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# Improving access to medicines and promoting pharmaceutical innovation

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## STUDY

Panel for the Future of Science and Technology



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# Improving public access to medicines while promoting pharmaceutical innovation

Health is a fundamental human right, and achieving equal access to medicines is crucial to ensuring public health. The current system of pharmaceutical innovation relies strongly on the private sector, and remuneration of innovation is mainly based on exclusivities. This system presents several challenges, such as innovation being driven by market size, the partial misalignment between industry research and development priorities and public health goals, market access constraints, and the prevalence of incremental over disruptive innovation. In this context, this study analyses the impact of different research and development incentive mechanisms and alternative frameworks for pharmaceutical innovation and public health. It places specific emphasis on their effects on innovation and patient access to medicines, in terms both of affordability and of availability.

Based on an extensive review of the literature combined with interviews with expert stakeholders, the study offers a range of policy options. These seek to ensure the development of accessible drugs in all clinical areas, improve availability, price and research and development cost transparency, and ensure preparedness in the event of emergencies. Policy options suggested include strengthening EU coordination on intellectual property rights and medicine procurement, reducing the length of exclusivities, and introducing specific incentives (subscription models) de-linked from market size for specific unmet medical needs (antimicrobials and rare diseases with extremely low prevalence). A further suggestion is the creation of a public infrastructure active throughout the whole drug research and development process. A combination of policies would exceed the sum of its components, by generating additional synergies.

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## Executive summary

### Introduction

The United Nations Declaration of Human Rights and the Sustainable Development Goals state that **health is a fundamental human right**. Equality in patient access to medicines is a crucial aspect of ensuring public health. The recent COVID-19 pandemic brought some of the vulnerabilities of the current framework even more to the fore. The European Commission is working on a pharmaceutical strategy for Europe, aiming to 'help ensure Europe's supply of safe and affordable medicines to **meet patients' needs** and **support the European pharmaceutical industry** to remain an innovator and world leader'.

The current pharmaceutical system of innovation and care rests on two fundamental conditions: i) the ability to develop new **innovative drugs**; and ii) the possibility for patients to **access** them. Different actors with different ethos and capabilities are involved in the development of new drugs over long periods. Public and private institutions contribute to the early stages of innovation, whilst the private sector dominates the later stages of development. To launch a new drug on the market, clinical trials are required to prove the drug's safety and efficacy. Data from these trials are used by regulatory authorities in the authorisation process. In the EU context, pricing and reimbursement decisions fall under the responsibility of national authorities. In contrast, most industry decisions are taken with a global perspective.

Against this backdrop, the development of new medicines takes many years and is fraught with uncertainty, with a large proportion of new drug candidates never reaching the market owing, for instance, to a lack of safety or efficacy. To ensure that innovation efforts are rewarded, intellectual property rights (**IPRs**) **play a key role for private investors**, by granting monopoly rights to the patent holder. However, while supporting innovation efforts, **IPRs** create a **potential barrier to access (availability and affordability)**, so that the two key conditions mentioned above – innovation and access – can become **difficult to reconcile**. This makes it challenging to strike a balance between providing sufficient incentives to invest in research and development (R&D – dynamic efficiency) and ensuring price levels at which new products are accessible and affordable (static efficiency). In addition, the set of incentives provided is not suitable to stimulate research across all areas, with expected market value being among the main determinants of the direction of R&D investments. To ensure access, it is also important not to introduce undue delays to the possibility for generics/biosimilars to enter the market.

In this context, the STOA Panel of the European Parliament launched the present study to examine the **impact of regulatory mechanisms on public health**, as determined by access and innovation for patients. The study also explores **alternative frameworks** that could be adopted to achieve a proper balance between static and dynamic efficiency. Particular attention is paid to **unmet medical needs (UMN)**, including drugs for rare diseases, the development of antibiotics to address the growing burden of resistance, and medicines for paediatric use.

### Methodology

To achieve its objectives, the study **combines** a critical analysis of the evidence provided by a review of the **scientific literature and technical reports**, with **semi-structured interviews with selected international stakeholders** (researchers and clinicians, public health experts, public officers, representatives of the pharmaceutical industry and patient organisations). Interviewees were identified on the basis of several criteria, including international reputation, their position in key organisations, and their representativeness of the different stakeholders. We contacted 35 experts, of whom 24 (from 23 different organisations) agreed to be interviewed and were included in the study. The interviews took place between July and September 2023. Respondents were guaranteed anonymity and the results of the interviews are presented in aggregate form.

## Results

Combining the literature review with the views gathered through the interviews, the main results of the study can be summarised as follows.

- Reforms to the current system of incentives are demanded, to **better balance the need to sustain innovation and to ensure access to medicines**.
- **Market exclusivities** (including patents and their extensions, and regulatory exclusivities) have an **important role in stimulating private sector R&D activities**. Under the current system, where the **private sector plays a prominent role in R&D investment**, several innovations have been brought to the market with **significant impacts on life expectancy and quality of life**. Nevertheless, unless explicitly targeted (as is the case for market exclusivity granted to orphan medicinal products, or patent extension for paediatric clinical trials), the **ability of exclusivities to address UMN is limited**, because the size of the reward is linked to the size of the relevant market. As a side effect, such exclusivities may have a **negative impact on patient access**, owing to (sometimes excessively) high prices or limited availability. In the case of patents, concerns have been raised that they may delay scientific progress. In some cases, exclusivities have been used strategically, to delay the entry of generics/biosimilars upon expiry, thereby limiting competition.
- The fact that individual Member States are responsible for pricing and reimbursement decisions leads to **significant disparities in prices and timing of access across countries**.
- The proposed reform of the pharmaceutical regulation would introduce a **transferable (data) exclusivity voucher (TEV)**, to be granted for the development of priority antimicrobials. The voucher could be redeemed by its holder for another product, or sold. By focusing on a specific therapeutic area, the voucher could be expected to stimulate research into eligible conditions. **Evidence on this measure is limited** as, to the best of our knowledge, this would be its first implementation. Vouchers have been used in the United States in selected areas, but these take the form of priority review vouchers, which allow faster market access. **Concerns** have been raised about TEVs, including the distribution of rents they imply, the impact on patients in other therapeutic areas, the sustainability for national pharmaceutical budgets, and the risks of increased uncertainty around the end of exclusivity periods. However, it is recognised that some **urgent action is needed to stimulate research for the development of antimicrobials**, and TEVs have the advantage of being **easy to implement** in the EU, requiring virtually no coordination among Member States and no upfront payment from the health system. Although more difficult to implement in the EU context, subscription models may be an interesting alternative.
- **Advance purchase agreements (APAs) and subscription models (SMs)** have been **invoked in the context of UMN**, where rewards based on exclusivities fail to stimulate sufficient research effort. Such APAs and SMs could also reduce uncertainty related to market dynamics. In particular, SMs have the ability to de-link revenues from quantity, which is essential to stimulate research for UMN. This could also be achieved through **innovation prizes** (milestone payments and market entry rewards, with the latter being preferred because they reward solely products with proven therapeutic effect). A difficulty relating to the introduction of APAs, SMs and prizes is that a product's characteristics and the value of a 'right reward' need to be defined ex-ante. In the EU context, it may also be challenging to reach consensus on the dimension of each country's contribution.
- **Tax credits** may be useful to support sponsors in the early stages of development, but are currently not feasible at EU level.
- **Public-oriented approaches such as open science, public-private partnerships (PPPs) and public R&D infrastructures** are also considered in this study as **a complement to a strong and competitive private industry**. In the **open science model** research outputs are made freely and

publicly available. The model has mainly been **adopted in clinical areas characterised by a very limited market size and for drug repurposing, with successful results**. Such PPPs may or may not adopt an open science model. They have proved effective in the development of pre-competitive research topics and product development, as well as in enhancing access. As an advantage, PPPs provide **transparent information on R&D costs**. **Public R&D infrastructures** can lead to **improved access** to products and **better alignment between R&D choices and public health priorities**. To this end, governments could take a more active role in specific areas where investment is likely to remain insufficient even in the presence of a well-designed system of incentives for the private sector, by investing throughout the entire innovation chain. This would give the public sector more decision-making power over development choices, prices and distribution of publicly funded innovations.

## Policy options

The study suggests five policy options in addition to the 'baseline' case, or policy option 0:

**Policy option 0 – current regulatory framework.** This is the baseline scenario, intended to reflect the current situation and serve as a benchmark against which to assess the alternatives.

**Policy option 1 – strengthening EU coordination in IPR and procurement.** EU coordination in IPR is increasing with the recent institution of the 'unitary patent', and the proposal to create a 'unitary supplementary protection certificate'. This option proposes extending coordination to procurement. An EU procurement authority could be established alongside an EU pharmaceutical fund. This would allow for centralised price negotiation and definition of an 'EU price', while prices paid by the Member States to the EU fund could take into account ability to pay (proxied by suitable measures to be agreed upon). Countries could be given the **option to opt-out** of the coordinated procurement. An experimental phase could be envisaged where coordinated procurement is limited to selected products/areas. This policy would require significant up-front investment and broad consensus among Member States. However, it could be beneficial for patients, who would benefit from earlier access to new products and reduced disparities in availability between countries; for the pharmaceutical industry, the option could improve efficiency by reducing the costs associated with national market access procedures; for national regulators/payers, and by reducing transaction costs associated with pricing and reimbursement decisions.

**Policy option 2 – adjusting current incentives to limit excess profits.** This option aims to reduce over-protection of R&D investment and the scope of pharmaceutical company profits and facilitate access to medicines that have either been financed with public funds, or where the innovation already received substantial compensation. To be implemented, this policy would require both greater transparency on public funding and/or private sector R&D costs, as well as the definition of a fair level of profits. To the extent that this policy option would reduce exclusivities and prices, it could also bring benefits in terms of patient access.

**Policy option 3 – redesigning incentives.** This option involves a revision of existing incentives, and proposes some new solutions. The option confirms the role that **patents and SPCs** play under the current framework, but would reduce the scope of data exclusivity and market protection. This option also aims to stimulate R&D directed towards UMN by proposing the use of **SMs managed at the EU level as an additional tool** for ultra-rare diseases (i.e. diseases with particularly low prevalence among those formally defined as rare), and in the context of antimicrobials, de-linking revenues from quantities sold. Efforts to study repurposing of existing medicines would also be incentivised by providing an extension to market protection.

**Policy option 4 – European infrastructure for pharmaceutical R&D.** This option would involve the establishment of a public R&D infrastructure focused on UMN, to better match public health needs with R&D investment and to stimulate the dissemination of results. The European infrastructure could also be

active in conducting independent superiority trials and repurposing studies. The time needed to set up the infrastructure and the significant up-front investment required could pose a challenge, however.

**Policy option 5 – A comprehensive approach.** This option is the most ambitious and combines policy options 1, 3 and 4, and would involve greater EU coordination on IPR and procurement (PO1), a redesign of the incentives (reducing the duration of existing exclusivities, whilst introducing new incentives targeted at UMN – PO3), and the creation of a European infrastructure for pharmaceutical R&D (PO4), complementing private initiatives and by focusing on areas where the private sector is under-investing, relative to public health needs. This combination could allow synergies to be exploited and reduce systemic risk through the diversification of the actors involved in the entire R&D chain.

Policy option 5 is the suggested option. This is because the hurdles identified in the study would require a general reform of incentive schemes and tailored solutions for UMN, which would involve determined EU action and a broader involvement of public actors.



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## List of abbreviations

AMC:	Advance Market Commitment
AMR:	Antimicrobial resistance
APA:	Advance Purchase Agreement
APC:	Advance Purchase Commitments
APPC:	Advance Price or Purchase Commitment
BARDA:	Biomedical Advanced Research and Development Authority
DNDi:	Drugs for Neglected Diseases initiative
EMA:	European Medicines Agency
EPC:	European Patent Convention
EPO:	European Patent Office
EU:	European Union
FDA:	Food and Drug Administration
GDP:	Gross Domestic Product
HERA:	European Health Emergency Preparedness and Response Authority
HTA:	Health Technology Assessment
IP:	Intellectual Property
IPR:	Intellectual Property Rights
JAMRAI:	Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections
OECD:	Organisation for Economic Co-operation and Development
NGO:	Non-Governmental Organisation
NIH:	National Institutes of Health
PCT:	Patent Cooperation Treaty
PPP:	Public-Private Partnership
PRV:	Priority Review Vouchers
PTE:	Patent Term Extension
R&D:	Research and Development
SM:	Subscription Model
SPC:	Supplementary Protection Certificate
TEV:	Transferable Exclusivity Voucher
TRIPS:	Trade Related Aspects of Intellectual Property Rights
UMN:	Unmet medical needs
UN:	United Nations
US:	United States
X	

UK:	United Kingdom
WHO:	World Health Organization
WIPO:	World Intellectual Property Organization
WTO:	World Trade Organization

## Glossary

**Access:** possibility for patients to receive treatments, which requires availability (presence of products in the market) and affordability (in terms of price).

**Advance Purchase Agreement:** pledge to purchase a predetermined amount of product at a predetermined price.

**Biological product:** a product obtained from biological substrates or originating from biological material appropriately modified by genetic engineering.

**Biosimilar product:** generic version of a biological product.

**Breakthrough innovation:** a product that achieves technological dominance over the comparator(s) meaning that it achieves superiority in all the characteristics including efficacy.

**Compulsory licensing:** when the authorities license companies or individuals other than the patent owner to use the rights of the patent – to make, use, sell or import a product under patent (i.e., a patented product or a product made by a patented process) – without the permission of the patent owner.

**Data exclusivity (or data protection):** the exclusive right for the marketing-authorisation holder to use the results of preclinical tests and clinical trials for a given period of time.

**Dynamic efficiency:** ability to create a framework where the incentive to invest in R&D is sufficiently strong, to ensure availability of innovation in the future.

**Exclusivity:** whenever a party is granted the sole rights with regard to a particular business function. Patents, SPCs, market protection, data exclusivity and market exclusivity are all forms of exclusivity.

