is that substantial effort is invested in promoting new

medicines approved on the basis of limited evidence, increasing patient exposure to risks and exacerbating inefficiency [31]. Sales and marketing expenditures stably surpass R&D spending, in some cases by a factor of two [32,33]. Moreover, evidence from Canada suggests that more resources are invested in promoting medicines with little or no therapeutic gain [34]. Based on industry data, the growth rate of selling, general and administrative expenditure in the decade 2005 to 2015 rose less rapidly than that of R&D spending [35].

Finally, the imperfect alignment of new approvals and medicines in the pharmaceutical pipeline with population unmet need mentioned above further detracts from total societal benefit [24,36]. Given the uncertain and/or limited returns for certain conditions or population groups (see above), this lack of commitment is not surprising in the context of the pharmaceutical business model. However, the allocation of public funding also seems to leave room for improvement in tackling unmet need [37].

**Fig. 2: Improvements in overall survival – clinical benefits from 53 cancer medicines licensed between 2003 and 2013**



## Policy questions

Against this backdrop, it is important to understand current practices and existing regulatory pathways and explore the potential of alternative solutions. This policy brief will focus on the following areas:

- How can we stimulate more (and more meaningful) productivity in terms of R&D?
- What is the evidence on approaches that support the alignment of R&D efforts with addressing unmet clinical needs?
- How can we optimize the availability and utilization of evidence on the safety and effectiveness of pharmaceuticals at market entry and during the technology's life cycle?
- What is the potential of increased collaboration among European countries across these issues?

The approach taken to address these questions is outlined in Box 2.

### Box 2: Methods

This policy brief draws on evidence identified through literature review (including peer-reviewed and grey literature) and policy experiences in recent years, mainly in Europe. It builds on the policy agenda developed under previous EU Presidencies, especially the Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States adopted under the 2016 Dutch Presidency, as well as the evidence presented in other publications of the Observatory, like the policy brief on voluntary cross-border collaboration in public procurement and the special HiT Review on pharmaceutical regulation [38,39]. Since the authors are involved in policy-related research, policy support and knowledge brokering in Europe and beyond, the voices and key concerns of policy-makers are also reflected. In particular, the brief includes information discussed during open sessions at international conferences such as the Alpbach Health Symposium and the European Health Forum Gastein, as well as other related meetings carried out in the period 2016–2018.

## The evidence

### Optimizing R&D investments to deliver better innovation for society's needs

Public financing of R&D largely aims to improve the alignment of innovation with unmet clinical needs. In the context of its Europe 2020 strategy, the European Commission set the aim of increasing combined public and private investment in R&D to 3% of gross domestic product by 2020. However, it is still unclear how much of this investment would be pooled towards common, global, challenges [40]. Efforts to address some of the challenges related to the paucity in genuine clinical advantage offered by many new medicines and the perceived disconnect in the type of innovation (those developed versus those which society most needs) have been initiated at national, supranational and global level. They have been progressing slowly and unequally, probably reflecting the complexities of

many of these issues. The overarching policy goal seems to entail introducing greater discrimination within the system by increasing the relative rewards to the most desirable and needed forms of innovation while decreasing the relative rewards to less socially valued innovation. A typology of mechanisms to stimulate R&D is presented in Box 3.

### Box 3: Mechanisms for steering and incentivizing biomedical R&D

- **Push Mechanism:** Direct funding for R&D, often in the form of a grant, as well as indirect incentives, such as tax breaks and in-kind contributions, which help finance R&D upfront and so mitigate the R&D investment required.
- **Pull Mechanism:** Mechanisms to incentivize R&D activities through the promise of financial rewards once specified objectives or milestones have been met, creating viable market demand.
- **Pooling Mechanism:** Two distinct types that can occur independently or jointly. (i) Pooling of funds that are aggregated and managed jointly by an established entity to be allocated based on priority setting in order to distribute risk and finance biomedical R&D. (ii) Pooling of intellectual property, typically via a patent pool, an agreement between two or more patent owners to pool their patent rights and license the rights to use these patents together to one another as well as third parties.
- **Collaborative Initiative:** Involves a network, consortium, or partnership between two or more academic or research institutions, non-profit-making organizations, nongovernmental organizations, governments, government entities, or members of the private sector including biotechnology and pharmaceutical companies and is often used to facilitate knowledge sharing.
- **Open Initiative:** Applies open source, open access, open data, or open knowledge principles. Interested parties are able to contribute knowledge or know-how, data, technology, etc. to be shared in the public domain and, in the case of open source, in coordination with patent-free research. *Source:* [41].

**Push-financing tools** are used increasingly by governments nationally or transnationally as vehicles for increasing collaboration and providing technical and capital support to potential innovators. Although not new or specific to life science, push funding generally subsidizes R&D inputs, thus lowers costs and thereby decreases risk. Push funding is also pivotal to finance the knowledge base (basic research) essential to the discovery of health technologies. It generally takes the form of direct project funding, research grants, fellowships, SME funding and indirect support through tax relief and other benefits. In Europe, the European Commission's Directorate-General for Research and Innovation through its framework programmes (2014–2020 Horizon 2020) and EU structural funds are important sources of R&D financing. Table 1 provides a breakdown of advantages and disadvantages of selected push-financing tools, while Table 3A highlights some developments in this space in recent years. Some of these represent new financing tools introduced by national governments to address specific challenges in pharmaceutical markets and some represent new tools to overcome challenges or limitations of push financing.

**Table 1: Advantages and disadvantages of push-financing tools**

Financing tool	Advantages	Disadvantages
<b>Grants for scientific personnel</b> <i>(funding training and development of personnel specializing in R&amp;D of desired areas)</i>	<ul style="list-style-type: none"> <li>• Lowers competition for skilled researchers,</li> <li>• can complement other collaborative efforts such as open access to research.</li> </ul>	<ul style="list-style-type: none"> <li>• Research interest does not guarantee tangible results,</li> <li>• funded scientists may not be committed to R&amp;D in the needed area,</li> <li>• long lead-time for investment.</li> </ul>
<b>Direct funding</b> <i>(subsidies offered to organizations for the R&amp;D of novel medicines for specific areas of care/conditions)</i>	<ul style="list-style-type: none"> <li>• Lowers early R&amp;D costs that prohibit participation of SMEs,</li> <li>• allows direct targeting of R&amp;D towards specific priorities,</li> <li>• attached expert technical and managerial help useful to SMEs with less experience.</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of project failure placed on funder,</li> <li>• prone to problems of transparency and principal–agent discrepancies,</li> <li>• risk of changing political agenda,</li> <li>• not well-suited to support late stages of development.</li> </ul>
<b>Conditional grants</b> <i>(subsidies offered to organizations for the R&amp;D of novel medicines for specific areas of care/conditions that are specifically tied to conditions regarding the use of successfully developed products, for example, conservation for novel antibiotics)</i>	<p>In addition to the advantages of direct funding (see above):</p> <ul style="list-style-type: none"> <li>• element of antibiotic stewardship</li> </ul>	<p>In addition to the disadvantages of direct funding (see above):</p> <ul style="list-style-type: none"> <li>• challenge to ensure developers honour their commitments</li> </ul>
<b>Funding translational research</b> <i>(funding for facilitating co-operation and interaction throughout the entire supply chain including research, commercial development, and clinical application)</i>	<ul style="list-style-type: none"> <li>• Promotes synergy across the value chain</li> </ul>	<ul style="list-style-type: none"> <li>• Potential for conflicts of interest,</li> <li>• may impose perverse incentives to researchers,</li> <li>• requires new intellectual property laws to address innovation born from collaboration.</li> </ul>
<b>Tax incentives</b> <i>(tax credits, allowances, or deferrals that are tied to early R&amp;D and reduce a developer's current tax liability)</i>	<ul style="list-style-type: none"> <li>• Easy to implement and familiar to governments with lower administration costs,</li> <li>• reduces problems with information asymmetry,</li> <li>• the government dictates broad goals but the market remains in charge of determining where investment is profitable,</li> <li>• allows firms to innovate in ways that suit their particular strengths,</li> <li>• lowers incentive for firms to direct R&amp;D towards high-profit, short-sighted projects,</li> <li>• can be tailored to specifically benefit SMEs over large firms.</li> </ul>	<ul style="list-style-type: none"> <li>• Less transparent than direct funding,</li> <li>• no mechanism to control cost incurred by government,</li> <li>• government is not able to direct R&amp;D into areas of high social return,</li> <li>• risk of failure borne by government alone,</li> <li>• incentive to employ creative accounting to maximize tax claim,</li> <li>• not (as) beneficial for firms that make low revenues – generally SMEs.</li> </ul>
<b>Refundable tax credits</b> <i>(tax credits that can be redeemed in cash instead of reducing current tax liability)</i>	<p>Promotes participation of SMEs on top of the advantages of tax credits (see above)</p>	<p>See disadvantages of tax incentives (see above).</p>

Source: Adapted from [42].

However, push financing is not output-based: it rarely directly results in a new product being brought to market. It is largely implemented nationally, leading to great duplication and fragmentation at global level. On the other hand, any output-based (or **pull-** **financing tool** (see Table 2) would require the pooling of financial resources across a minimum of a few countries to offer a reward substantial enough to lure developers to a discrete, defined target. Determining the size of the financial reward that both

motivates developers and safeguards cost-effectiveness, and setting the right targets are complex. To sufficiently curb financial risk and uncertainty so as not to deter participation, particularly by smaller companies, such initiatives require long-term political commitment that is usually difficult to realize. One example of such an initiative is the Longitude Prize, which promises a £10 million prize for the development of diagnostics in the context of antimicrobial resistance [43].

**Table 2: Advantages and disadvantages of pull-financing tools**

Pull-financing tool	Advantages	Disadvantages
<b>Lump sum monetary prize</b> <i>(a large financial reward for the successful development of a novel medicine)</i>	<ul style="list-style-type: none"> <li>• Rewards only successful projects,</li> <li>• promotes clear communication between funder and developer and avoids principal-agent problems,</li> <li>• requires minimal additional infrastructure or regulation,</li> <li>• can be offered by nongovernmental organizations as well as governments,</li> <li>• provides strong incentive for developers to carry pharmaceutical R&amp;D through phase III clinical trials.</li> </ul>	<ul style="list-style-type: none"> <li>• Does not help SMEs overcome initial R&amp;D barriers,</li> <li>• all risks are borne by the developer,</li> <li>• difficult to set optimal scope of reward,</li> <li>• sets a maximum value for the medicine thus limiting the level of R&amp;D into the medicine,</li> <li>• is prone to changes in the political agenda, challenge to determine how to reward follow-on innovators.</li> </ul>
<b>Milestone monetary prizes</b> <i>(incremental monetary rewards paid at various stages of the development process)</i>	In addition to the advantages of lump sum prizes (see above): <ul style="list-style-type: none"> <li>• allow funders to direct R&amp;D and</li> <li>• pull SMEs through the entire R&amp;D process.</li> </ul>	In addition to the disadvantages of lump sum prizes (see above): <ul style="list-style-type: none"> <li>• risk of funding projects that ultimately fail.</li> </ul>
<b>Research tournament</b> <i>(competitive milestone prizes awarded to the first developer to reach certain checkpoints)</i>	<ul style="list-style-type: none"> <li>• Competition may stimulate an increase in quality of submissions,</li> <li>• multiple rounds allow for selection of a few promising ideas,</li> <li>• attracts developers that believe they have a competitive advantage or a promising molecule.</li> </ul>	<ul style="list-style-type: none"> <li>• Collusion may reduce the quality of submissions,</li> <li>• winner is not incentivized to produce and distribute product,</li> <li>• risk of funding projects that end up failing final goals,</li> <li>• not well suited to promote new medicines development in the expensive and risky late stages of R&amp;D,</li> <li>• SMEs may not have the resources to compete with large capacity firms, limiting the effect of competition.</li> </ul>
<b>Pay-for-performance</b> <i>(developers receive rewards for achieving quality goals relating to predetermined outcome targets – including consumption in the case of antibiotics)</i>	<ul style="list-style-type: none"> <li>• Can be implemented within existing regulatory frameworks and</li> <li>• allows government to establish clear stewardship goals and rewards.</li> <li>• In the case of antibiotics under conservation, prescribers and developers have a direct incentive to minimize overuse.</li> </ul>	<ul style="list-style-type: none"> <li>• Difficult to use as a direct incentive to stimulate research,</li> <li>• technically challenging (monitoring effectiveness and, for antibiotics, resistance and appropriate use),</li> <li>• measures may provide perverse incentives to game the system.</li> </ul>

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Pull-financing tool	Advantages	Disadvantages
<b>Patent buyout</b> <i>(large end prize given in exchange for the intellectual property rights to a successfully developed medicine)</i>	<ul style="list-style-type: none"> <li>• Funder gains control over the medicine's price and volume,</li> <li>• supports access goals (and, for antibiotics, conservation),</li> <li>• rewards only successful development,</li> <li>• promotes clear communication regarding desired medicine characteristics and avoids principal-agent problem,</li> <li>• intellectual property (once bought out) can be licensed out by funder.</li> </ul>	<ul style="list-style-type: none"> <li>• All development risk is borne by the developer and there may be industry barriers to public ownership of IP;</li> <li>• it requires large financial outlay from funder and these high costs make political support challenging;</li> <li>• pricing buyout is technically difficult and</li> <li>• a new agency may be needed to manage acquisition of intellectual property;</li> <li>• there is a risk of funding suboptimal medicines with little remaining funding to purchase improvements (especially relevant for antibiotics).</li> </ul>
<b>Payer license</b> <i>(developer sells an annual license for unlimited access to a medicine at marginal cost)</i>	<ul style="list-style-type: none"> <li>• Funder gains control over the medicine's price and volume,</li> <li>• supports access goals (and, for antibiotics, conservation),</li> <li>• rewards only successful development,</li> <li>• permits competitive pricing for license in multi-player systems,</li> <li>• does not entail a permanent commitment to licenses if medicines become suboptimal (for example, for antibiotics),</li> <li>• patent ownership remains with developer.</li> </ul>	<ul style="list-style-type: none"> <li>• All development risk is borne by the developer;</li> <li>• requires annual renegotiations of licenses entailing expensive transaction costs and technical difficulty in pricing licenses,</li> <li>• provides minimal R&amp;D incentive over other mechanisms,</li> <li>• sensitive to changes in political agenda.</li> </ul>
<b>Advanced market commitment</b> <i>(an agreement to purchase a set volume of the medicine for a pre-specified price upon successful development)</i>	<ul style="list-style-type: none"> <li>• Only rewards successful development,</li> <li>• price guarantee lowers risk for developer,</li> <li>• prices can be set based on a country's ability to pay improving patient access,</li> <li>• it does not require significant changes in regulatory statutes or laws,</li> <li>• reward determined through the market.</li> </ul>	<ul style="list-style-type: none"> <li>• Challenging to set medicines specifications beforehand,</li> <li>• can maintain artificially high prices in some countries and limit patient access,</li> <li>• government commitment to purchase may lead to acquiring inferior products,</li> <li>• all development risk is borne by the developer.</li> </ul>

Source: Adapted from [42].