**Health technology assessment:** an evidence-based process that independently and objectively assesses a new or existing health technology and compares it with other health technologies and /or the current standard of care.

**Incremental innovation (or me-too drug):** product that has similar characteristics to an existing one.

**Innovation prize:** monetary reward or recognition to individuals or organizations that successfully develop groundbreaking products or solutions.

**Knowledge spillovers:** flow of knowledge from one creative party to one or more other parties.

**Market exclusivity:** period of time during which similar medicines (defined as those relying on the same active substance, or on an active substance with the same principal molecular structural features and which acts via the same mechanism) targeting the same disease can enter the market only if they demonstrate clinical superiority (e.g. being safer or more effective) with respect to the product benefiting from the exclusivity.

**Market protection:** period of time during which a generic, hybrid or biosimilar cannot enter the market, even if the medicinal product has already received a marketing authorisation.

**Non-assert declaration:** see 'Patent waiver'.

**Orphan medicinal products:** drugs intended for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect a small number of individuals (rare diseases).

**Parallel trade:** the cross-border sale of pharmaceutical products. For example, traders can buy pharmaceuticals in any EU/EEA country and then, under strictly regulated conditions, sell them at a lower price than the standard local price, in competition with that same identical product sold by the manufacturer or its local licensee. This is possible because prices of individual drugs vary between Member States.

**Patent waiver:** a commitment by the right holder not to enforce certain patents in a defined group of countries or under certain circumstances.

**Priority review voucher:** right to benefit from an accelerated authorisation process that may be transferred from one product to another.

**Pull incentive:** a type of incentive that reduces revenues uncertainty for the producer and increases market attractiveness by creating a viable demand once the therapeutic product has been developed (e.g., subscription models and APAs).

**Push incentive:** a type of incentive to innovation designed to facilitate the transition from research and development stages to commercialisation by reducing the costs of R&D (e.g., subsidies and tax credits).

**Rare disease:** a life-threatening or very serious condition affecting less than 5 in 10,000 people in the EU.

**Repurposing:** is the process of investigating new indications and therapeutic uses different from the ones for which a drug was initially approved. The process may apply also to drugs that were abandoned or failed to be approved for their initial use.

**Supplementary Protection Certificate:** extension of the length of patent protection to recover the time spent in clinical trials and regulatory approvals.

**Static efficiency:** ability to ensure that access to a treatment is granted to all patients for whom the benefits outweigh the costs (without considering R&D costs).

**Subscription model:** lump-sum payment to the manufacturer, delinked from the volume of drugs provided.

**Superiority trial:** investigates whether one treatment is clinically better than another by demonstrating superiority over placebo or an active treatment.

**Transferable exclusivity voucher:** right to extend regulatory protection that may be transferred from one product to another.

**Ultra-rare disease:** a disease with particularly low prevalence among those formally defined as rare.

**Unmet medical needs:** Article 4 paragraph 2 of Commission Regulation (EC) No 507/2006 (about conditional marketing authorisation) defines 'unmet medical needs' as a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.





# 1. Introduction

## 1.1. Background

**Health is a fundamental human right**, as stated in the Declaration of Human Rights and the Sustainable Development Goals of the United Nations. **Achieving equality in access to medicines is crucial to reduce mortality and promote the health of populations** (Khachigian, 2020; Lichtenberg, 1998). On 1 June 2020, the European Commission published a roadmap for a pharmaceutical strategy for Europe, which was subsequently adopted in November 2020. The overall goal of the initiative is to 'help ensure Europe's supply of safe and affordable medicines to meet patients' needs and support the European pharmaceutical industry to remain an innovator and world leader'.

The ability to produce an impact on patients' health through innovation rests on two fundamental conditions: i) the ability to develop new products that are more effective than the existing therapeutic options (**innovation**); ii) the possibility for patients to have access to them (**access**). The ability to achieve these two conditions is the result of a complex interaction among several actors over long periods of time. In the **discovery** of new medicines both **public and private** actors play a role, although they respond to different incentives. On the other hand, the **private** sector dominates in the **late stages of development** of new products.

Pharmaceutical research and development (R&D) processes tend to be lengthy and costly (Wouters et al., 2020; DiMasi et al., 2016), meaning that a private investor would only undertake the process if there exists an expectation of sufficient return on investment. Under the system that is by far most widely used globally, intellectual property rights (IPR) play a key role in incentivising innovation for private companies, by granting a monopoly to the patent holder. The key role played by prices under this system means the two key conditions mentioned above – innovation and access (availability and affordability) – may be hard to reconcile. This makes it challenging to find a **balance** between providing sufficient incentives to invest in R&D (**dynamic efficiency**) and ensuring that price levels are such to ensure products are available and affordable (**static efficiency**).

The system of remuneration of innovation mainly based on patents and regulatory exclusivities (henceforth referred to as exclusivities), is widely adopted on a global scale and led to remarkable results in terms of patients' outcomes (Lichtenberg, 2022). However, it is not without problems. Among the **most widely discussed issues of the current system** are:

- **Innovation is driven by market size** (Dubois et al., 2015; Acemoglu & Linn, 2004) **and is less likely to occur when economic returns are expected to be small** (Iizuka & Uchida, 2017)). As a result, therapeutic areas characterised by small patient populations (e.g., rare diseases), high uncertainty (e.g., Alzheimer and dementia), or limited ability to pay (e.g., neglected tropical diseases) may experience **unmet medical needs (UMN)**.<sup>1</sup> This may lead to a **misalignment between industry's R&D priorities and public health goals**;
- There is discussion on **what a fair level of profitability for the pharmaceutical industry should be**. However, even if there were a consensus on this point, estimating actual returns is more complicated than in other sectors for several reasons. Firstly, a sufficiently precise estimate of the costs of each specific R&D process is needed. However, this is difficult to achieve, because there are costs that are common to several R&D processes and the industry

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<sup>1</sup> As an example, only 1% of clinical trials conducted between 2011 and 2016 involved neglected tropical diseases (Mazzucato & Li, 2021).

retains a clear information advantage vis-à-vis the regulator on the size of these costs. It is no surprise then that the range of available estimates of bringing one product to the market is wide (DiMasi et al., 2016; Wouters et al., 2020). The few comparative estimates of profitability available tend to indicate that returns are higher in the pharmaceutical industry than in other sectors (Ledley et al., 2020; Thakor et al., 2017) even after adjusting for risk. However, the size of this difference should be interpreted with caution (Cutler, 2020). Moreover, on average, figures look more favourable for large companies than for smaller biotech companies (Thakor et al., 2017);

- Even more than in the past, the pharmaceutical industry is characterised by **strong interactions between innovations**, and by a high degree of cumulativeness, so that it is difficult to assess the contribution of each inventor to the innovation process. While in the case of COVID-19 vaccines a lawsuit was considered convenient by many companies because of the high profits generated by these products, in many other cases lawsuits are not filed just because transaction costs exceed expected returns (Williamson, 1979);
- Even in those cases where a product is potentially available in the market, **access is not always granted to patients, even in cases in which public R&D investments play a crucial role**. The issue is exacerbated by the fact that single Member States are responsible for reimbursement and pricing decisions, giving rise to a complex landscape where manufacturers make strategic decisions with potentially serious implications in terms of patients' outcomes. Missing or delayed launches in some countries have a crucial impact on patients' access. Although the length of launch delays has decreased over time (Büssgen & Stargardt, 2022), they are still an issue, especially for small markets and areas where GDP per capita is comparatively low. Moreover, access may be unequal not only across but also within countries, especially when co-payments are high;
- **A large proportion of new medicines offers limited therapeutic advance** in comparison to existing ones. Only a third of new drugs approved by the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) from 2007 to 2017 have high therapeutic value, according to appraisal by independent organisations (Hwang et al., 2020);
- As demonstrated by the COVID-19 pandemic, extreme and unforeseen crises have significant impacts on people's health (roughly 7 million deaths for COVID-19 worldwide, as of July 2023)<sup>2</sup> as well as on healthcare and economic systems (in 2021, global economic growth was still 3.5 % lower than projected before the pandemic) (OECD, 2021). Similar circumstances occur with very low probability but, when they do, they may have tremendous impacts on public health and put health systems under huge pressure. The large uncertainty surrounding the occurrence of such extreme circumstances and the related long-term perspective that is needed to build up **preparedness** makes this an **unattractive area for private R&D investment**. More generally, a risk of underinvestment in prevention vis-à-vis treatments exists (Kremer & Snyder, 2015; Dranove, 1998).

Awareness of these challenges led to the adoption of a number of regulatory provisions. Examples include the introduction of special legislation for the development of medicines for rare diseases and some innovative approaches adopted during the COVID-19 pandemic. An additional source of complexity is the fact that most industry decisions are made adopting a global perspective. This is in contrast with the fact that regulatory decisions are typically made at the national level. Even

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<sup>2</sup> <https://covid19.who.int/>

within the EU, the fact that reimbursement and pricing decisions are still under the responsibility of national authorities has relevant implications. A consequence of this complex landscape is that single regulators cannot ignore the global context when making their decisions.

## 1.2. Objective

The study investigates the **impact of regulatory mechanisms on innovation and accessibility for patients, both in terms of prices (affordability) and availability on the market**. The study also explores which frameworks could be adopted to achieve a proper **balance between static and dynamic efficiency**.

To examine the impact of regulatory mechanisms on public health, this study compares various incentive models adopted to stimulate private R&D in the pharmaceutical sector. The recently proposed EU pharmaceutical legislation aims to stimulate innovation, in particular for unmet health needs, while improving access for patients. To reach this goal, new incentives are proposed in the legislation. This report assesses the advantages and disadvantages of current and alternative incentives that have been considered in the debate.

While public incentives try to stimulate private R&D, other frameworks, such as open science, partnerships and public health infrastructures, may advance pharmaceutical innovation while ensuring accessibility. These frameworks are also presented.

Particular attention is paid to **UMN**, where **the tension between public health needs and private interest is potentially greater**. Three examples of UMN, particularly relevant for the EU market, will be considered:

- **Drugs for rare diseases**. Despite the significant impact of rare diseases on patients, these diseases are often deemed areas of low market potential due to the small patient populations involved. Drugs for rare diseases are called 'orphan', due to the lack of incentives to invest in their development, even when available data suggest they may be effective. Currently, an approved treatment for the specific indication exists for less of 6 % of rare diseases.<sup>3</sup>

- **Antimicrobials**. In the last decades, the antibiotics market has been characterized by low profitability (very few antimicrobials end up being blockbuster drugs) (Monnet, 2005) leading to company and government underinvestment with respect to other drug classes (Glover et al., 2023). This led to a pace of innovation far slower than in other areas, with only 16 % of antibiotics now in the pipeline classified as novel and no new major class of antibiotics discovered since the 1980s (Boluarte & Schulze, 2022). Moreover, less than 5 % of the total venture capital investment between 2003 and 2013 was directed towards antimicrobial development (Renwick et al., 2016). This absence of innovation represents a crucial problem given the rise of antimicrobial resistance (AMR): microbes acquire and transmit drug resistance genes that overpower existing treatments, making them ineffective. This natural evolutionary process is accelerated by an abuse and misuse of antimicrobials (on humans, animals and the environment), often as a result of, and as an easy fix to, lack of proper hygiene and prevention and control measures due to decades of underinvestment in public health services. The Canadian Institute for Health Information (2017) reports that misuse is as high as 60 percent of total consumption in OECD countries (Eswaran & Gallini, 2019). While for antibiotics launched from the 30s' to the 50s' the average time to resistance was 11 years, for those launched in the last 30 years of the 20<sup>th</sup> century it was only two to three years (Boluarte & Schulze, 2022). As a consequence of AMR, the number of people dying is increasing because there is no effective way to treat their illness. **AMR represents a growing global threat that affects both**

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<sup>3</sup> <https://irdirc.org/pluto-project-disregarded-rare-diseases/>

**developed and developing countries.** Given the infective nature of the diseases, the problem cannot be solved locally, since resistant microbes spread from one country to another. A global, inclusive and rapid solution is therefore required. Proper stewardship and monitoring are urgently needed to avoid misuse and overuse of antimicrobials that may aggravate the already-growing AMR (Barlow et al., 2022; Towse et al., 2017). New treatments should be used with utmost care to hinder the spread of resistance. However, this implies that it would be ideal to have a large number of products with very specific targets (Årdal et al., 2020), hence small markets, which clashes with the characteristics of markets that are particularly attractive for the industry under patent protection. Considering the natural process of AMR, a consistent, long-term solution cannot be achieved without sufficient investment in good-quality public health services, relieving the pressure of antimicrobial usage.

- **Drugs for paediatric use.** Children are often treated with off-label medicines. While it was previously considered unethical to involve minors in trials, it is now recognised that there is a **knowledge gap regarding the efficacy and safety of medicines in children as compared to adults.** Paediatric clinical trials present unique challenges related to the small population involved, the procedure for consent, age-dependent pharmacodynamics and pharmacokinetics related to the different stages of development and maturation of young ages. Competences in the design, planning, co-ordination and organisation of paediatric clinical trials are required, and there is a need for specific research infrastructures and networks (Lagler et al., 2021).

This report relies on two pillars: an overview of the scientific and grey literature, and interviews conducted with several stakeholders.

### 1.3. Structure

This report is structured as follows:

Section 2 presents the methodology and resources used for the literature review and the interviews.

Section 3 discusses the results of the literature review, focusing on incentives that are currently used or debated, as well as on alternative frameworks that could be used to grant advancement in pharmaceutical innovation and access.

Section 4 presents the results of the interviews with expert stakeholders.

Section 5 summarises the main findings from the literature review and the interviews (a copy of the questionnaire is reported in Annex 1).

Section 6 presents the policy options, while Section 7 concludes.

## 2. Methodology

The methodology employed to draft the document at hand combines a selective literature/documentary review with interviews conducted with several stakeholders.