As a separate or complementary alternative, many different **pooled funds** for R&D have been proposed over the years by a multitude of actors. Many are narrow in focus looking at a single disease or therapeutic area, others are broader in their ambition such as the proposal for the establishment of a biomedical R&D treaty. No real progress has been made in this area and evidence on the effectiveness of such funds is sparse. In 2016, the European Parliament proposed the establishment of "an EU public platform for R&D funded by contributions from profits made by the pharmaceutical industry through sales to public health systems" and called for transparency on the costs of R&D [44]. Two of the key features of this more recent proposal include R&D priorities driven by health needs rather than commercial potential and binding obligations on governments to invest in R&D. It also highlighted the potential for funded research to produce essential medicines in cases of market failures:

The Committee on Petitions (...) invites the Member States, in cooperation with the Commission, to consider the possibility of the establishment of a pooled public platform for R&D financed by all Member States via a minimum contribution of 0.01% of their GDP; considers that this

platform should also be able to directly produce life-saving medicines in the EU in the event of a market failure being identified [44].

Follow up on this proposal has been slow.

Improving the efficiency of innovation by (a) reducing portfolio/project risk, (b) reducing R&D costs and/or (c) increasing innovation potential presents the greatest opportunity for industry to re-embrace revolutionary or even disruptive innovation. The European Commission's Expert Panel on Effective Ways for Investing in Health defined the latter as "an innovation that creates a new market or expands an existing market by applying a different set of values, which ultimately (and unexpectedly) overtakes an existing market". Such innovation may entail improved health outcomes, creating new professional cultures, serving new groups or consisting of new products/services, creating new players and disordering old systems [45].

Cost-sharing opportunities such as **pre-competitive collaboration, public-private partnerships and collaborative innovation models** vary in the extent to which they share knowledge, costs and/or risks and in their level of maturity (see examples in Table 3B).



Table 3: Approaches towards optimizing public R&amp;D funding to serve society's needs

National	Multilateral	Global
<b>3A: Push-funding initiatives to increase R&amp;D resources</b>		
<p><b>United Kingdom: Global Antimicrobial Resistance Innovation Fund (GAMRIF), 2016</b></p> <p>The United Kingdom committed £50 million until 2021 (its initial £10 million investment has been matched by the Chinese government and private sector) to fund innovative initiatives to tackle resistant infections. It will focus on organizations struggling to access traditional financing routes, for example, SMEs.</p>	<p><b>InnovFin infectious disease finance facility, 2014</b></p> <p>A financial instrument jointly developed by the European Commission and European Investment Bank. It offers loans between €7.5 and €75 million for the development of innovative health technologies and novel research infrastructures. It is a risk-sharing initiative, as the loan is only paid back if the project is successful.</p>	<p><b>Global Observatory on Health R&amp;D</b></p> <p>Its establishment was mandated by the World Health Assembly in 2013 and reinforced in 2016 to address information gaps by monitoring, integrating information and reporting on financial flows in support of global health needs. While focusing on R&amp;D need for low- and middle-income countries and building on existing data collection mechanisms, it also looks at potential areas with market failures and antimicrobial resistance trends. It supports coordinated actions on health R&amp;D based on collected information.</p>
<b>3B: Collaborative innovation models</b>		
<p><b>USA: Biomedical Advanced Research and Development Authority (BARDA) Broad Spectrum Antimicrobials programme, 2010</b></p> <p>BARDA is tasked with enhancing development of health technologies for public health emergencies. BARDA's Broad Spectrum Antimicrobials programme uses innovative business models to establish public-private partnerships with industry, both large pharmaceutical companies and SMEs. Through one of its models BARDA has established flexible cost-sharing partnerships with two large pharmaceutical companies to fund an entire portfolio of products over 5 years.</p>	<p><b>Innovative Medicine Initiative (IMI)-2, 2014–2024</b></p> <p>IMI is a public private partnership between DG Research of the European Commission and the European Federation of Pharmaceutical Industries and Associations aimed at removing research bottlenecks in the medicine development process. IMI pools resources, facilitates collaboration among key stakeholders in the development process and shares the financial risk of R&amp;D outlays. IMI's strategic plan has four pillars: target validation and biomarker research, adoption of innovative clinical trial paradigms, innovative medicines, and patient-tailored adherence programmes.</p>	<p><b>Coalition for Epidemic Preparedness Innovations (CEPI), 2016</b></p> <p>CEPI was established to foster vaccine development to facilitate the containment of infectious diseases with epidemic potential. The model is to share the risks and benefits of vaccine development (the steps between discovery research and delivery). It finances both permanently dedicated (warm base) and project-based capabilities.</p>
<b>3C: Reorienting R&amp;D to priority areas</b>		
<p><b>Germany: Concerted agenda against antimicrobial resistance, 2008 to present</b></p> <p>The Federal Research Ministry, the Federal Ministry of Health, the Federal Ministry of Agriculture and numerous relevant associations jointly drafted the German Antibiotic Resistance Strategy in 2008. Various research projects are being funded to promote prudent use of antibiotics and the development of new methods for detection, control and treatment of resistant strains, such as InfectControl 2020 (a collaboration between research institutes and industry) and the German Centre for Infection Research (DZIF), which focuses, among others, on the development of novel methods for prevention and treatment of resistant pathogens.</p>	<p><b>European Medicines Agency's (EMA's) PRiority MEDicines (PRIME) scheme, 2016</b></p> <p>The EMA developed PRIME to build on other accelerated review pathways by (a) fostering early dialogue between the regulator and the developer (particularly for micro-, small- and medium-sized enterprises and academia) and (b) speeding up evaluation. The scheme focuses on medicines that address an unmet medical need and that have the potential to bring a major therapeutic advantage to patients. Ninety-six requests were processed between April 2016 and April 2017 and PRIME is similar to the US FDA's breakthrough therapy programme (2012).</p>	<p><b>WHO's R&amp;D Blueprint (2016) and Priority Pathogen List (PPL), 2017</b></p> <p>The R&amp;D Blueprint is a global strategy and preparedness plan that allows the rapid activation of R&amp;D activities during epidemics. It aims to (a) improve coordination, (b) accelerate R&amp;D and (c) develop norms and standards, for example, for clinical trial designs and sample sharing. Priority diseases are identified annually, based on their potential to cause a public health emergency and the absence of efficacious drugs and/or vaccines and, for each, an R&amp;D roadmap is created, followed by target product profiles. Similar but narrower in scope, WHO's PPL was launched in 2017 to guide the prioritization of incentives and funding, aligning R&amp;D priorities with public health needs and supporting global coordination in the fight against antibiotic-resistant bacteria.</p>

Source: Authors' own compilation.

The European Commission's "Open Innovation, Open Science, Open to the World" initiative brings together some of the most recent interactions between Europe's knowledge institutes and pharmaceutical manufacturers; it places emphasis on **making science and innovation more open**, collaborative and global. The Commission has established three pillars of action for its Open Innovation Policy, namely reforming the regulatory environment, boosting private investment and maximizing impacts [40]. This sets the foundation for considering expanding both the depth and breadth of such collaborations. Beyond these initiatives, there have been a number of calls in recent years for "open source" approaches in the development of medicines, highlighting advantages such as improved efficiency, quality and relevance of research as well as an increase in engagement from the scientific and patient communities, as well as successful applications in conditions like malaria [46,47]. They also recognize, however, that open source methodology requires further testing, adaptation and evaluation before it can become mainstream.

The United Nations High-Level Panel on Access to Medicines recently described efforts to improve the alignment of innovation with unmet clinical needs to date as "tend[ing] to be fragmented, disparate and insufficient to deal with priority health needs on a sustainable, long-term basis" [48]. Indeed, as an example, during the past decade, over 50 major international and national initiatives aimed at incentivizing antibiotic R&D have been implemented. A very important aspect in this respect is the issue of transparency and availability of information. Policy-makers perceive the issue of what research is being conducted as a "black hole". Better data are needed to improve both priority setting and coordination for pharmaceutical R&D. Efforts in this direction need to balance the level of uncertainty regarding the R&D process and outputs and the costs of collecting, processing and disseminating relevant information. Examples of initiatives in this direction and at different levels can be seen in Table 3C. In July 2017, the G20 Leaders' meeting culminated in a Declaration for Shaping an Interconnected World, wherein "a new international R&D Collaboration Hub to maximize the impact of existing and new anti-microbial basic and clinical research initiatives as well as product development" was called for. While the G20 did not commit to a joint pooled funding mechanism, as had been discussed, they expressed the intention of looking for practical market incentive options to complement the work of the collaboration hub. The implementation of these action points remains an imperative.