### 2.1. Literature review

To guarantee that the literature we identify covers the most relevant issues, both the **academic literature and different types of technical reports** were considered. Once the relevant body of the literature was collected, the documents/publications were classified by topics and keywords.

As for the scholarly literature research, well-established databases such as SCOPUS and PUBMED were used. A **systematic approach** was followed. First of all, a list of the relevant keywords was defined. This list was refined in an iterative process, where the results obtained from applying the search terms to the body of the literature determined whether it is necessary to adjust the terms or include additional ones.

**Publications by the most relevant stakeholders** were also screened. These include publications by the European Commission, the European Parliament and other European Union (EU) institutions, as well as some official publications by the governments of EU Member States. The reviewed literature also includes publications by international organisations such as the Organisation for Economic Co-operation and Development (OECD), the World Health Organisation (WHO) and others. We also considered selected publications by relevant think-tanks, consultancies, as well as patients and industry associations. Additional references were collected following advice provided during the interviews.

To understand and describe the situation characterising different countries, the **relevant legislation** was also reviewed.

We start by discussing the role of patents in pharmaceuticals. In addition to patents, several other tools used, or proposed, by governments to influence companies' R&D decisions are reviewed. These incentives can increase manufacturers' expected revenues upon market entry (pull incentives), or provide upfront support for drug development, lowering barriers to entry, e.g. through subsidies and tax credits (push incentives). They can be general incentives or targeted to specific areas, like paediatric diseases, rare diseases, or antimicrobials. Indeed, in most countries, patents and several other incentives often work together. Other frameworks, such as open science, partnerships and public health infrastructures that may advance innovation are also presented.

### 2.2. Interviews with stakeholders

This part of the study is based on **semi-structured interviews with selected international experts**. The goal of the interviews is to collect informed opinions about possible incentives addressing the objectives pursued through the reform of the EU.

The **following process** was adopted:

1. **Preparation of the questionnaire**, based on the results obtained from the literature review;
2. Adjustment of the questionnaire based on the comments from our counterpart at STOA;
3. **Pilot interviews**, carried out by the principal investigator with the aim of collecting preliminary opinions about the study topic from a selected shortlist of informed stakeholders, as well as feedback on the questionnaire. Pilot interviews took place in July;
4. Recruitment of participants;

## 5. **Interviews**, carried out in July, August and September.

Since no criticality was detected during pilot interviews, the questionnaire was not modified, so that the analysis of the main points discussed during the interviews considers all responses obtained during pilot and full-scale interviews.

A copy of the questionnaire is provided in Annex 1.

### 2.2.1. Participants

Interviewees were identified according to several criteria, including international reputation, their position in key organisations, and their representativeness of different stakeholders. The different group of stakeholders are listed in Table 1.

Table 1 – Number of interviewed experts for each stakeholder group

Stakeholder group	Number of experts interviewed
Researchers, clinicians	5
Pharmaceutical industry representatives	6
Public health experts	8
Public officers	2
Patients' representatives	3

After pilot interviews, a broader enrolment was launched. In total, 35 candidates were identified and contacted. Out of them, **24 (belonging to 23 different organisations) accepted the interview** and their responses are considered complete enough to be analysed.

Table 1 shows the number of interviewed experts belonging to each stakeholder group.

### 2.2.2. Interviews

Potential interviewees were approached via an invitation email with enclosed the letter of presentation from the European Parliament. Upon showing interest to participate by replying to the invitation, the interviewees received the list of questions for the interview. This allowed them to prepare their responses beforehand, which improved the overall flow of the interview session.

All interviewees were asked the same questions; however, depending on the answers they provided, in some cases some additional questions were posed with the intent of further clarifying their views. The interviewees were given the opportunity to decline to answer part of the questionnaire if the question(s) fell outside their competences and expertise areas.

Interviews were conducted via videoconference systems between July and September 2023. Interview sessions lasted about 45 minutes. Interviewees were informed that their replies were recorded (unless consent was denied), but they were assured anonymity in any reports and publications.

### 3. Literature review

This section provides an overview of the literature on the impact and the properties of selected tools that can be part of a regulatory framework aimed at promoting innovation and access in the pharmaceutical sector. The **main criteria** according to which each instrument is assessed are:

- Ability to incentivise or provide **innovation**;
- Ability to orient the **direction of R&D** (e.g. to address UMN);
- **Access**: availability and affordability;
- **Predictability** for generic/biosimilar companies and competitors on when the market becomes contestable.

Most of the instruments considered are part of the existing regulatory framework, whereas others are proposed to address specific shortcomings of the current setup.

#### 3.1. Patents

**Patents** can be granted by a government authority and **confer** for a fixed period of time **the right to exclude others from making, using, or selling the protected invention**. To be granted the patent, an invention must be **new, industrially applicable and involve an inventive step**.<sup>4</sup> In the pharmaceutical domain, patents protect products from generic drug competition until patent expiration, but they do not prevent competition from non-infringing molecules targeting the same disease.

At the global level, **the last decades have witnessed an increase in IPR protection culminating in the multilateral trade agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)**, subscribed by World Trade Organization (WTO) members. With this Agreement, which came into force in 1995, all WTO members agree to provide a minimum standard in the protection and enforcement of IPR. The length of protection is set to 20 years.

An organization seeking protection to its invention in the European countries can follow different procedures, depending on the geographical coverage it is searching for:

- If the organization is seeking protection only in few countries, it can directly apply for national patents to each national office;
- For EU-wide coverage, application can be submitted at the European Patent Office (EPO). Since June 2023, a unitary patent system is available in Europe that strengthens the existing centralised European patent granting system;<sup>5</sup>
- Those organisation seeking wider coverage can apply under the Patent Cooperation Treaty (PCT).

##### 3.1.1. Do patents foster pharmaceutical innovative R&D?

**Patents have long been recognized as a crucial mechanism to incentivize R&D investments in the pharmaceutical industry**. This industry is characterized by **long development time, high uncertainty, knowledge spillovers, and significant R&D costs** associated with establishing the safety and efficacy of new drugs (Prasad & Mailankody, 2017; DiMasi et al., 2016; Henderson & Cockburn, 1993). The cost of developing a new drug, including the cost of unsuccessful projects, is the subject of a lively debate. Estimates range from \$314 million to \$2.8 billion (Wouters et al., 2020).

<sup>4</sup> <https://www.epo.org/applying/basics.html>

<sup>5</sup> <https://www.epo.org/applying/european/unitary.html>

After a product is launched, the **costs of imitation** are significantly lower, allowing generic versions of the original drug to be sold at lower prices and capture a significant market share. Patent protection provides exclusivity and monopoly power to the patent holder, allowing the recoup of R&D investment and the innovation's reward (Magazzini et al., 2009).

**Patents can promote the development of new products and processes in two ways.** Patents act as pull incentives and **provide ex-ante incentives to innovate by securing exclusive rights and monopoly power for a fixed period.** To mitigate the costs to society, patent rights are granted in exchange for the **disclosure of the characteristics of the protected innovation**, thus **fostering the diffusion of knowledge** – that would be otherwise protected by secrecy (Sampat, 2018). **Patent literature** is indeed perceived as a **valuable source of knowledge** in the innovation process (Giuri et al., 2007).

Evidence based on surveys shows that, **absent patent protection, 60% of pharmaceutical sector innovations would not have been introduced**, and 65% would not have been developed (Mansfield, 1986). Patent protection is effective in safeguarding returns for innovative drug development, making it the sector with the highest share of product innovations benefiting from patent protection and secrecy (Cohen et al., 2000). **Among European companies, 79.2% of product innovations** and 45.6% of process innovations **are patented in pharmaceuticals** (average values being, respectively, 35.9% for products and 24.8% for process innovations) pointing to a **higher value of pharmaceutical patents as means for appropriating investments from innovation as compared to other sectors** (Arundel & Kabla, 1998).

Empirical analysis to **assess the role and effect of IPR protection on innovation** have exploited the changes in the stringency of IPR protection due to patent laws across countries and over time. **Results from this empirical literature are heterogenous**, showing positive as well as little/no effect, depending on time periods and sample of countries (Gamba, 2017; M. Liu & La Croix, 2015). Evidence also points to an inverted-U relationship with an **'optimal' level of IPR regulation that, when crossed, may be detrimental to innovation activities** (Qian, 2007).

The effect of patent protection on domestic innovation and R&D investments in pharmaceuticals (as measured with patents and clinical trials) is stronger for developed countries as compared to developing ones (Gamba, 2017; Kyle & McGahan, 2012).

In cancer research, evidence is provided that **expected patent length also drives R&D priorities**. Smaller efforts are recorded for early-stage treatments or cancer prevention that have longer trials (shorter effective patent life) as compared to late-stage cancer treatments (Budish et al., 2015). As a note of caution, the finding may also be related to short-termism of companies, making it difficult to discriminate the two effects.

Contrasting this prevailing view, based on the insights from an evolutionary agent-based model, Dosi et al. (2023b) claim that strong patents may be detrimental to innovation outcome (variety and quality of products) and may hamper industry competition. Patenting and productivity are not correlated, while competition is claimed to be the main factor leading to innovation and greater productivity – not patents (Boldrin & Levine, 2013). Relatedly, because correlation between patents and profitability is found to be more prevalent at the company level as compared to correlation between patents and R&D expenditure, patents are claimed to secure appropriability and monopoly profits rather than incentivise innovation (Dosi et al, 2023a).

Furthermore, **strategic patenting practices** are identified in the context of pharmaceuticals, with companies introducing multiple related patents over the drug lifetime to **extend protection provided by patents and regulatory exclusivities** (known as 'evergreening strategies') (e.g., Garattini, 2022; Gupta, 2020; Gurgula, 2020; Kesselheim, 2011). However, new drug formulations can **improve convenience and tolerability for patients**.



Against this background, **biopharmaceutical research is characterized by a high degree of cumulativeness**, with today's new drugs being also input for follow-on discovery (e.g., reduced side effects or better administration routes). It is therefore **necessary to find the right balance between incentives for first-generation innovation** (in pharmaceuticals, first-in-class compounds) **and follow-on drug discovery** (see the theoretical work of Scotchmer, 1991; Merges & Nelson, 1990).

A case for a 'tragedy of anti-commons' has been advanced, warning about the possibility that proliferation of IPR in biomedical research may undermine downstream development with **'too many' owners blocking each other research efforts** (Heller & Eisenberg, 1998). One strategy to empirically test this claim exploits the citation patterns to scientific discoveries that are also covered by a patent, i.e. 'patent-paper' pairs. Contrasting (both positive and negative) results are provided (Sampat & Williams, 2019; Fehder et al., 2014; Williams, 2013; Murray & Stern, 2007) (see also the discussion in Sampat, 2018). An alternative strategy considers the effect of patent invalidation on the number of (forward) patents' citations.<sup>6</sup> Even if a significant increase in downstream innovation spanning from patent invalidation is reported across all industries, **no significant effect is detected in the case of drugs** (Galasso & Schankerman, 2015). In the EU, to avoid patents blocking science, Member States define research and experimental use exemptions related to research activities (Jaenichen & Pitz, 2015).

Recent studies investigate the effect of Markush patent structure, that is molecular description that do not specify every single molecule, but rather includes placeholders to represent broad sets of chemical (sub)structures. About one quarter of patents filed at EPO from 1992 to 2008 claim a Markush structure. Markush structures are deemed important in maintaining ex-ante incentives to innovate, because they prevent obtaining unpatented substitutes with similar pharmaceutical characteristics. However, Markush structures have a higher potential to hamper follow-on R&D compared to non-Markush patents and to facilitate the construction of broad patent fences (Wagner et al., 2022).

Finally, it is important to mention that IPR (in particular, patents) **facilitate transactions in the 'market for technology'**, which has come to play a central role in innovation within the pharmaceutical sector (Cockburn, 2009). Patents allow a 'division of innovative labour', fostering the interactions between the different actors that populate the pharmaceutical landscape (Kyle, 2022; Arora & Gambardella, 2010).

### 3.1.2. Patents and public health

On the patients' side, **patents can be detrimental to drug access**, by providing exclusive rights and thus **preventing generics' competition**. The tension that emerges between static versus dynamic efficiency is particularly relevant in the pharmaceutical domain, in which **access to medicines is essential to reduce mortality and promote the health of populations** (Khachigian, 2020; Lichtenberg, 1998). This is the reason why the TRIPS Agreement received criticism in its application to pharmaceutical products, previously excluded from patent protection in many emerging economies. To address this concern, the Agreement allows national governments to issue **compulsory licensing** to supply generic versions of patented treatments (through domestic production or imports; in exchange of a royalty fee to the patent holder). In the case of public health

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<sup>6</sup> Even if it is a noisy measure, the use of patent citation as a proxy of knowledge spillover and transfer is widely accepted in the literature, as the fact that patent A cites patent B is taken as evidence that patent A builds upon knowledge embedded in patent B (Jaffe et al., 2000).

crises, compulsory licences can be issued even without negotiating with the patent holder (Doha Declaration).<sup>7</sup>

Against this background, it is questioned whether **the cost of patents implied by reduced access may exceed the benefits in terms of stimulus to innovation** (Boldrin & Levine, 2013; Jaffe, 2000). **From a consumer perspective**, the removal of patent rights would lead to large benefits because of the **greater access to the available drugs**. However, this positive effect **may be offset by the decrease in the future flow of new drugs** (Hughes et al., 2002).

To gain insights on the level of competition spanning from the removal of patents, it is possible to evaluate the market dynamics at patent expiration. When the patent expires, **price competition introduced by generic producers can substantially lower medicine cost**. Based on US data, at the time of entry, generic price is 25% lower than the originator brand price, **further decreasing** to about one-fifth of the initial average generic price **as more generics enter the market** (Kanavos et al., 2008). Correspondingly, the market share of originator brand is eroded (Magazzini et al., 2004; Pammolli et al., 2002). Stricter price regulation, by imposing lower prices, may reduce the scope for generic competition (Danzon & Chao, 2000). **Within the EU, countries are heterogeneous with respect to generic use in the off-patent market** (Kanavos, 2014; Watal, 2014). Furthermore, generic market entry depends on market characteristics, being more likely in markets with larger revenues, more hospital sales, and treating chronic conditions (Scott Morton, 1999). Biotechnology drugs are also subject to 'generic entry', with biosimilars that can enter the market at patent expiration. In 2005, the EU defined a regulatory pathway for approval of biosimilars by the EMA (Grabowski, Guha, et al., 2014). **Diffusion of biosimilars is much slower in Europe as compared to generics** (Böhm et al., 2023).