Summing up, while many steps have taken place in recent years, largely due to WHO leadership, more could still be done to improve coordination and priority setting across R&D. While this would probably be best led from a global level, the EU could refine/adapt relevant tools to reflect regional priorities. Collaboration with the WHO's R&D Observatory could be institutionalized to ensure that knowledge is shared with other funders to improve efficiency, synergies and coordination of increasingly scarce financing [43]. Recent proposals on collaborative oversight and pooling of funds should be kept on the agenda. In particular, the creation of an entity that would monitor need

in conjunction with inequalities in accessing essential medicines related to ability to pay both at the system and at the individual level, merits consideration.

### **Focusing on the building blocks of medicines development – options for improving efficiency in the area of evidence generation and dissemination**

Clinical development needs to assess the effects – wanted and unwanted – of health care interventions in people. Proving the safety and efficacy of new medicinal products is required for obtaining marketing authorization to sell. The randomized controlled trial (RCT) serves as the reference standard for clinical research and has made a substantial contribution to advances in patient care – largely through the voluntary participation of millions of people. However, most clinical trials are conducted in a "one-off" manner with significant time, energy and money spent on bringing together resources. Noted challenges with RCT-based clinical development of new health technologies fall into three broad categories: economic, technical and ethical.

On the economic side, long duration, large sample sizes and growing cost and complexity of RCTs have been the cause of much debate, leading to concerns over the impact of the traditional model of clinical development on innovation and patient access on one side and patient safety and affordability on the other. In the context of a business model that favours incremental innovation, the demonstration of small effect differences requires larger sample sizes and therefore more expensive trials. The global fragmentation of clinical trial requirements for marketing authorization also increases trial cost and complexity and the resulting duplication exposes patients to unnecessary risk.

On the technical side, the debate is two-fold: first, there are concerns over the ability of RCTs to truly evaluate overall efficacy or comparative efficacy, that is how well the medicine works vis-à-vis other medicines. Second, questions remain about what happens when technical challenges in the conduct of trials for specific patient groups/therapeutic areas lead to important evidence gaps or labels that align suboptimally with patient needs (for example, research in children or pregnant women).

On the ethical side, concerns have arisen over perceived conflicts of interest in RCTs largely being conducted by sponsors who have a vested interest in a certain outcome. It is through the medical literature that knowledge of trial conduct becomes public; however, published information is known to present an incomplete and potentially biased sample of clinical trials. It is estimated that perhaps only around 50% of all clinical trials conducted are ever published [49], with a strong tendency to favour trials showing positive results.

From the challenges throughout the product life cycle, the clinical phase has so far been the lesser target for policy intervention. To date, solutions have focused on the following three possible approaches, all of which largely aim to improve efficiency in the existing system: clinical trial networks (CTNs), adaptive trial designs/master protocols, and increased transparency/trial disclosures.

**Clinical trial networks** (CTNs) aim to streamline the clinical trial infrastructure so that the investigation of new research questions can quickly draw on resources already in place instead of reinventing the wheel for each trial; the efficiency of such approaches is widely acknowledged. Centres of excellence have long been the cornerstone of complex trials in mainstream areas such as cancer or diabetes. However, the therapeutic/population areas where current discussions are more ambitious and for which implementation is being expedited are those characterized by both economic and technical challenges. An example here is antibiotic trials, where enrolment is plagued by identifying critically and acutely ill patients in a timely manner; furthermore, frequent resistance to comparator therapies make non-inferiority designs the norm.

In this area, work from the United Kingdom's Wellcome Trust indicated that a Globally Connected Trial Sites system, expediting sponsor product enrolment, could reduce the costs of Phase II and Phase III trials by 23%. In a second, more ambitious approach, allowing trials to share control groups and potentially use control data from previous trials could reduce the cost of trials by 40%–60% [50]. Several CTNs have emerged across Europe and the world. Examples of initiatives based on the CTN concept are shown in Table 4.

Although further research is necessary in the area, it would seem that further public backing of independently run, publicly subsidized clinical trial networks is warranted. It will be important, moving forward, that these are not developed in therapeutic, geographic, patient-population or CTN-model based silos but rather collaboratively, in order to maximize learning and synergies. All CTNs will face the same ethical, administrative, regulatory, logistical and contract requirements as they build their infrastructure and capacities. Resources should be pooled as much as possible to ensure sustainability and maximum efficiency gains. This is especially the case if upfront financial support continues to be largely public.

**Adaptive clinical trial designs** allow (prospectively) planned modifications of one or more specified aspects of the study design and hypotheses based on interim data accumulation. The aim of an adaptive trial is to more quickly identify medicines that have a therapeutic effect, and to zero in on patient populations for whom the medicine is appropriate and the patients who are most likely to derive (most) benefit from a therapy [51]. The promise of greater flexibility and efficiency stimulates increasing interest in adaptive designs from clinical, academic and regulatory parties [52,53]. When adaptive designs are used properly, efficiencies can include a smaller sample size, a more

**Table 4: CTN initiatives in challenging areas of clinical development**

<b>National</b>	United States, FDA: Global Pediatric Clinical Trials Network, 2017	To "support the development and maintenance of a scientific and organizational infrastructure that can plan, start up, conduct, and close out pediatric clinical investigations", the FDA provided US\$ 1 million awards each to the Institute for Advanced Clinical Trials for Children (IACT for Children) and to Duke University under the Global Pediatric Clinical Trials Network Cooperative Agreement. The Network's goals include work on optimizing extrapolation from adult data and deepening understanding that will enable valid modelling and simulations for optimizing dosing strategies in paediatric patients, developing innovative trial designs, including ones that can study multiple therapies at one time (see also Master protocols, below), standardizing a broad spectrum of information sources including clinical trials, registries, natural history studies and electronic health records, developing biomarkers for use in paediatric trials and clinically meaningful short- and long-term efficacy and safety end-points for paediatric trials.
	Innovate UK AMR	Focused on creating an infrastructure that will fast-track the research, development, evaluation and commercialization of relevant technologies by establishing a global multicentre clinical trials network for medicines, diagnostics and vaccines, with a focus on antibiotic resistance.
<b>Multilateral</b>	European Organization for Research and Treatment of Cancer (EORTC), 1962	EORTC was founded in 1962 with the aim of coordinating and conducting international translational and clinical research to improve the standard of cancer treatment for patients. Both international and multidisciplinary, EORTC's Network comprises over 4600 collaborators involved in cancer treatment and research in more than 800 hospitals across 35 countries. Their 1400+ studies have resulted in practice-changing treatments and the establishment of new standards of care or have shown that other treatments are ineffective or redundant.
	The European Clinical Research Infrastructure Network (ECRIN), 2004 / IMI-2 COMBACTE, PedCRIN and PREPARE	A pan-European research infrastructure, ECRIN was developed and matured through a series of EU-funded projects (FP6, FP7 and H2020). It aims to support mostly academic sponsors and investigators across Europe to overcome the barriers to multinational clinical research while facilitating European/international collaboration on noncommercial and SME-sponsored trials. A number of newer EC-funded initiatives go in a similar and complementary direction (for example, Paediatric Clinical Research Infrastructure Network or PedCRIN, COMBACTE and PREPARE – both the latter perform trials in the field of infectious diseases but are both sharing and building clinical trial network infrastructure and capabilities).

Source: Authors' own compilation.