To facilitate generic entry as soon as the patent expires, the US Hatch-Waxman Act (1984) introduced patent exemptions to allow the use of a patented compound in the preparation of the regulatory data needed to get approval of the generic version of the original drug. These exceptions are commonly referred to as **Bolar provisions**. In Europe, Bolar exceptions were introduced with the Directive 2001/83/EC (Art. 10(6)).<sup>8</sup> Absent the Bolar exception, generic entry would be delayed by 2-3 years or more, even in economies with established generic pharmaceutical manufacturing capability (Watal, 2014). During patent life, **patent waivers, non-exclusive voluntary licences and patent pools may improve drug access** (see Box 1).

At the country level, **patent protection speeds up drug diffusion** (Cockburn et al., 2016) with pharmaceutical product patents increasing the probability of launch of an innovative medicine by 14% (Dai & Watal, 2021). Relatedly, **a decrease in expected market protection** (due to patent invalidation) **leads to a loss in the likelihood of drug approval** (Gaessler & Wagner, 2022). Besides the role of patent protection, health policy institutions and economic and demographic factors are also important: what makes markets more profitable also affect innovation and how quickly new drugs become commercially available (Cockburn et al., 2016; Qian, 2007). An additional source of heterogeneity in the timing of market launch in the EU is due to **price regulation regimes** (Danzon & Chao, 2000; Varol et al., 2012; Kyle, 2006, 2007).

All in all, when reward to innovation relies on patent protection and exclusivities (discussed in the following sections), company profits are linked to market rewards. As a consequence, the current approach to innovation is not apt at stimulating sufficient R&D investments in all the desired

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<sup>7</sup>[https://www.wto.org/english/tratop\\_e/trips\\_e/public\\_health\\_faq\\_e.htm](https://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm).

<sup>8</sup> See <https://cms.law/en/int/expert-guides/cms-expert-guide-on-bolar-provisions> for the application of the Bolar provision in the Member States.

directions. Monopoly power granted by **patents does not sufficiently reward R&D** (and thus, does not sufficiently stimulate research efforts) **in areas where expected revenues are low, even when innovation is urgently needed** (Kyle, 2022; Sampat, 2018), as may be the case of orphan medicinal products and antimicrobials (see Box 2).

## PATENTS



- Well defined way to reward innovation
- Innovation disclosure



- Restricted drug availability and high prices for medicines
- Incentive to innovate increasing with the size of the market
- Room left for strategic behaviour by patent holders to delay generic competition

### Box 1: Patent waivers, non-exclusive voluntary licences, patent pools and accessibility

**When patent owners grant a patent waiver, or non-assert declaration, they commit to refrain from enforcing the patent under certain circumstances or within specific nations.**

This is what Moderna did during the coronavirus pandemic concerning its patents for COVID-19 vaccines (but not for the use of the technology for other emergency and existing diseases) in 92 selected low- and middle-income countries. This, however, had a limited impact on accessibility, since information included in waived patents was not sufficient for generic producers to manufacture their own products, as part of it was covered by secrecy (Garattini, 2022). Moreover, in many cases, the drug may be covered by other regulatory exclusivities, or a single drug may rely on patents belonging to different companies (Garattini, 2022).

**A non-exclusive voluntary licence is an authorization given by the patent holder to numerous manufacturers to create and produce generic versions of the medication. This lowers drug cost.** The licence agreement with generic producers might encompass one or more countries for the distribution of the generic product. In 2016, seven pharmaceutical corporations employed non-exclusive voluntary licences to enable generic versions of their products, targeting communicable diseases such as HIV or hepatitis C (Access to Medicine Foundation, 2018). More recently, non-exclusive voluntary licences were also granted for tuberculosis and COVID-19. In 2020, a total of 22 compounds from 7 pharmaceutical companies were covered by non-exclusive licences. **All licences involve low- and middle-income countries**, with a more pronounced focus on low-income countries (Access to Medicine Foundation, 2021). Indeed, pharmaceutical companies are more inclined to offer voluntary licences at minimal or zero price for less lucrative market (Friedman et al., 2003). **Voluntary licences have substantially improved treatment uptake in eligible countries** (Simmons et al., 2019).

The authorization of non-exclusive voluntary licences may be provided directly to manufacturers through bilateral agreements between the manufacturer and the patent holder. Alternatively, NGOs and international entities, such as the WHO, can be involved in the creation of patent pools and the management of the related voluntary licences. **A patent pool consists of various patents relating to a same technology** (OECD, 2021). Patent pools have existed in other technology sectors for over a century, like electronics, information technology, aviation, and rail

transport, with the purpose of limiting access to the market by other players, or to establish a common technological standard. However, they are relatively novel in the realm of public health, where they have been recently applied to address accessibility challenges in low- and middle-income countries (Galasso & Schankerman, 2022; Burrone, 2018). **In contrast to patent pools in other industries, those in public health operate on a non-profit basis, primarily focusing on humanitarian goals, which include ensuring drug availability.** They additionally tackle the need of paying royalties to multiple patent holders (royalty stacking problem) and reduce transaction costs (Mattioli & Merges, 2017). The initial effort to establish a patent pool for public health aimed at facilitating the development of a vaccine against the SARS outbreaks. However, their sudden disappearance interrupted the experiment, and the pool was never applied (Simon et al., 2005). The Medicines Patent Pool, initiated by the United Nations in 2010, stands as the first successful public health patent pool. While the Pool's current focus is on treating HIV, tuberculosis, and hepatitis C (the latter two were incorporated in 2015) and is more geared toward small-molecule medications than biotherapeutics, there have been calls for an expanded mandate by entities like the WHO and the Lancet Commission on Essential Medicines Policies (Wirtz et al., 2017). The US National Institutes of Health (NIH) were pioneers in licensing their HIV drug patents to the Pool in 2010 (UNITAID, 2010) and by 2018 the Pool held licences for 17 products (Simmons et al., 2019). **The Medicines Patent Pool negotiates licences with patent holders (licensors), stipulating sustainable royalty terms** (royalties were 3 to 5% of generic sales for the products involved in the first licensing agreement signed by the Pool with a pharmaceutical company). **The organization sublicenses these patents, sometimes bundled, to generic manufacturers (licensees), thereby supporting access to treatments in less affluent nations.**

By adopting patent pools, licensors cut negotiation expenses, while licensees benefit from potential search cost economies and reduced negotiation overhead. Furthermore, licences negotiated through the pool encompass the most access-friendly provisions (Access to Medicine Foundation, 2021). The pooling of patent bundles proves especially advantageous for developing and launching new products when the involved patents belong to distinct organizations (van Zimmeren et al., 2011; Van Overwalle, 2009).

**Numerous studies examining the Medicines Patent Pool highlight positive outcomes.** The projected net present value of savings derived from licences for patented antiretroviral medications negotiated by the Medicines Patent Pool until 2028 amounts to USD 2.3 billion. The estimated cost-benefit ratio is 1:43 (Juneja et al., 2017). Moreover, **the Pool has facilitated the innovation of new drug formulations**, diverging from the trend seen in other industries where innovation waned (Lampe & Moser, 2016). **Enhanced drug accessibility is another achievement**, attributed to increased competition among generic manufacturers and, partly, the reduction of information asymmetry about patent coverage (Martinelli et al., 2020). Consequently, also the number of uptakes increases, reducing (Morin et al., 2022). Licensing also increases in countries within the agreement when the patent is included in the Pool, but the impact on actual market entry and sales is more modest (Galasso & Schankerman, 2022). While licensees respond with a greater number of product launches, larger quantities, and lower prices (as corroborated also by Wang, 2020), licensors are less inclined to enter the market. This behaviour could extend the time required for the product to be introduced since, if the originator hasn't registered the product in the country, this challenge transfers to generic manufacturers. Additionally, it's important to acknowledge that smaller markets might dissuade generic manufacturers from entering (Access to Medicine Foundation, 2021).

**Box 2: Patents and antimicrobial resistance (AMR)**

To deal with AMR, drug overuse or misuse should be reduced, and new antimicrobials should be developed. A solution to reduce the incentive for the industry to push intensive use of new antimicrobials might be to grant a permanent patent, which would force firms to consider the effect of misuse on future antibiotic resistance. However, this solution is not efficient in the case of cross-resistance, i.e. when antimicrobial X also reduces the effectiveness of antimicrobial Y (Horowitz & Moehring, 2005). Narrower patents instead may contribute to increase competition and stimulate the creation of substitute drugs. However, additional incentives to innovation would be needed, not dependent on sales, that may complement the patent regime, such as prizes, subsidies and expedited regulatory review (Eswaran & Gallini, 2019).

### 3.2. Supplementary protection certificates

For pharmaceutical products, **the requirement of clinical trials and marketing authorization procedures, needed to assess the quality, safety and efficacy of drugs for human use, erodes the period of protection granted by patents**, so that the length of 'effective' protection is sometimes perceived as inadequate for pharmaceuticals -as compared to other goods. An average of 8 years from the authorization of clinical trials to drug approval in the US over the period 1983-2018 was reported (Darrow et al., 2020). **To overcome patent term lost during trials and authorization procedures, patent holders can apply for a supplementary protection certificate (SPC) on the patent protecting the compound, which allows for the extension of the original patent** (Garattini et al., 2022).

Over the period November 2018-April 2019, the World Intellectual Property Organization (WIPO) undertook a survey on the 'grant and publication of supplemental protection certificates and patent term extensions'. The following patent offices responded to the survey, reporting application of SPC, or Patent Term Extension (PTE) (both measures allow for continued patent protection for certain products) also for pharmaceuticals: Australia, Belgium, Canada, Switzerland, Costa Rica, Czech Republic, Germany, Dominican Republic, Eurasian Patent Organization (EAPO), Estonia, Spain, France, United Kingdom, Croatia, Italy, Japan, Republic of Korea, Republic of Moldova, Russian Federation, Sweden, Slovakia, Ukraine, United States of America; whereas Brazil and China reported not granting SPC or PTE.<sup>9</sup>

In the **US**, the extension of the patent protection is called 'patent term restoration' and it was introduced with the US Drug Price Competition and Patent Term Restoration Act of 1984 (known as the Hatch-Waxman Act). The Act aimed at facilitating entry of generic drugs at patent expiration, while introducing complementary protection for originator products in order to maintain incentives for innovation (Grabowski et al., 2014). All the time spent in the agency phase (time spent by the authorities in reviewing the marketing application) plus half of the time spent in testing the product is eligible for restoration (Copenhagen Economics, 2018), with a **maximum 5-year duration of patent restoration, and the maximum effective patent protection period** (that is, the time between granting of marketing authorisation, and expiry of the patent) **being limited to 14 years**.

**In Europe**, SPCs for medicinal products were introduced in 1992 and amended under the Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009.<sup>10</sup> SPCs enter into force at the end of the statutory 20-year patent protection period and extend patent

<sup>9</sup> See <https://www.wipo.int/standards/en/surveys/spc-pte/collated.html>, accessed May 31, 2023.

<sup>10</sup> See <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R0469-20190701>.

coverage for a time equal to the time elapsed between the filing date of the 'basic patent' and the date of the first market authorisation<sup>11</sup> of the medicine, reduced by a period of 5 years. **SPCs can be granted for a maximum of 5 years, while the effective patent protection period cannot exceed 15 years. SPCs are granted nationally**, even if there is a **proposal** to create a **unitary SPC title at the EU level**, in place of national SPCs, in accordance with the new unitary patent system of the European Patent Office.<sup>12</sup> Application for an SPC on a product patent can be made within six months from the marketing authorization in any Member State (EU Commission, 2009). SPCs are intended to extend the 'basic patent' only, i.e., the product should not have already benefited from an SPC.<sup>13</sup> A further extension of six months can be granted to compensate companies for the obligation to conduct paediatric studies for every product developed, independently from the outcome of the trial.<sup>14</sup> To foster generic competition, the recent amended EU regulation (2019) introduces a 'manufacturing waiver' to allow generic and biosimilar production for export to third countries and a 'storing' option permitting generic production six months pre-SPC expiration to prepare generic products for market launch in the EU (de Jongh et al., 2021).

As in the case of patents, the functioning and impact of SPCs is debated. On the one side, it is argued that **restoration of patent terms lost during trials and regulatory review is needed to ensure sufficient return on pharmaceutical R&D expenditures and to sustain the flow of future drug introduction**.

On the other side, scholars pose questions on the **negative impact of SPCs on timely access to affordable medicines** (Hu et al., 2020), **since they delay even further the entrance of generic competitors** (Beall et al., 2019). A case study based on three molecules (sofosbuvir, trastuzumab and imatinib) provides evidence that SPCs exclusivity can **delay competition and maintain high medicine prices in European countries** (Hu et al., 2020).

**Drug development time is increasing in Europe, implying a decreasing effective patent protection period, making SPCs more relevant over time** (Copenhagen Economics, 2018; Kyle, 2017). Indeed, in the period 1990-1994, 75% of new drug introductions in continental Europe had an SPC in at least one country, and on average, an SPC in 6-7 countries. In more recent periods (2010-2016), the share is 86%, and each drug has on average an SPC in 18-19 countries. This evolution is driven by an increase in the percentage of drugs which can benefit from the SPC (having a drug development time included between 5 and 15 years), as well as by the expansion of the EU and the increased tendency to apply for SPCs in smaller markets. This pattern notwithstanding, there exists substantial heterogeneity across Member States in the number of SPC applications and in the probability that an SPC is granted: on average, the share of SPC application over patents is 27.1% (ranging from 15.6% in Croatia to 39.6% in Norway); of these, 75.8% have been granted (Kyle, 2017; our computation on Table 19). Related to this, **the proposal of a unitary SPC system may reduce**

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<sup>11</sup> This implies that only products with a valid marketing authorisation can benefit from SPCs.

<sup>12</sup> [https://ec.europa.eu/commission/presscorner/detail/en/qanda\\_23\\_2455](https://ec.europa.eu/commission/presscorner/detail/en/qanda_23_2455).  
[https://single-market-economy.ec.europa.eu/publications/com2023222-proposal-regulation-unitary-supplementary-certificate-medicinal-products\\_en](https://single-market-economy.ec.europa.eu/publications/com2023222-proposal-regulation-unitary-supplementary-certificate-medicinal-products_en)



<sup>13</sup> Generally, multiple patents are associated with a new medicine. The primary (basic) patent protecting the new compound is filed first, early in the R&D process. Then, "secondary" patents (protecting, for example, dosage forms and use) may also be filed.

<sup>14</sup> In the US, this obligation is rewarded with 6 months of exclusivity. Importantly, in this case exclusivity is granted to all products (independently from the formulation, the dosage and the indication) with the same active moiety for which the paediatric study has been carried out. In addition, it does not run concurrently with other forms of protection (such as patents and regulatory protection), but it adds to existing patents or exclusivity, whichever expires at the latest date (thus, it may imply extra 6 months of patent protection, or market exclusivity, or data exclusivity) (Wroblewski et al., 2009).

**the uncertainty related to the availability of national SPCs.** Heterogeneity is also detected in terms of generic entry and time lag, with markets that are unattractive to originators also unattractive to generics, and the average lag between the expiration of legal protection and generic launch ranging from few months (Finland, Austria and Netherlands) to almost 3 years (Slovenia and Bulgaria; Kyle, 2017; Table 20).

All in all, empirical evidence of the effects and impact of SPCs is scant. **A clear answer as to whether SPCs provide the right balance between R&D incentive and drug access is still missing.** However, the SPC regulation has been recently evaluated by the European Commission<sup>15</sup> (de Jongh et al., 2021; Copenhagen Economics, 2018; Kyle, 2017). SPC Regulation appears to support research on new active ingredients and has brought EU added value (de Jongh et al., 2021).

#### SUPPLEMENTARY PROTECTION CERTIFICATES

	<ul style="list-style-type: none"> <li>• Compensation of patent length lost due to clinical trials</li> </ul>
	<ul style="list-style-type: none"> <li>• Delayed generic entry and competition</li> <li>• Incentive to innovate increasing with the size of the market</li> <li>• Complexity due to country level decisions</li> <li>• Limited predictability for generic/biosimilar companies and competitors on when the market becomes contestable</li> </ul>

### 3.3. Data exclusivity, market protection, market exclusivity

Although **not required by the TRIPS Agreement**, several countries (including EU Member States, Canada, China, Chile, Colombia, Japan, Malaysia, Taiwan, South Korea, Taiwan and the US) provide a few regulatory instruments of protection. Like patents, these tools provide a **temporary exclusive right as a compensation for R&D costs and/or as an incentive for innovation**. These additional forms of protection differ in the terms of protection, as well as in the scope of protection, and **they may overlap. Similarly, they add to patent protection, can overlap with it, can run concurrently with it and can exist even in the absence of a patent (they can be granted even to unpatentable products)**. The names of these tools vary from country to country. In what follows we consider the terminology used in the EU. Importantly, while these tools represent different incentives in Europe, in other countries (such as the US) the differences among them are less straightforward.

#### 3.3.1. Data exclusivity

To obtain marketing approval for a drug, the applicant must demonstrate, through preclinical and clinical tests data, the quality, efficacy and safety of the drug. The production of such data is costly and time-consuming: for this reason, several countries protect them using data exclusivity. Data exclusivity, or data protection, **grants the marketing-authorisation holder the exclusive rights to use the results of preclinical tests and clinical trials for a given period of time**. During this period, a third-party applicant cannot rely on these data for the purposes of submitting an application, obtaining marketing authorisation or placing the product on the market. After the

<sup>15</sup> [https://single-market-economy.ec.europa.eu/industry/strategy/intellectual-property/patent-protection-eu/supplementary-protection-certificates-pharmaceutical-and-plant-protection-products\\_en](https://single-market-economy.ec.europa.eu/industry/strategy/intellectual-property/patent-protection-eu/supplementary-protection-certificates-pharmaceutical-and-plant-protection-products_en)

expiration of the data exclusivity period, the marketing authorisation holder is obliged to release information concerning preclinical tests and clinical trials to companies wishing to develop generic versions of the medicine. Differently from patents, data exclusivity is granted automatically when the marketing authorisation is granted, and it is enforced through the regulatory system.

According to the **TRIPS Agreement**, members of the agreement shall protect data, required as a condition for marketing approval and the origination of which involves a considerable effort, against unfair commercial use and disclosure (Article 39.3). However, **no data exclusivity obligation is set**, so differences emerge among countries.

Data exclusivity was firstly introduced in the **US**, in 1984, through the Hatch-Waxman Act (although the term 'data exclusivity' was not used). Protection lasts **five years and is provided for new chemical entities**. During the exclusivity period the FDA cannot accept applications from other manufacturers relying on originator's data for their submission (Wroblewski et al., 2009). **A data exclusivity period of four years is also granted to biologics** (PHS Act).<sup>16</sup>

**The EU** introduced data exclusivity in 1987, and at present it **provides the most extensive data exclusivity regime in the world**. Under the current legislation (Article 14(11) of Regulation (EC) No 726/2004), the data exclusivity period lasts **eight years** from the first marketing authorisation granted in the EU. Data exclusivity is granted only once for each product. To limit evergreening strategies, if a company obtains a new marketing authorisation for the same product (for example for a different strength, form, administration route), this does not trigger a new period of exclusivity since each subsequent authorisation falls within the same Global Marketing Authorisation. Still, a non-cumulative period of one year of data exclusivity is granted where an application is made for a new indication for a well-established substance (that is, a substance for which at least 10 years have elapsed since the granting of the first marketing authorisation), provided that significant preclinical or clinical studies were carried out in relation to the new indication (Art. 10(5), Dir. 2001/83/EC). Moreover, where a change of classification of a medicinal product has been authorised based on significant preclinical tests or clinical trials, one year of market exclusivity is granted for those tests or trials (Art. 74(a), Dir. 2001/83/EC). This extra protection should incentivise a change of classification or the development of new indications. In the proposal for a new EU pharmaceutical legislation, the length of data, as well as market exclusivity, would depend on the characteristics of the products and their fulfilment of given criteria (art. 71 and art. 72 of the Regulation, and art. 81 of the Directive). **Linking the extension of the protection to the product's effectiveness and price could incentivise the development of high impact, low-cost products** (Beall et al., 2021). For example, access could be enhanced by granting longer exclusivity if prices are lower.

**A data exclusivity period of six years is provided also in Canada** (Copenhagen Economics, 2018).

**Japan** provides a **post-marketing examination period during which no other company can apply for marketing authorisation using data provided by the originator company**. The goal of this measure is to provide a timespan during which the efficacy and safety of the drug is tested on a larger population. **The length of the examination period varies**: it is 8 years for new active entities, 4 years for new indications of existing drugs (if less than 4 years remain of the original period), 6 years for new routes of administration, and 10 years for orphan medicinal products (as an incentive for these products) (Copenhagen Economics, 2018). Moreover, there-examination period

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<sup>16</sup> In Europe no special rules apply for biologics.



may be extended by two years for the production of paediatric data (but it may not exceed a total of 10 years).<sup>17</sup>

Also in **South Korea**, a **post-marketing examination period** applies, lasting 6 years for new drugs, new routes of administration or new combination drugs; 4 years for new indications; 10 years for orphan medicinal products.<sup>18</sup>

Many middle-income countries do not provide data exclusivity. Sixteen countries do (among which China, Malaysia, Chile, Colombia), and the origin of these regimes often are free trade agreements with the US or the EU (Copenhagen Economics, 2018; 't Hoen, 2022).

The goal of data exclusivity is to protect the economic investments made by originator companies to run preclinical and clinical tests, and to stimulate further innovation. However, **data exclusivity seems to have limited effect in stimulating innovation** (de Jongh et al., 2018; Wroblewski et al., 2009), **although evidence is not exhaustive**. Indeed, since data exclusivity adds to patents, SPCs and market protection, it is difficult to disentangle its effect on innovation. Nonetheless, a limited effect on innovation may find different justifications. Firstly, data exclusivity has two opposite effects on innovation. **On the one hand it stimulates innovation by providing a monopoly on the use of data, while on the other hand it limits subsequent incremental innovations**. Indeed, data produced by the originator could be useful also for other companies to develop derivative, but not equivalent, drugs. Differently from patents, data exclusivity does not stimulate subsequent innovation through disclosure and consequent dissemination of scientific and technical information. For this reason, to the extent that data exclusivity replaces the need for the patent (which, however, does not seem to represent the current situation) a negative impact on innovation may emerge. Secondly, **innovation may have already been incentivised through patent** (Wroblewski et al., 2009). Thus, a **stronger impact on innovation may be expected for unpatentable products**, such as molecules in the public domain (Roin, 2009).

**Data exclusivity has a strong impact on generic and biosimilar companies. Indeed, these companies can rely on data generated by the brand-name manufacturer to achieve regulatory approval for their medicines** ('abridged procedure' in Europe, or 'abbreviated new drug application' in the US).<sup>19</sup> However, this option is precluded during the data exclusivity period. During this period, generic companies can still apply for marketing authorisation if they generate their own data by running clinical tests. However, this would affect generics' prices, given the high costs of producing these data, and present ethical issues, since some patients involved in the (unnecessary) clinical trials would be excluded from a proven effective treatment ('t Hoen., 2022). Thus, de facto, generic companies do not file for a marketing authorisation during the data exclusivity period. Therefore, **data exclusivity may delay generics' entry, implying additional costs to the health system**. This delay is even more salient for biosimilar drugs, for which the comparability studies require a degree of clinical research which may last longer than simply prove the chemical equivalency, as for small molecule generics; on the other hand, biologicals already benefit from a sort of natural monopoly, given their complexity of production (de Jongh et al., 2019). Moreover, **since regulatory agencies typically need at least a year to review an application, competition is postponed by more than the length of the data exclusivity period**.

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<sup>17</sup> <https://www.iam-media.com/global-guide/global-life-sciences/2020/article/market-exclusivity-pharmaceutical-products-in-japan>

<sup>18</sup> <https://thelawreviews.co.uk/title/the-pharmaceutical-intellectual-property-and-competition-law-review/south-korea>

<sup>19</sup> According to Art. 30 of the TRIPS Agreement (also known as "Bolar provision"), States may allow generic companies to do research on patented products and to use the patented invention to obtain marketing approval before the patent has expired.

Another consequence concerns the use of TRIPS flexibilities. Indeed, **few countries providing data exclusivity also provide waivers to it in case of emergency or public health need** (among these, Chile, Colombia, Malaysia, Panama, Peru, the US) (see 't Hoen, 2022). **The absence of waivers to data exclusivity may limit the use of flexibilities provided by the TRIPS Agreement on patent protection.** The reason is that, while a government, through compulsory licences, may authorise a generic company to produce and commercialise a patented product, data exclusivity may prevent the generic companies from using the originator test data to obtain the marketing authorisation, thus blocking its entrance into the market. In Europe, where waivers to data exclusivity are limited to the case of compulsory licences to address third countries needs for affordable medicines (Article 18, Regulation (EC) No 816/2006), the current European legislation on data exclusivity interferes with the Member States right to issue compulsory licences and to determine the grounds for granting them. The recent proposal for a new general pharmaceutical legislation would partly solve this concern by providing the suspension of data exclusivity (and market protection) when a compulsory licence is issued by the European Commission to tackle a public health emergency. In June 2022, the WTO adopted the Ministerial Decision on the TRIPS Agreement ('WTO Decision')<sup>20</sup>, which allowed the use of protected clinical trial data for regulatory approval of vaccines. While this waiver has helped some countries, like India, where already-existing infrastructure could facilitate an increase in manufacturing capacity, other countries have not benefited from it.

All these drawbacks are particularly relevant if all social costs of experimentation are considered, including those incurred by patients participating in clinical trials (Gøtzsche, 2011). Indeed, **through data exclusivity, data stop belonging to patients, and become the property of pharmaceutical companies for a given period of time.**

**An alternative to data exclusivity may be a 'data compensation regime', in which the originator company receives adequate compensation for the use of data by other companies, but cannot deny it** (Boulet et al., 2019), similarly to compulsory licences for patents. This regime would be compliant with TRIPS requirements.

#### DATA EXCLUSIVITY



- Stimulus to innovation for unpatentable products



- Limited impact on innovation
- Potential delay of generic entry depending on expiration date relative to patents and SPC
- Limit to the use of TRIPS' flexibilities
- Delayed generic entry and competition
- Incentive to innovate increasing with the size of the market
- Complexity related to country level decisions
- Additional complexity related to the overall extent of protection

<sup>20</sup> <https://docs.wto.org/dol2fe/Pages/SS/directdoc.aspx?filename=q:WT/MIN22/30.pdf&Open=True>

### 3.3.2. Market protection

Market protection grants to the marketing-authorisation holder a **period of time during which a generic, hybrid or biosimilar cannot enter the market, even if the medicinal product has already received a marketing authorisation.**

Although market protection limits competition, it does not completely protect companies against it. **Originators with distinct products for the same indication may enter the market**, giving origin to originator-originator competition.