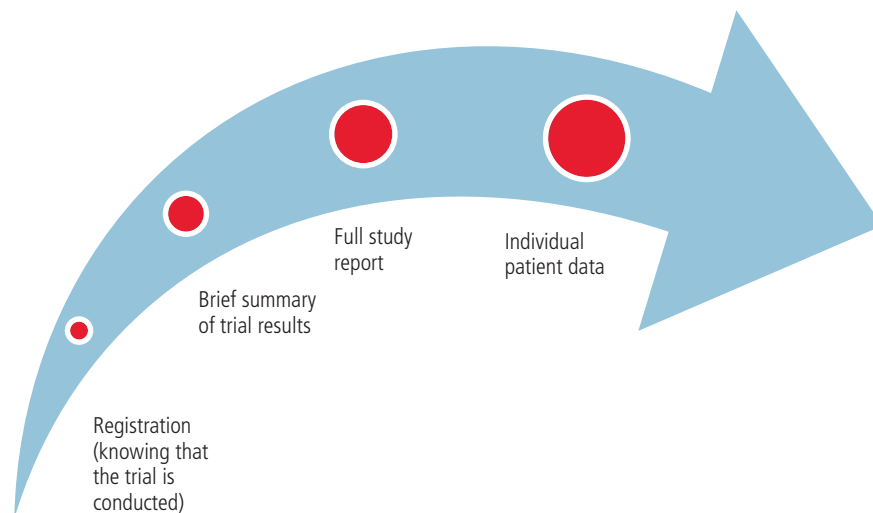
efficient treatment development process, and an increased chance of correctly answering the clinical question of interest as well as facilitating the use of international clinical trial networks. However, improper adaptations can lead to poor design and/or biased studies [54]. Regulators themselves have proceeded cautiously due to lack of experience with such designs and indeed some biostatisticians remain sceptical of their value [55]. Recent work found that there has been some growth in the reporting of adaptive designs globally; still, only 12% of these trials were used by the EMA for marketing authorization purposes (the percentage was lower for the FDA, at 9%) and regulators seemed to be sceptical and/or careful regarding design features [56]. The authors conclude that a wider adoption of such designs would necessitate early interaction between developers and regulatory scientists and better reporting practices.

Another methodological innovation aiming to enable answering more questions more efficiently and in less time has been described with the overarching term “**master protocols**”, entailing one protocol designed to answer multiple questions for either single interventions for multiple conditions or several interventions for one condition with multiple subtypes. Such trials can take the form of umbrella, basket and platform trials. All three designs aim at achieving better coordination compared with single trials [57]. Here too, potential efficiency gains [58,59], have to be weighed against statistical considerations regarding robustness [60], and acceptability for regulatory purposes.

The extent and structure of available knowledge on the benefits and harms of (new) medicines is further compounded by the issue of **publication bias** (see above). Even though the phenomenon was first described 30 years ago, the movement supporting the removal of barriers to the public dissemination of complete and unbiased research findings has only recently gathered sufficient traction. The tension between the proprietary nature versus the public value of clinical trial data [61], has led to the development of incrementally ambitious transparency goals, initiated and led by civil society (Fig. 3).

Laying the foundation, the Declaration of Helsinki – the World Medical Association’s statement of principles for medical research involving people – states that every investigator running a clinical trial should register it and report its results. Voluntary and early forms of transparency regulation were largely perceived as being too weak, ambiguous (with a paucity of clear, unequivocal legislation for the registration and reporting of all clinical trials) or otherwise ineffective even when requirements were mandatory [63]. More recent legislation on both sides of the Atlantic – EU No. 536/2014 and FDAAA 801 – have increasingly and notably become more stringent and punitive with fines for noncompliance by sponsors [64]. Monitoring implementation and evaluating its impact needs to be prioritized for these steps to actually succeed. Examples of relevant initiatives are shown in Table 5.

**Fig. 3: Incremental stringency of transparency requirements at international level**



Source: Adapted from [62].

**Table 5: Initiatives to promote transparency in evidence generation**

<b>National</b>	United States: ClinicalTrials.gov	The world's largest clinical trials registry has recently been bolstered by new clinical trial transparency legislation. This increased the stringency of disclosure requirements, makes trial registration mandatory within 21 days of enrolling the first patient (NIH-funded Phase I trials must also be registered) and failure to do so can result in civil monetary penalties or withholding of grants for federally funded studies.
<b>Multilateral</b>	WHO Registry Network, 2004	The WHO Registry Network had the objective of facilitating the establishment of: "a network of international clinical trials registers to ensure a single point of access and the unambiguous identification of trials". It provides prospective trial registries with a forum to exchange information and work together to establish best practice for clinical trial registration.
	AllTrials campaign, 2013	This United Kingdom-centred, not-for-profit campaign is a collaboration between a number of activists, scientific journals, and academic and government institutions and calls for all past and present clinical trials to be registered and their results reported. In the United States of America they have an information service to help the public and patients navigate some of the issues: Center for Information and Study on Clinical Research Participation.
	EU trial database created by EU Clinical Trials Regulation 536/2014	The EU Clinical Trials Regulation 536/2014 mandates the EMA to set up (by October 2018) an operational database for clinical trials and a portal for submissions. Six months after they become functional, the Regulation will go into effect.  The Regulation requires sponsors to provide summary results of clinical trials in a format understandable to laypersons that will be made available in the new database. Until now, the EudraCT Results data model, launched in July 2014, has been used for posting scientific results written in technical language.

Source: Authors' own compilation.

A number of steps have been taken to reduce hurdles for developers and overall R&D costs by ensuring harmonization of requirements for the conduct of clinical trials at European and international levels. Before Directive 2001/20/EC (the Clinical Trials Directive), it was feasible to imagine that a trial sponsor would face as many different submission requirements as the number of European countries in order to be able to conduct a clinical trial. The Directive had the objective of harmonizing clinical trial processes and detailing the legal provisions for Good Clinical Practice and Good Manufacturing Practice across the EU. It was recently

replaced by Regulation 536/2014, which details new requirements for authorizing, conducting and reporting clinical trials and aims to simplify and harmonize processes, making clinical trial conduct in Europe more appealing for developers while increasing transparency. It is considered a harmonized procedure, providing a single entry point for submissions across the 28 member states (see also Table 5). Two related multilateral initiatives are shown in Table 6.

**Table 6: Harmonization of requirements for the conduct of clinical trials**

International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)	Formed in the 1990s by regulators and industry in the EU, United States of America and Japan, the ICH developed harmonized guidelines to avoid duplication in registrations. Its work included the common technical document for regulatory submissions and good clinical practice, an international quality standard for clinical trial conduct. Governments can transpose their guidelines into national regulations for clinical trials involving human subjects. It is more procedural and less moral than the voluntary Declaration of Helsinki.
IMI: European Health Data Network (EHDN), 2017	Across entities, different standards are used to code diagnosis, laboratory results, medicines or procedures. In most health care systems, a majority of the core clinical data are buried in unstructured (text) notes, making data analysis even more challenging. The EHDN was created to provide a harmonized model to address the structural heterogeneity and the use of different coding standards, expediting efficiencies in the research process.

Source: Authors' own compilation.