In the **US**, multiple types of 'exclusivities' exist that, differently from Europe, do not run concurrently. Thus, while some products benefit from a sort of data exclusivity, others benefit from market protection. **Previously-adopted medicines for which a new indication is approved**, excluded those benefiting from an abridged procedure, benefit from **three years of protection**: during this period, generic companies can still submit an abridged new drug application, but FDA cannot approve it (Hatch-Waxman Act).<sup>21</sup> **Twelve years** of market protection are also granted to **biologics** (Biologics Price Competition and Innovation Act of 2010) (U.S. Department of Health and Human Services et al., 2014), to compensate for the very lengthy development process.<sup>22</sup> In this case, market protection and data exclusivity run concurrently. Finally, under the Generating Antibiotic Incentives Now Act (2012), **antibiotics also benefit from a five-year extension of the patent or market protection**, whichever expires at the latest date (Copenhagen Economics, 2018; Outtersson & McDonnell, 2016).

In **Canada** the market protection period lasts **eight years** and can be extended by **six months if paediatric studies are undertaken** (Copenhagen Economics, 2018).

In **Europe**, under the current legislation, the market protection period lasts **10 years from the first marketing authorisation granted in the EU**, but may be extended to 11 years if, 'during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies' (Article 14(11) of Regulation (EC) No 726/2004). This extension cannot be cumulated with those for data exclusivity.

In most countries offering market protection (such as Europe and Canada, the exception being the US), this runs in parallel with data exclusivity and has a longer duration. The rationale for this is to give the generic company the possibility to obtain the marketing authorisation during the period covered by market protection for the originator product, but not by data exclusivity, so that the generic product can be put on the market as soon as the market protection period expires, without further delay (if IP protection has already expired). Thus, **in the case of Europe, from the 8<sup>th</sup> to the 10<sup>th</sup> year from the marketing authorisation of the branded product, the producers of generics, hybrids, and biosimilars can apply and obtain a marketing authorisation using the abridged procedure.** Also pricing and reimbursement policies may be carried out for the generic, hybrid or biosimilar product. However, this **cannot be sold on the market until the market protection period ends and potential patents and SPCs expire.**

Market protection guarantees the innovator company a minimum of intellectual property protection of its new medicinal product for a given period, even if the original patent and the SPC

<sup>21</sup> <https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-new-drug-product-exclusivity>

<sup>22</sup> <https://www.allucent.com/resources/blog/types-marketing-exclusivity-drug-development#:~:text=Biologic%20exclusivity%20conveys%2012%20years,an%20application%20may%20be%20ap%20proved>

would sum up to a shorter time. Thus, **whether market protection brings marketing authorisation holders extra benefits with respect to patents and SPCs, and thus extra incentives to R&D, depends on the timing of the patent filing with respect to the product lifecycle.** If a short time elapses from the patent grant until the product is marketed, patent protection would provide the longest period of protection.<sup>23</sup> Thus, **the relevance of this incentive mainly depends upon the time needed for the company to run pre-clinical and clinical tests, as well as on the length of the regulatory process.** Since these timespans are particularly long<sup>24</sup>, and according to some evidence might also be increasing (in Europe the time that elapses from patent filing to marketing authorisation increased from 10 years in 1996, to 15 years in 2016) (Copenhagen Economics, 2018; Kyle, 2017), this incentive may be relevant. As highlighted by the Copenhagen Economics' report, **for 39% of the 558 unique products considered in the analysis, data exclusivity or market protection were the last measures of protection to expire, bringing on average 4.8 years of additional protection with respect to patents and SPCs.**

Like patents and SPCs, market protection **interferes with competition, possibly delaying generics' entry, although it does not prevent originator-originator competition.** However, since the incumbent company may dump the price to avoid competition, it is **plausible that new products are developed only for highly profitable markets, in which expected profits may be high enough despite competition.** Moreover, like for patents and SPCs, the value of the incentive increases with the size of the market, being lower for example for less common diseases (Gamba et al., 2021).

In Europe, where patents, SPCs and marketing authorisation are granted at the national level, a product may be covered by market protection in one country, by patent protection in another, and by an SPC in a third country. Similarly, the end of IP and regulatory protection may differ from one country to another. This generates further uncertainty for generic companies. This situation may improve with the creation of a European patent and with the potential creation of a unitary SPC at the European level.

### MARKET PROTECTION



- Stimulus to innovation for unpatentable products
- Additional stimulus to innovation depending on expiration date relative to patents and SPCs
- Incentive to innovate increasing with the size of the market



- Potential delay of generic entry depending on expiration date relative to patents and SPCs
- Additional complexity related to the overall extent of protection

<sup>23</sup> For example, in Europe, if a product experiences 3 years from the patent grant until the medicine receives the marketing authorisation, it will be protected from generic competition for 17 years by the patent. In case the number of years between obtaining the patent and marketing authorisation is 18, the product will be protected from generic competition for 10 years, thanks to market protection (versus the 2 years left from patent protection).

<sup>24</sup> Practices such as conditional marketing authorisation for UMN are meant to reduce these timespans.

### 3.3.3. Market exclusivity

**Market exclusivity grants protection from similar medicines** (defined as those relying on the same active substance, or on an active substance with the same principal molecular structural features and which acts via the same mechanism) **targeting the same disease**. To enter the market, a new medicine with the same indication must demonstrate non-similarity or clinical superiority (e.g., being safer or more effective) to the product benefiting from exclusivity.

Market exclusivity is commonly used to **incentivise the development of orphan medicinal products and paediatric studies**. It runs in parallel with normal rules on data exclusivity, market protection, and IP rights.

Introduced in the **US** in 1983 as a stimulus for **orphan medicinal products** and those with no hope of recovering the initial investment (independently from prevalence), market exclusivity lasts **seven years** for the orphan indication.

In the US, market exclusivity is also granted for other products. Since 1997, **6 months of exclusivity (FDA Paediatric Exclusivity Extension) incentivise companies to conduct trials in paediatric populations** and are granted independently of the study outcomes. Exclusivity protects against all other formulations, dosage forms and indications containing the same active moiety. It adds to existing patent or regulatory exclusivities, whichever expires at the latest date.<sup>25</sup>

Under the Hatch-Waxman Act, the first generic drug applicant to submit a generic application that includes a challenge to the brand-name drug's patents may be eligible for six months of exclusivity (Brougher, 2010).<sup>26</sup> According to the Biologics Price Competition and Innovation Act of 2010, market exclusivity is also provided for the **first approved biosimilar product**, granting **12 to 42 months of exclusivity**, depending on a number of factors. **This compensates the first biosimilar products for the risk of defending a patent infringement suit** (Copenhagen Economics, 2018; Brougher, 2010).<sup>27</sup> Only at the end of this period other biosimilar products can enter the market.

In the **EU**, the current legislation (EU 'Orphan' Reg. No 141/2000) (EU Parliament, 2000) grants **10 years** of market exclusivity from the authorisation of the medical product. During this period, the EMA cannot consider applications for similar products (de Jongh et al., 2019). **Orphan medicinal products receive stronger protection** compared to products for more common diseases (10 years of market exclusivity compared to 8 years of data exclusivity and 2 additional years of market protection). The holder of the marketing authorisation for orphan medicinal product can still benefit from the 11<sup>th</sup> year of market protection or an extra year of data exclusivity if the requirements mentioned in Article 14(11) of Regulation (EC) No 726/2004 or conditions described in Art. 74(a), Dir. 2001/83/EC or Art. 10(5), Dir. 2001/83/EC are satisfied. The 10-year market exclusivity can be extended by **two years for completing a paediatric investigation plan**. Instead, if the product receives an authorisation for a new indication for a separate orphan designation, the product is granted 10 years of market exclusivity with respect to this new indication starting from the authorisation for the new indication. If the criteria are no longer met after five years on the market, the market exclusivity can be reduced to six years. After the six-year period, the marketing authorization holder can still benefit from two years of data exclusivity and two years of market protection (along with possible additional years) (de Jongh et al., 2019; EU Parliament, 2000).

<sup>25</sup> <https://www.fda.gov/drugs/development-resources/qualifying-paediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently>

<sup>26</sup> <https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity#howlongexclusivity>

<sup>27</sup> No specific incentives are available in Europe for these drugs.

The use of market exclusivity to incentivise **paediatric studies** in the US has provided important information about drugs' safety and effectiveness in children, but there is evidence of **overcompensation of trial costs** (Sinha et al., 2018). Alternative incentive schemes for such studies, such as direct public funding, should be considered.

In Europe, 30% of authorised orphan medicines had no patent or SPC at the start of the exclusivity period, resulting in a full 10-year additional protection. However, **for 48.3% of authorised orphan products, the market exclusivity period ends before the patent or SPC**. For the remaining 21.7% of orphan products, the patent or SPC expired during the exclusivity period, providing an average of two years and three months of additional protection (de Jongh et al., 2019).<sup>28</sup>

Orphan products undergo a centralised marketing authorisation procedure at the EU level, and the exclusivity period begins upon authorisation. This should encourage companies to place the product on the market in all EU countries at once, in order to benefit from the full period of protection. However, **disparities persist among EU Member States, with 126 orphan medicinal products available on the German market, while only 32 available in Lithuania in 2018** (de Jongh et al., 2019). Differences in national reimbursement systems, pricing policies and companies' strategic decisions contribute to these variations.

**Market exclusivity not only delays generic entry, but also hampers the development of competing alternatives**, leading to market concentration and **strong bargaining power** for companies during price negotiation (Côté & Keating, 2012). This can **negatively impact patients who, for clinical reasons, do not benefit sufficiently from the existing product** ('t Hoen, 2022). In Europe, most **rare diseases** with authorized treatments have only one available product (de Jongh et al., 2019). However, market exclusivity is not the primary reason for this; rather, factors such as time and market size play a significant role (Côté & Keating, 2012). **Generic competition is often limited even after regulatory protection expires, granting companies an extended monopoly** (de Jongh et al., 2019).

The possibility of benefiting from market exclusivity may provide an unintended incentive for manufacturers to pursue the so called '**salami-slicing**' strategy, **by creating artificial subsets of non-rare diseases**. This strategy could become even more relevant in the future, with the emergence of personalised medicine. Another strategy deals with '**indication stacking**': **companies seek an orphan designation for the same product more than once, for different orphan indications, since each entitles the product to a period of market exclusivity for the new indication**.<sup>29</sup> Although the repurposing of existing drugs for new indications is clearly positive both for patients and for companies, concerns about the instrument of exclusivity arises since, as a consequence of these strategies, **exclusivity is granted even to highly profitable products and to drugs with a substantial market size** (Côté & Keating, 2012): 15% of orphan medicines sold in Europe have annual sales revenues exceeding euro 100 million (de Jongh et al., 2019). The European Orphan Drug Regulation formally provides a countermeasure to this, through the re-assessment of the orphan designation after five years (Article 8(2)). However, this re-assessment is done against the original criteria on which the product was designated. Thus, if the drug was granted the orphan designation based on a prevalence assessment (as all but one orphan medicinal product authorised in the EU) (de Jongh et al., 2019), it will maintain its designation even if it is a highly profitable product, or if new indications have been discovered. Moreover, the shortening of the exclusivity period needs to be invoked by a Member State, and this is seldom done (de Jongh et al., 2018).

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<sup>28</sup> Data exclusivity and market protection were not considered in the analysis, but given their duration these protections would almost never exceed the protection offered by market exclusivity.

<sup>29</sup> Differently from what happens for the other forms of regulatory protection, the European legislation does not introduce the concept of global marketing authorisation for market exclusivity.

Another consequence of these strategic behaviours is to make entry by competitors less likely due to the **uncertainty and complexity related to the multiplicity of market exclusivities for the same active principal ingredient** (de Jongh et al., 2018). Nevertheless, this problem should not strongly affect Europe, where the extent of the 'indication stacking' phenomenon seems to be limited: most authorised products (86%) have a single orphan designation (de Jongh et al., 2019).

It is important to notice that the conditions to be defined an orphan medicinal product are determined at the country level (or at the European level, in case of European countries). Thus, a product may be defined as orphan in one or more countries even though, at the world level, the product has a substantial market size and grant relevant profits. Moreover, since there is a considerable overlap between orphan designations between the EU and the US (less between the EU and Japan) (de Jongh et al., 2019), **orphan products may benefit from the incentives provided by different countries.**

**In addition to market exclusivity, several countries offer other incentives to stimulate the development of orphan medicinal products**, including tax credits, reduced application fees, protocol assistance and subsidies for clinical trials (see Table 2, which compares the incentives provided in the three largest markets), in addition to research funding.<sup>30</sup> Other countries, such as Australia<sup>31</sup> and Singapore<sup>32</sup>, provide these other incentives, but no market exclusivity.

Several studies demonstrated the **positive effect of orphan legislations in stimulating R&D towards rare diseases** (see Braun et al., 2010; Lichtenberg & Waldfogel, 2009; Yin, 2008 for evidence about the US and Westermarck, 2011 for the EU). Importantly, however, **incentives adopted for rare diseases may have contributed substantially to widening the gap between more and less rare diseases classified as orphan**, with the majority of new orphan medicinal product approval being concentrated in therapeutic areas characterised by a relatively higher prevalence (Gamba et al., 2021). Pull incentives may exacerbate this tendency, by relying on market size (see Box 3).

For the same reason, **although several diseases affecting developing countries are classified as orphan in developed countries, the current incentives scheme do not stimulate R&D for these pathologies.** Indeed, the grant of exclusivity in the developed country has a limited effect if the burden of disease is concentrated in countries other than the one granting exclusivity (WHO, 2006). **The same holds for orphan paediatric diseases for which there is no adult indication** (Connor & Cure, 2011; de Jongh et al., 2018).

<sup>30</sup> At the European level, research funds are provided both by Member States and by the European Commission.

<sup>31</sup> [https://www.tga.gov.au/how-we-regulate/supply-therapeutic-good/supply-prescription-medicine/application-process-prescription-medicines/orphan-drug-designation#:~:text=An%20orphan%20drug%20is%20a,of%20Therapeutic%20Goods%20\(ARTG\).](https://www.tga.gov.au/how-we-regulate/supply-therapeutic-good/supply-prescription-medicine/application-process-prescription-medicines/orphan-drug-designation#:~:text=An%20orphan%20drug%20is%20a,of%20Therapeutic%20Goods%20(ARTG).)