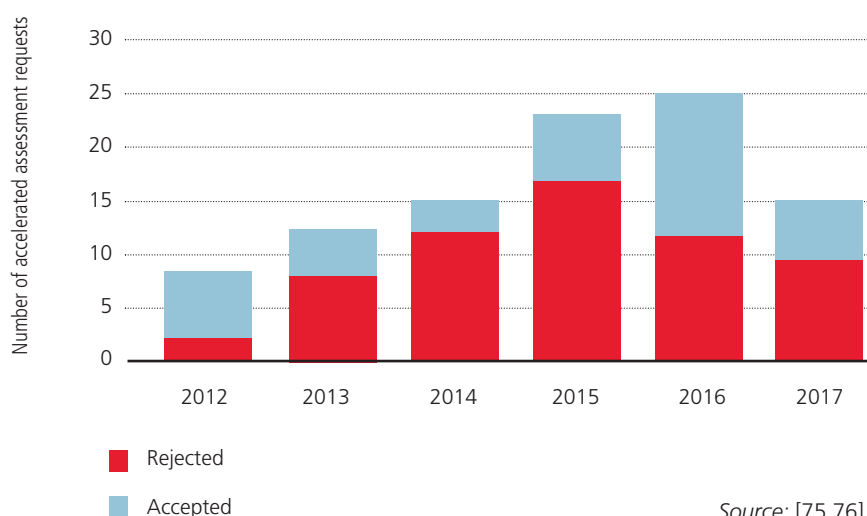
## Incentivizing valuable innovation by reconsidering evidentiary requirements for marketing authorization, priority status designation and reimbursement

One topic that has long been recognized but that has received relatively little policy attention to date is the possibility of including comparative evidence into marketing authorization requirements as a step towards ensuring that approved medicines do in fact contribute to patient benefit [65]. This would mean making market entry itself dependent on a product demonstrating superiority (or at least equivalence) to existing alternatives – this is currently not the case. In fact, medicines in many areas are approved based on non-inferiority studies, which – over successive approvals – can lead to medicines being accepted without any proof of efficacy compared with placebo.<sup>1</sup> Proposals have been put forward in both the United States of America and Europe as to what such an increase in approval standards would entail and how it could be differentiated [67,68]. Such approaches could potentially encourage manufacturers to focus on therapeutic areas with limited treatment options, due to the number or efficacy/safety profile of available comparators, as products in those areas would face a lower bar for authorization [69]. Concerns have been voiced that requiring manufacturers to generate comparative evidence in an overarching manner could lead to more expensive trials, inflated R&D costs and impact prices, and/or delay patient access to innovation. Both the novel trial designs described in previous sections, as well as a differentiated application of comparative evidence requirements (for example, maintaining the possibility for non-inferiority evidence in cases of few or suboptimal alternatives, high unmet need) could serve to mitigate these phenomena.

However, specifically in the context of unmet need, provisions for accepting evidence more leniently have been in place for a while, both in Europe and internationally. Accelerated or conditional approval mechanisms have been in place since the FDA introduced its priority review voucher 25 years ago. The aim was to allow faster approval of medicines for serious conditions that fill an unmet medical need by lowering the evidentiary requirements for developers before product launch. Since then, both the FDA and EMA have established a number of different pathways that include this feature: priority review, fast track designation and emergency use authorization in the United States of America and accelerated approval, exceptional circumstances, conditional approval and most recently PRIME in Europe (see also Table 3C). One retrospective study looking at FDA approvals through the early years of its fast track programme showed that it resulted in an overall reduction in average development time of about 3 years. The EMA's accelerated approval pathways guarantee approval in 150 days as opposed to 210 days under a normal pathway. In the last couple of years these tools have been revised to allow more medicines to reach patients earlier. In the United States of America this was codified through the passage of the 21st Century Cures Act in 2016. The EMA issued revised guidance following discussions at the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) in 2015.

However, as experience with the implementation of these tools grew, increasing disquiet was voiced that they would become the norm, rather than the exception, while not ensuring an appropriate balance between speed and safety of access (Fig. 4). From 2015, there seems to be a receding trend in such approvals. Specifically, concerns focus on whether products represent the therapeutic added value that these approaches are meant to foster [70], and whether patients are being exposed to acceptable safety risks [71].

Fig. 4: Number of EMA accelerated approval requests by year, 2012–2017



Source: [75,76].

<sup>1</sup> "After a non-inferiority clinical trial, a new therapy may be accepted as effective, even if its treatment effect is slightly smaller than the current standard. It is therefore possible that, after a series of trials where the new therapy is slightly worse than the preceding drugs, an ineffective or harmful therapy might be incorrectly declared efficacious; this is known as "bio-creep" [66].

Some commentators believe that there may be limited circumstances that justify rapid access to new medicines on the basis of minimal data, and point to evidence that indicates that regulators have been too permissive in their interpretation of existing criteria for expedited approval, which were originally intended and reserved for areas of high or unmet medical need [72]. Safety concerns arise because it has been shown that medicines approved through these pathways are associated with more and higher-risk safety-related label changes following approval [73]. Importantly, there are also concerns about how quickly these risks come to light, with most developers failing or delaying the submission of (often conditional) post-approval data on time [74]. Finally, dispute remains as to whether surrogate end-points (which may be the only ones available in this context), even when supplemented by real world evidence, can truly and reliably predict clinical risk and benefit.

Introducing comparative evidence for marketing authorization purposes could also lay the groundwork for increasing the convergence of evidence requirements between regulators and payers. So far, this has been complicated to implement [77]. This is in part because evidence on efficacy (required for marketing authorization) often considers surrogate outcome measures, and not clinical and patient-relevant end-points as is commonplace in health technology assessment (HTA) used in post-marketing evaluations for coverage decision-making purposes; furthermore, coverage decision-making usually already requires comparative evidence rather than comparisons against placebo only. A closer look at the role of HTA in determining reimbursement and price of new medicines is provided in the concurrent policy brief [2]. Here, we focus on the potential of increased collaboration in HTA and related activities for steering R&D investments towards meaningful innovation.

HTA programmes for the evaluation of pharmaceuticals evolved organically in the majority of European countries; as a result, they differ considerably regarding process and methodology. However, assessments uniformly summarize (best) available evidence to provide the basis for decision-making on reimbursement and/or pricing, depending on the system. The varying set-up of pharmaceutical HTA systems in Europe has been well documented [39,78,79]. At the European level, it was recognized quickly by the European Commission that the variable levels of experience among Member States as well the potential for substantial duplication of work (with the same newly approved medicine being evaluated in a number of European countries) lend themselves particularly well to knowledge exchange and collaboration. At the same time, aligning criteria and methodologies would simplify evidence generation for manufacturers. A brief overview of European developments in HTA is shown in Box 4.

On 31 January 2018, the European Commission issued a proposal for regulation based on the impact assessment and the consultation process described in Box 4. The proposal opts for mandating joint assessments of clinical elements (effectiveness and safety), while leaving the consideration of other domains such as the economic and organizational impact to national authorities. In brief, the draft regulation

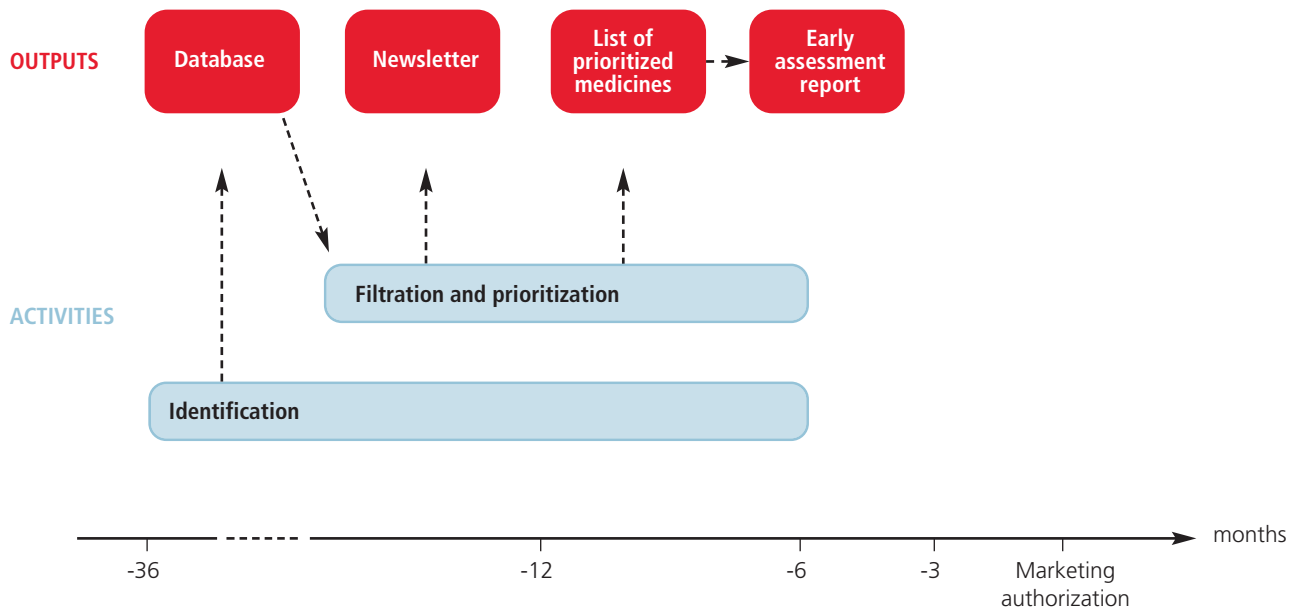
proposes four main changes to current systems of post-marketing evaluations for medicines approved by the EMA:

- Joint clinical assessments of new pharmaceuticals as well as certain medical devices and in vitro diagnostics. Following a phase-in period of 3 years, participation in the centralized assessments and use of the joint clinical assessment reports at Member State level will be mandatory.
- Joint scientific consultations: these will allow developers of pharmaceuticals and medical devices to seek advice from the Coordination Group of HTA agencies (newly instituted in the draft regulation and hosted by the European Commission) on the data and evidence likely to be required as part of a potential joint clinical assessment in the future. These consultations can potentially be held in conjunction with scientific advice from the EMA. After the phase-in period, equivalent consultations at the Member State level are not to take place for technologies covered by the joint scientific consultation.
- Identification of emerging health technologies (“horizon scanning”): the Coordination Group is to carry out an annual study to ensure that health technologies expected to have a major impact on patients, public health or health care systems are identified at an early stage in their development and included in the joint work of the Coordination Group.
- Support for continuing voluntary cooperation and information exchange on nonclinical aspects of HTA.

The proposal has been met with criticism from various sides, regarding three main points: (a) the lack of flexibility regarding (additional) national assessments in light of different standard practices of care that influence comparator therapies and choice of outcomes, (b) the lack of an obligation for the industry to submit full trial data despite increased traction in transparency expectations in recent years (see above) and (c) the loss of flexibility in decision-making at national level in the presence of a binding assessment. Alternative or interim solutions could entail, for example, a clearinghouse option, wherein available HTA reports on one medicine can all be presented together, with at least comparative summary tables in English.

Nevertheless, an increase in the intensity of collaboration is generally welcome, particularly regarding the identification (and evaluation) of new technologies addressing unmet needs. In fact, experiences from the EuroScan International Network, a voluntary global network of publicly funded early awareness and alert systems for health technologies, show that member agencies saw value in enhanced collaboration activities [80]. Horizon scanning can be linked to early assessment reports, as can be seen in an example from Sweden in Fig. 5. Considerations of unmet need and subsequent prioritization of evaluation for marketing approval and reimbursement are conceivable. In May 2018, the Belgian Minister of Health announced a collaborative horizon-scanning effort for high-priced medicines to inform the work of the BENELUXA collaboration. The set-up of this initiative, which has the potential for global application, is based on a proposal by the Belgian Health Care Knowledge Centre, which recognizes unmet medical and societal need as prioritizing criteria for scrutiny [81].

Fig. 5: National example of the potential contribution and embeddedness of horizon scanning from Sweden



Source: [82].

**Box 4: European developments in HTA**

The European Commission has supported collaboration in HTA across countries since the early 1990s. In 2004, it set HTA as a political priority, followed by a call towards establishing a sustainable European network on HTA. The call was answered by 35 organizations throughout Europe and led to the introduction of the European network for Health Technology Assessment (EUnetHTA) Project in 2007. On the basis of the project’s results, the European Commission has consistently funded a number of continuing initiatives: the EUnetHTA Collaboration 2009, the EUnetHTA Joint Action 2010–2012, EUnetHTA Joint Action 2 2012–2015 and EUnetHTA Joint Action 3 2016–2020. This research has mainly focused on developing joint methodologies for assessment, perhaps most importantly the so-called Core Models for different types of technologies, but also piloting them in carrying out joint assessments. It also maintains a database of European HTA reports accessible to its member organizations.

Cross-border collaboration in HTA was anchored in EU law through Directive 2011/24/EU on the application of patients’ rights in cross-border health care. Article 15 states that “The Union shall support and facilitate cooperation and the exchange of scientific information among Member States within a voluntary network connecting national authorities or bodies responsible for health technology assessment designated by the Member States.” The Directive sets out both the network’s goals and activities for which additional EU funds may be requested. It also explicitly reinforces the principle of

subsidiarity, stating that adopted measures should not interfere with Member States’ competences in deciding on the implementation of HTA findings or harmonize any related laws or regulations at national level.

In October 2016, the European Commission launched a public consultation on strengthening EU cooperation on HTA. The European Commission’s impact assessment offered different policy options ranging from maintaining the status quo of project-based collaboration to cooperation on the production of fully fledged joint HTA reports including the evaluation of cost-effectiveness and organizational aspects (which are more topical) along with clinical effectiveness and safety. The impact assessment was based on evidence from the EUnetHTA activities of previous years, which showed that collaboration in producing joint methodologies and assessments themselves can improve both the quality and quantity of produced assessments while avoiding duplication of work. However, evaluative research on these collaborative activities also highlighted challenges, particularly for the alignment of the joint HTA process with national needs and processes. This primarily concerned the timely availability of joint assessments, the relevance of each jointly selected topic for individual HTA agencies and difficulties with integrating jointly produced reports in national templates and procedures [83]. The consultation culminated in the new proposed regulation described in the main text.

Source: Authors’ own compilation.



The provision of scientific advice to manufacturers by regulators and HTA institutions is also established practice. However, processes so far have not been consistently integrated neither horizontally (across countries) nor vertically (involving both regulators and HTA institutions). Considerations of increased interaction could be integrated in the models of scientific advice already in place. A recent initiative from a multitude of European stakeholders put together a set of recommendations to reorient how scientific advice is provided by the EMA (Box 5).

#### Box 5: Recommendations for reshaping the EMAs scientific advice process

Scientific advice is currently carried out behind closed doors, involving individual companies. A joint statement from civil society and a number of HTA institutions issued in November 2017 provides an alternative approach.

According to the statement, scientific advice should be conducted in a transparent way, including:

- General guidelines on scientific principles for conducting randomized clinical studies, including comparative trials against standard treatments using patient-relevant end-points, assessing efficacy as well as harms;
- Disease-specific guidelines to clarify disease-specific requirements (for example, on patient populations, interventions and comparators, outcomes and study duration);
- Public general or disease-specific workshops to clarify upcoming questions at shorter notice and guidance on how to avoid any undue influence on the workshop outcomes;
- To increase efficiency and remove the need for the EMA to collect user fees for scientific advice
  - a requirement that questions of individual companies to EMA (and/or HTA bodies or payers) are posed and answered in writing (without confidential meetings) and made publicly available,
  - preparation of publicly available frequently asked question and answer documents; new requests for advice should be limited to as yet unanswered questions;
- Public processes to avoid confidential waiver negotiations to existing guidelines;
- Independent advisors, not involved in the marketing approval or pharmacovigilance process and independent from industry.

Source: [84].

In the context of evidentiary requirements, no current reflection is complete without the relatively recent discussion on the role and usability of **real world evidence** to inform decision-making for marketing approval and/or reimbursement. In general, there is no concrete agreement on the definition of what constitutes real world evidence [85]. The FDA distinguishes between the terms real world *data* (“... the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources including electronic health records (EHRs), claims and billing activities, product and disease registries, patient-

related activities in out-patient or in-home use settings and health-monitoring devices.”) and real world *evidence* (“the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real world data”). Although the FDA has long used such information to monitor post-market safety and make related decisions, the 21<sup>st</sup> Century Cures Act put real world evidence firmly on the map by requiring that the FDA develop a framework for their use in marketing approvals; these efforts are ongoing.