<sup>32</sup> [https://www.orpha.net/consor/cgi-bin/Education\\_AboutOrphanDrugs.php?lng=EN&stapage=ST\\_EDUCATION\\_EDUCATION\\_ABOUTORPHANDRUGS\\_SIN](https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_SIN)

Table 2 – Comparison of orphan drugs regulations in the US, Japan and the EU

	US (1983)	Japan (1993)	EU (2000)
<b>Rare disease:</b>	< 200 000 in US (6.25/10 000) or not profitable	< 50 000 in Japan (4/10 000)	< 5 in 10 000 in EU or not profitable, and life-threatening and without other treatments authorised (or adding significant benefits)
<b>Main incentives:</b>			
tax credits	Yes (25% clinical costs)	Yes (6% clinical and non-clinical costs)	Member-State specific
exclusivity	7-year market exclusivity	10-year market exclusivity	10-year re-examination period
reduced application fees	Yes (waved)	No	Yes (reduced)
protocol assistance	Yes	Yes	Yes
subsidies for clinical trials	Yes	Yes	No



**Box 3: Orphan drugs legislation and R&D incentives for rare diseases**

Gamba et al. (2021) combine theoretical and empirical analysis to evaluate the effectiveness of existing incentives for R&D targeting rare diseases, with a focus on the difference between push and pull incentives. The theoretical findings indicate that **both pull and push incentives tend to favour diseases with higher prevalence within the class of rare diseases, although the impact is more pronounced for pull incentives.**

The empirical analysis uses FDA orphan designations granted from 1983 to 2016 as a proxy for R&D efforts. The overall, positive impact of orphan legislation (starting from the one introduced in the US in 1983) shown in some previous analyses (Westermarck, 2011; Braun et al., 2010; Yin, 2008) is confirmed. However, a significant majority of rare diseases still lack approved treatments for their indications.

Unlike previous analyses, Gamba et al. (2021) specifically examine the distribution of R&D efforts among rare diseases with different prevalence levels. The empirical results showed that the increase in R&D efforts primarily focused on less rare diseases within the orphan class. The estimated difference between the predicted number of orphan designations per year for a disease in the highest and the lowest class of prevalence was 5.6 times larger after 2008 than in the period 1983-1992. These findings align with the theoretical predictions regarding the impact of different incentive types, particularly pull incentives. A simulation, based on a model calibration, suggests that replacing a hypothetical system purely based on pull incentives with one based only on push incentives, keeping the total number of new designations constant, would substantially increase the likelihood for patients with ultra-rare diseases (i.e., diseases with particularly low prevalence among those formally defined as rare) to benefit from innovation.

The authors argue that, if providing some therapeutic option for as many diseases as possible is a priority, then **a revision of the incentive toolkit should be considered. Strengthening push incentives could help address the growing disparity between less rare and more rare orphan-diseases.** Alternatively, a more radical reform could involve tailoring incentives based on disease prevalence, **introducing stronger incentives for ultra-rare diseases.** The current system treats all rare diseases equally in terms of incentives, despite significant variations in prevalence, whereas an approach similar to the distinction between orphan and non-orphan medicinal products could be implemented to better address the specific needs of different rare diseases or disease classes.

**MARKET EXCLUSIVITY**

- Stimulus, together with other incentives provided by the orphan legislations, to innovation for orphan diseases
- Potential incentive to undertake clinical trials in specific areas (e.g. paediatrics)



- Unable to grant equal availability of orphan products among EU countries
- Delay of generic entry and hampered originator-competitor competition (less relevant in the orphan market)
- Incentive to innovate increasing with the size of the market
- Additional complexity related to the overall extent of protection
- Room left for strategic behaviour to qualify for the incentive (e.g. salami slicing and indication stacking)

### 3.4. Transferable exclusivity vouchers

Transferable exclusivity vouchers **extend regulatory protection (data or market exclusivity)**. **Vouchers can be used by the owner on any authorised product, or can be sold** to other companies, thus **generating an additional revenue**. Vouchers are meant to provide an additional benefit that exists even for drugs that might not generate large profits despite their substantial public health value. Transferability makes this **pull incentive** an indirect form of financing.

Vouchers have been mainly considered in the context of antimicrobials due to low efficacy of other incentive schemes (Dubois et al., 2022). In the **US**, transferable exclusivity vouchers were **proposed for priority antimicrobial products** under the 2018 US Re-Valuing Anti-Microbial Products Act, **but the programme has not been implemented yet**. The act grants an **extra year of market exclusivity** to priority antimicrobial products that address critical unmet medical needs caused by multi-drug resistant pathogens.<sup>33</sup> Vouchers can be sold, but the voucher user must notify the intended drug at least one year in advance to allow generic companies to adjust their production schedules.

In the **EU**, transferable exclusivity vouchers have been **included in the proposal for a new EU pharmaceutical legislation** to incentivise the development of priority antimicrobials.<sup>34</sup> These are antimicrobial products that provide significant clinical benefits to address AMR and meet specific criteria outlined in the regulation (art. 40 of the proposed Regulation). The voucher would grant an **additional year of data exclusivity**. To qualify for it, the marketing authorisation holder needs to fulfil strict criteria in terms of production capacities (a condition that is more challenging for smaller companies), and to disclose all funding received from any source for antimicrobial research, to avoid overcompensation of the investment. The voucher can be used for any centrally-authorised product within its first four years of regulatory data exclusivity, regardless of whether it belongs to the marketing authorisation holder or another company. However, the voucher can only be transferred once and, if sold, the new holder's identity and the transaction value must be made public. If the voucher is not used within five years from the granting date, it ceases to be valid. These requirements aim to enhance predictability for generic producers. The EU proposal limits the

<sup>33</sup> <https://www.congress.gov/bill/115th-congress/house-bill/6294>.

<sup>34</sup> To date, antimicrobials innovation has been mainly stimulated through push incentives.

number of vouchers to a maximum of 10, or to a 15-year period, whichever occurs first, allowing the EC to assess the scheme's impact, cost and risks (overcompensation, exploitation and unpredictability) based on experience. This cap also ensures that the revenue from, and incentive value of the vouchers do not diminish.

**Competition among vouchers' sellers would transfer the larger share of the rent to the voucher buyer, who is not the intended beneficiary of the incentive scheme** (EU Commission, 2023b). For this reason, the use of vouchers has been proposed only for priority antimicrobial, and not for rare diseases' products, which are more numerous. **The price of the voucher also depends on companies' market power and on the willingness to pay of the first buyer who does not buy the voucher.**<sup>35</sup> It has been estimated that, if only one voucher per year is granted, the seller rent would amount to less than 60% of the total rent; instead, the buyer captures 61% of the voucher's value if there are three vouchers per year (EU Commission, 2023a). As a consequence, **vouchers may grant larger profits to big pharmaceutical companies than to small biotech companies developing the innovation** (EU Commission, 2023a). Additionally, there is an issue of asymmetric information, with buyers having better knowledge of the voucher's value than sellers.

Fourteen EU Member States (Austria, Belgium, Finland, France, Hungary, Ireland, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Slovakia, and Slovenia) released a statement opposing vouchers.<sup>36</sup> They raised concerns about non-transparent financing, potential stifling of innovation and generic competition, and unpredictable costs to national health systems.

The use of transferable exclusivity vouchers comes at a **high cost for payers. Vouchers lead to prolonged monopoly distortions, higher prices, and a possible loss of social surplus.** Larger manufacturers tend to buy vouchers to **apply the added exclusivity to expensive blockbuster medicines**, increasing vouchers' value but also raising costs for other stakeholders. The transferability of the voucher implies that **the cost of this tool is unknown in advance**; this cost also depends on the number of vouchers granted, and on the impact of generics on prices (Anderson et al., 2023b; Dubois et al., 2022). Variations in competition levels after regulatory protection expires and differences in consumer brand loyalty among different clinical areas contribute to the heterogeneity of cost estimates. Estimates of costs vary, with some sources suggesting a cost to the European health system between €350 million and €840 million (Årdal et al., 2023), while others estimate a cost of €441 million for payers and patients, disregarding unserved patients' loss, and a loss for the generic industry of euro 54 million for each voucher lasting one year (EU Commission, 2023a). For the US market, the median estimated financial cost of a year of extended exclusivity is \$187 (Rome & Kesselheim, 2020). However, in most EU Member States, an incentive reward of €1 through a European voucher system would cost less than €1 to the consumers/taxpayers (Dubois et al., 2022). The ratio increases with buyers' market power and the degree of competition in the generics market.

Normally the market for the innovative product determines the value of the exclusivity; instead, the value of exclusivity for vouchers is determined by a different product's market (Otterson & McDonnell, 2016), and **the size of the reward is decoupled from the value of the innovation.** To address these issues, **the voucher's length can be adjusted for the clinical value of the rewarded product** (Anderson et al., 2023b), or a cap on protected revenues can be implemented (Otterson & McDonnell, 2016). Introducing a revenue cap could broaden the voucher market beyond blockbuster drugs. Another approach could involve setting a fixed reward level for the innovator, and regulating the voucher sale through an auction, where the buyer willing to pay the

<sup>35</sup> The smaller is the gap in the voucher's value between the buyer and the next potential one, the higher is the proportion of the value kept by the developer of the product.

<sup>36</sup> <https://www.permanentrepresentations.nl/documents/publications/2022/12/01/novel-stimuli-for-the-development-and-keeping-on-the-market-of-antimicrobials>.

predetermined amount and proposing the shortest voucher length becomes the winner (Dubois et al., 2022). However, both solutions require an informed estimation of the appropriate reward, whose definition should take into account criteria such as the size of R&D investment and/or the added value of the product. Alternatively, vouchers can be granted a few years after marketing authorization when sufficient effectiveness data have been collected.

Vouchers are easy to implement and have the advantage of **not requiring an upfront payment from the health system** (Anderson et al., 2023a). The introduction of vouchers **can attract private financing, such as venture capital, positively impacting innovation**. However, stringent eligibility criteria, necessary to prevent competition among vouchers' sellers, may limit the effect on innovation (Årdal et al., 2023). **Unlike purely market-based incentives, vouchers provide an incentive for R&D also in areas with small market size**. In the area of orphan medicinal products, **the incentive would be the same for more as for less rare diseases** (see Box 3).

It is important to note that **vouchers reward developers regardless of product accessibility**. This means that there is no guarantee that the product will be launched in all countries, regardless of expected profits. Provisions, such as revoking the voucher for unfulfilled supply requests (as in the EU proposal) or requiring an access plan, can address this concern (Boyer et al., 2022). However, **access, as well as stewardship agreements are challenging to enforce as vouchers are a one-off reward** (Anderson, et al., 2023a) and even with strict access conditions, the risk of developer bankruptcy remains (Anderson et al., 2023b).

Vouchers also **hinder affordability and competition in other therapeutic areas, raising fairness concerns** (Outtersson & McDonnell, 2016). They delay generics, biosimilars and competitors' entrance in those markets where the vouchers are used. Unexpected delayed entrance may also lead to increased biosimilars' prices due to downtime costs (Årdal et al., 2023). **Competition is also hampered by the increase in uncertainty as to when an exclusivity period over a drug expires**. Provisions like time limitations, buyer disclosure, one-time use, one-voucher pre product and use within the first period of regulatory protection can mitigate this effect.

#### TRANSFERABLE EXCLUSIVITY VOUCHER



- No need of upfront payment from the healthcare system
- Reward of innovation delinked from own sales, attracting financing also for areas with limited market size
- Innovation directed to eligible products



- Cost of the tool unknown in advance, but possibly high
- Size of the reward decoupled from the therapeutic value of the innovation for which it is awarded
- Access conditions to be defined
- Provisions to ensure predictability for generics to be defined
- Hindered affordability and competition in other therapeutic areas

### 3.5. Priority review vouchers

Several countries offer fast-track regulatory reviews for drugs with improvements in safety, efficacy, or treating serious conditions (Hwang et al., 2020). In the US, the Prescription Drug User Act (PDUFA) distinguishes standard and priority reviews, aiming for six-month review times for priority drugs. EMA provides an accelerated assessment with a target of 150 days, instead of 210 days for non-accelerated assessment (Ridley & Calles Sánchez, 2010). Clock-stop time is limited to 30 days for accelerated assessments. After marketing authorization, pricing and reimbursement decisions are made on a country-by-country basis within 180 days (EMA; Directive 89/105/EEC).

Priority review vouchers (PRVs) aim to stimulate R&D efforts in selected areas. To the best of our knowledge, PRVs are currently exclusively implemented in the US where they are granted upon approval of a treatment (drug, vaccine and biologic) for eligible diseases. PRVs can be used to **accelerate the regulatory approval process of any drug**. Initially **introduced for neglected tropical diseases** (2007), PRV eligibility was expanded to **rare paediatric disease** drugs and **medical counter-measure drugs** (US Creating Hope Act, 2012 and 2016). A PRV **can be used by the company who receives it, or it can be sold to another company** (Hwang et al., 2020; Kesselheim et al., 2015; Gans & Ridley, 2013), providing time savings of around four months in FDA regulatory approval (Robertson et al., 2012). PRVs serve as **pull incentives** (Dimitri, 2010), **enabling faster market entry** and potentially securing a first-mover advantage. Faster approvals can increase company profits by speeding up product launch (Kubler, 2018). The value of a PRV is estimated to be around \$300 million based on top-selling drugs in Europe (Ridley & Calles Sánchez, 2010), with similar estimates found in the US (Ridley & Régnier, 2016). However, maintaining the potential value of PRVs above a certain threshold and limiting their availability is crucial for their effective operation (Dimitri, 2010). The cost of the first transferred voucher in the US was \$67.5 million, but prices have since increased significantly, with a PRV sold for \$350 million in 2015 (Morrison, 2015). More recently, PRVs have been traded at an average of \$100 million due to programme expansion (Ridley, 2023).