In Europe, the IMI GetReal project defined areas in which such information can be used along the medicine's life cycle, including aiding trial design during development and post-market surveillance and described best practice for real world data in comparative effectiveness research [86]. However, integrating nonrandomized designs into decision-making has not taken off, as regulators and HTA bodies seem reluctant in light of methodological doubts [87]. It seems that future practice on HTA at European level would require further experience and common understanding before acceptable joint solutions can be found. Further exploring the potential of real world data to identify and monitor unmet needs should be considered. Coordination initiatives have started to emerge: for example, supported by the EMA, a resource for the identification of patient registries is being hosted by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.

## Policy implications

The initiatives discussed above were presented in a thematic manner, and thus somewhat in isolation. A more fitting consideration of the value chain of innovation, from discovery to disinvestment, would entail a comprehensive review of the system as a single “innovation entity”. For example, the brief does not touch upon the issue of intellectual property rights in the current patent system for pharmaceuticals, although these are the cornerstone of rewarding investment in pharmaceutical R&D: market exclusivity provides the possibility of high(er) prices, thus enabling manufacturers to recoup the costs of developing and marketing their products. However, it has long been argued that the current system is, potentially, too generous and that there are industry practices suggesting its misuse (e.g., evergreening, pay-for-delay, using regulatory loopholes to forestall generic competition). Perhaps more relevantly at this juncture, patents are currently awarded based on novelty of mechanism of action, not patient benefit; by definition this does not put the emphasis of awarding market exclusivity on addressing unmet needs or provide direct incentives for meaningful innovation. The incentives system for medicines based on intellectual property was reviewed in detail by the European Commission and the report was published in May 2018 [88]; results from a shadow report by the Dutch Government followed soon after [89].

In the same light, even if R&D priorities at national or European level are identified and signalled to the market, as long as the resulting products are not guaranteed high rewards (commercial or public), then the signal is meaningless. If products that contribute little to added therapeutic value are still afforded high prices, innovation will not be stimulated. Hence, an overall vision with greater policy coherence seems necessary to effectively tackle innovation deficits and maintain healthy reward systems. The multitude of promising initiatives highlighted above would in all likelihood produce better results in combination, as different elements address separate components that merit intervention in the current system.

A combination of – potentially centralized – push- and pull-funding mechanisms to include SMEs and non-entrepreneurial researchers and developers with a reconsideration of current (decentralized) patent-based price signals to guide innovation efforts is conceivable. Especially in the realm of ensuring sustainable financial resources for areas of unmet need with otherwise low desirability, more and more distinguishing pooled financial resources should be made available. Current initiatives often have the purpose of making the price of medicines independent of their R&D costs (“delinkage”), but more product pilots are required to demonstrate the fitness and suitability of such models. Nonetheless, some areas will not be addressable by modifying or refining present systems, as legal regulatory tools have their limits as to what they can achieve. The acknowledgement of areas of complete market failure will help to meaningfully pursue sustainable solutions to such challenges. Certain health problems and the

pharmaceutical industry are both global; fragmented national responses can only go so far in this respect. A pooled financing mechanism would be a necessary first step, but it would require an unlikely level of political commitment, especially if the EU were to continue along this path without support from the United States of America. Linked to sustained and sustainable funding is the concept of insisting on more evidence-based prioritization of these funds. The concept of global priority setting should be expanded to ensure that there is clarity for all parties regarding what is socially and clinically desirable and valuable, not least in the form of a distinguishing reward system.

In the context of evidence generation, more experience is required both regarding CTNs and novel trial designs. On the former, in addition to adopting a collaborative approach to further development, an avenue for the future lies in the need to make a sound business case to private developers as a way of converting tentative industry support into active participation and use of CTNs as contributors and beneficiaries. This would be essential both in terms of financial sustainability and fruitfulness of collaboration. Building on existing projects to create a truly pan-European CTN for infectious diseases could prove an interesting and timely test-case. More pilots involving novel trial designs seem necessary, with more concrete regulator involvement, to assess their suitability for regulatory purposes and their long-term efficiency contribution. Kicking off such an approach with a focus on areas of high unmet need seems fruitful. The continuing transparency movement, initiated by civil society, to get clinical data in the public domain could be bolstered with some regulatory support. For example, researchers should openly share their research, peer-review journals should ensure results are published in full, ethics committees and funders could mandate trial disclosure and results publication, and regulatory authorities could ensure that clinical study reports are made publically available (see also the results of the OPEN Project, funded by the European Commission). Open source initiatives should be further explored in this context. Based on experience to date, many of these tools will probably be ineffective without oversight, enforcement and penalties for noncompliance; in the interconnected environment described throughout the brief, this is a function best handled (or at least coordinated) at supranational level.

Efficiency gains in regulatory processes themselves, such as early dialogue and (parallel) scientific advice and the alignment of evidentiary requirements for regulatory and HTA purposes, are also candidates for increased policy focus, although efforts in this direction at least in Europe are already ongoing. The recent Lancet Commission on essential medicines emphasized the value of reducing duplication in national approvals by expanding data-sharing and mutual recognition (as already applied in Switzerland and many low-income countries). Such approaches may warrant greater and more immediate action than attempting to streamline access to new medicines by reducing the stringency of pre-market requirements. Indeed, recent experience with the EMA’s adaptive pathways pilots shows that until they can either be better supported by available evidence or insured

against through a) strengthening post-market obligation compliance and b) empowering regulatory agencies to act more swiftly and decisively on product withdrawals (delisting) and label changes, their implementation remains problematic. What is more, there is a fear that expedited regulatory pathways, for which evidence requirements are lower, are not sufficiently stringent in their distinction of priority medicines, and that the momentum towards increasing enforcement will proceed faster than addressing the legitimate concerns arising from their use. It is important that the relevant regulatory frameworks be reviewed to ensure that they (still) strike the right balance between enabling access to priority medicines for high (unmet) need and safeguarding against safety risks and inefficiencies.

As the European framework for collaboration in HTA is currently under discussion, it is an opportune time to reflect on how best to remove unnecessary inefficiencies while maintaining state-level flexibility and fostering transparency and true evidence-based decision-making. It is conceivable that future regulation incorporates specific provisions for prioritizing medicines addressing unmet need and promoting the common understanding of the potential and appropriate incorporation of real world data as well as further exploring the creation of European data systems.

Finally, there is a distinct lack of establishment and implementation of public interest provisions along the life cycle of pharmaceuticals. For example, EU-funded R&D currently has no mandatory and specific "access" provisions embedded as a condition of R&D grant disbursement. Reconsidering options to ensure "fair return of investment" for the public seems warranted, especially in light of the limited patient benefits offered by many new medicines.

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## Conclusions

A comprehensive approach encompassing initiatives to guarantee funding, optimize evidence generation and reconsider regulatory requirements is necessary to address the paucity of true innovation observed among newly approved medicines, particularly in the context of unmet needs. Despite a number of promising initiatives that are ongoing at different levels for each of these areas, no individual measure would produce the same level of results as an overarching vision backed by strong political commitment. Having looked at the different elements related to stimulating the right innovation to ensure patient benefit where it is most needed, it seems that the one cross-cutting theme is the need for information. Lack of transparency regarding R&D costs, medicines in the pipeline, and research already commissioned and/or funded by different sources – but also information on unmet needs in their dynamic nature as well as the willingness of public funders to support related work – have been compounding progress in the area.

From the European perspective, this dearth of information can be alleviated to a considerable degree by enhanced collaboration, for instance in specifying and actively signalling agreed research priorities, identifying promising emerging technologies and ensuring appropriate priority status for approval and coverage decision-making, and making available the necessary funding to overcome commercial unattractiveness. In support of all these activities, the development of European data systems should remain an area of focus.

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World Health Organization  
Regional Office for Europe  
UN City, Marmorvej 51,  
DK-2100 Copenhagen Ø,  
Denmark  
Tel.: +45 39 17 17 17  
Fax: +45 39 17 18 18  
E-mail: [postmaster@euro.who.int](mailto:postmaster@euro.who.int)  
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