**Based on economic modelling, PRVs are apt to effectively stimulate R&D for eligible diseases** by incentivising companies with drug portfolios that also include potentially profitable compounds (Dimitri, 2010). Value of the voucher also depends on its tradability and the holder bargaining power (Gans & Ridley, 2013).



**Empirical analysis provides mixed evidence** on the effectiveness of PRVs. Drug development for PRV-eligible tropical diseases increased after the introduction of PRVs (Kerr et al., 2018; Ridley et al., 2021). In the case of rare paediatric diseases, evidence shows no significant change in new clinical trials. However, shorter phase progression and more first-in-class therapies are detected (Hwang et al., 2019). Companies report PRVs to be a major consideration for initiating or continuing neglected disease projects (Robertson et al., 2012). However, the overall impact of PRVs on drug development is challenged (Meyer, 2021; WHO, 2012).

Supporters of PRVs stress the fact that they have **zero cost**. Furthermore, compared to patent term extensions (e.g., due to TEVs), PRVs seem to be more efficient and fairer as they do not affect patent length. As a result, they are **not detrimental to predictability for generic producers** and the costs of a PRV are not shifted to patients in areas other than the one incentivized (Gans & Ridley, 2013). Relatedly, PRVs are more desirable as compared to TEVs with a more competitive generic market (Dubois et al., 2022).

PRVs are not without limitations. **Safety concerns arise with abbreviated reviews** (Jena et al., 2017), and the additional burden on regulatory agencies may act as a **resource constraint** to their public health mission (Ridley & Calles Sánchez, 2010; WHO, 2006). The quicker introduction in the

market allowed by PRVs may alter the entry order of competitors, **altering market competition and potentially favouring follow-on drugs** (Gans & Ridley, 2013; Kesselheim, 2009). Existing drugs are excluded from the incentive, **limiting their potential use for developing new indications** (Kesselheim, 2009). **The size of this incentive may be insufficient to affect decisions by large pharmaceutical companies, whereas non-profit organizations and small manufactures may be more responsive** (Ridley et al., 2021; Kesselheim et al., 2015). **Affordable access to treatments is not ensured**, as exemplified by the high drug prices (a PRV-granted drug in the US, Elosulfase for the treatment of Morquio A syndrome, costs \$380.000 per year; (Hwang et al., 2019; Kesselheim et al., 2015). To address these issues, complementary provisions and considerations of pricing and reimbursement should accompany PRVs (Ridley et al., 2021; Ridley & Calles Sánchez, 2010).

#### PRIORITY REVIEW VOUCHER

	<ul style="list-style-type: none"> <li>• No extension of monopoly rights granted by patents: generics/biosimilars unaffected</li> <li>• Innovation directed to eligible products</li> <li>• Reward of innovation delinked from own sales, attracting financing also for areas with limited market size</li> </ul>
	<ul style="list-style-type: none"> <li>• Distortion of regulatory priorities</li> <li>• Alteration of market entry order</li> <li>• Innovation incentives distorted towards follow-on drugs</li> </ul>

### 3.6. Advance Purchase Agreements

**Advance Purchase Agreements (APAs)** are mechanisms through which **sponsors**, international agencies, governments or philanthropic foundations, **pledge to purchase a predetermined amount of a product** (e.g., a new treatment, vaccine or diagnostic) **at a predetermined price, even if the product does not exist yet**. APAs are also known as Advance Purchase Commitments (APCs) or Advance Price or Purchase Commitments (APPCs). These agreements are commonly associated and merged with Advance Market Commitments (AMC), where contracts are made with groups of prospective suppliers, rather than individual manufacturers (Thornton et al., 2022).

APAs are a form of pull incentives. One key aspect is that the pharmaceutical company **receives payment only upon successful development of an eligible product that meets the criteria outlined in the agreement**. Consequently, **potential innovators bear the risk of successfully developing a suitable product** (Ravvin, 2008; Glennerster R & Kremer M, 2001).

However, APAs serve an important **de-risking role by reducing uncertainty for the industry related to demand variability** (Thornton et al., 2022; Kremer et al., 2005). By assuring future pricing or purchase volume, and by creating an immediate market for future products, **APAs may stimulate R&D efforts** and expedite the development of products, as in the case of H1N1 ('Swine flu') and COVID-19 vaccines (Thornton et al., 2022; Turner E MR, 2015). Moreover, **long term contracts**

**enable companies to invest in productive capacity, increasing supply, reducing unitary costs** and ultimately yielding higher profits (Kremer et al., 2005). See Box 4 for H1N1 vaccine example.

Several aspects should be considered regarding the determination of APAs value. To ensure the company has a per-dose profit margin, APAs must **balance pricing to cover R&D costs against the risk of overpricing** (Towse & Kettler, 2005). **However, the link between pricing and R&D costs is not trivial:** R&D costs are often not fully disclosed and the share paid for by governments and philanthropic organizations through other incentives and tax subsidies should be also taken into account (Martin et al., 2020; Berndt et al., 2007). On the other hand, purchasers have a strong incentive to keep APA prices low once private R&D investments have been made. Benchmarking against existing profitable products can also help determine the value to be ensured to the manufacturer, given also the difficulty in forecasting the market size for the product. The value should account for the opportunity cost of committing available resources and manufacturing capacity to produce the drug.

For APAs involving vaccines in less developed countries, a two-part price model is commonly used, where the recipient country pays production costs and the sponsor provides extra revenues to cover R&D and manufacturing costs (Martin et al., 2020; Snyder et al., 2011). This approach achieves dynamic efficiency while ensuring long-term convergence to marginal production cost (Berndt & Hurvitz, 2005).

It has been argued that APAs discourage cooperation providing strong incentives to retain knowledge and discoveries thus gaining the entire market (Shamnad Basheer, 2014). There is no doubt that the way subsequent entrants are handled is crucial for the success of APAs. **Adopting a winner-takes-all strategy encourages market entry and timely product availability, generating substantial health benefits; however, not covering R&D costs for subsequent entrants reduces incentives to compete, potentially harming society if competitors could offer superior products** (Berndt & Hurvitz, 2005; Towse & Kettler, 2005). A more sensible approach might be to reward subsequent products with a lower unitary price, reflecting their lower incremental benefits compared to the initial product (Berndt et al., 2007).

Finally, APAs can **ensure availability and accessibility** to drugs and medical equipment, a crucial aspect during emergencies like the COVID-19 pandemic. In extreme emergency situations, buyers can diversify risks related to R&D manufacturing by concluding multiple APAs for different products (Thornton et al., 2022).

Until now, APAs have been predominantly implemented for vaccine procurement (see Box 4), but several propositions have been made to stipulate them for orphan medicinal products (Boeras et al., 2022; Kremer et al., 2005, 2022). APAs may be particularly helpful for vaccine procurement given the positive externalities that may arise in this area. Other externalities may be related to cross-country spillovers in scientific and technological development.

### ADVANCE PURCHASE AGREEMENT



- Reduced uncertainty related to market dynamics and payers' priorities
- Innovation directed to eligible products
- No payment for unsuccessful R&D
- Enhanced access



- Need for a precise ex-ante definition of the product characteristics
- Difficulty in setting the price ex-ante

#### Box 4: The use of APAs

Early discussions on APAs took place in the 1990s. The UK Ministry of Health initiated a call for the development of a meningitis C vaccine, resembling an APA without a legal guarantee of final purchase. In 1996, at the Denver G8 summit, organizations proposed an APA for an HIV vaccine purchase program (Towse & Kettler, 2005; Kremer, 2000a).

Following these discussions, Kremer (2000a, 2000b) explored the theoretical applications of APAs. In 2003, the Center for Global Development, with support from the Bill & Melinda Gates Foundation, established a working group to run a pilot program (Barder et al., 2005). Initially focused on malaria, the attention shifted to **pneumococcal vaccines** due to the severity of the disease, particularly in developing countries where it caused child mortality. Second-generation vaccines were close to availability, making pneumococcal vaccines an appropriate case study to expedite manufacturing and demonstrate commitment viability (Snyder et al., 2011; Stéphenne, 2011; Kremer et al., 2020). The pneumococcal Advance Market Commitment (AMC) was launched in 2007 by the GAVI alliance, supported by the Bill & Melinda Gates Foundation and five donor countries (Canada, Italy, Norway, Russia, and the UK). Most of the literature attests highly positive effects of the pilot pneumococcal AMC programme. Second-generation pneumococcal vaccines spread faster in developing countries compared to first-generation vaccines, resulting in substantial social benefits (Snyder et al., 2011). The pneumococcal vaccine rollout was demonstrated to be cost-effective in 69 out of 72 GAVI-eligible countries (Tasslimi et al., 2011). By 2016, the vaccine was distributed in 60 out of 73 eligible countries, preventing 570 000 future deaths in Gavi-supported countries by 2020 (AMC Secretariat of GAVI, 2020). During the H1N1 virus outbreak, many countries implemented APAs to secure vaccines (Thornton et al., 2022). In 2009, 20 out of 53 developed countries paid a 'Pandemic Preparedness Fee' to developers, ensuring priority access to H1N1 vaccines three months after the WHO declared it a Public Health Emergency of International Concern (Thornton et al., 2022; Turner, 2015).

APAs have also been successfully employed for **Zika**. UNICEF and United States Agency for International Development established an APA for Zika virus rapid diagnostic tests after WHO had announced that Zika was no longer a Primary Health Emergency of International Concern. The commitment involved two calls from 2017 to 2019, that led to the development of three eligible products by two companies. UNICEF committed to purchasing 1.2 million tests over three years, influencing manufacturers to enhance R&D investments and ensuring access to affordable and accurate rapid diagnostic tests (Boeras et al., 2022; Thornton et al., 2022; UNICEF, 2019).



During **COVID-19 pandemic**, UNICEF used APAs for the procurement of Personal Protective Equipment and Dexamethasone, a drug that was shown to decrease COVID-19 mortality for some individuals (Thornton et al., 2022; The Recovery Collaborative Group, 2021). APAs were also used with different vaccine manufacturers to increase the likelihood of obtaining at least one vaccine (Kremer et al., 2022). At the same time, however, the use of APAs during the recent pandemic highlighted important lessons regarding global vaccine distribution and the relevance of product specifications for APAs. While high and upper-middle income countries made significant progress in vaccinating their populations, almost reaching the target of two doses vaccination by June 2022, low-income countries lagged behind, with less than a quarter of their populations completing the vaccination cycle over the same time (Borges et al., 2022). Among the reasons for the evident imbalances in vaccine deliveries are the delays in signing purchase agreements and limited bargaining power in vaccine delivery of low-middle income countries (Agarwal & Reed, 2022).

### 3.7. Subscription models

The subscription payment model (also referred to as revenue guarantee as well as 'Netflix' or 'all-you-can-eat' models) involves buyers paying a **lump-sum 'subscription'** to the manufacturer for a set period, **delinking revenues from the volume of drugs sold**. Subscription models, categorized as pull incentives, reward pharmaceutical companies for successful products **reducing the uncertainty on demand they face**, thereby providing financial predictability. They are similar to APAs, but differ in that APAs value the quantity purchased by sponsors, while subscription models provide unlimited supply in exchange for sponsors' payment. As for APAs, revenue guarantees allow generics and biosimilars to evaluate their prospective entry date (Barlow et al., 2022; Anderson & Mossialos, 2020).

**Subscription models** were implemented for hepatitis C treatments by the Australian Government and the US states of Louisiana and Washington. These subscription financing contracts **provide unlimited access to medications**. In 2015, Australia entered into a five-year contract committing up to US\$ 776 million for hepatitis C drugs, resulting in increased treatment access by 550% and estimated government savings of US \$4.9 billion. Louisiana and Washington have recently concluded similar subscription agreements with Asequa Therapeutics and AbbVie Inc., respectively (Cherla et al., 2021; Liu et al., 2020).

Subscription models were proposed by Towse et al. (2017) to stimulate antimicrobial development by providing incentives and fixed payments for well-performing products. They may also **promote appropriate antibiotics stewardship by de-linking payment from consumption and reducing companies' incentives to boost sales** (Anderson et al., 2023a). Sweden and England are conducting tests on different versions of the subscription payment model for antimicrobials.

In Sweden, the pilot phase was launched in 2020 by the Public Health Agency and lasted two years, with possible extension. The payment was only partially de-linked from volume, with a fixed subscription component and a variable component based on treatment allocations. Four pharmaceutical companies received reimbursement of at least € 400,000 per product per year to preserve a security stock of five antimicrobials, guaranteeing dispatch to hospitals within 24 hours of ordering (Global AMR R&D Hub & WHO, 2023; Outtersson et al., 2022; Gotham et al., 2021). The subscription mechanism effectively **secured access to antimicrobials**, in a country characterised by a too small population to attract manufacturers, and manufacturers expressed positive attitudes

toward the agreement (Public Health Agency of Sweden, 2023). In this case, the model **was not designed to encourage R&D for new antimicrobials**, but as a strategy to ensure access.

In the UK, the Department of Health and Social Care announced a trial for a pilot subscription payment model in July 2019. Unlike Sweden, this scheme **completely de-links antimicrobial procurement from sales volumes**, providing manufacturers with a predetermined annual revenue to ensure access regardless of usage levels. The trial aimed to guarantee access to existing antimicrobials and spur R&D investments in new valuable antibacterials (Gotham et al., 2021).

Based on Sweden and UK promising experiences, the Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (JAMRAI) suggested the implementation of a voluntary EU subscription model for antimicrobials coordinated by the European Commission. This incentive mechanism would be **financially attainable both from European and national perspectives**. Indeed, the Commission would partially share the financial strain of the subscription payment with single Member States, which in turn could plan to return the payment over several years, allowing cost predictability (Anderson et al., 2023a). However, as pointed out by Dubois et al. (2022), enacting this incentive scheme at the EU level would pose **challenges in reaching consensus concerning the dimension of each country's payment instalment**. The European Health Emergency Preparedness and Response Authority (HERA) further investigated the possibility to complement revenues from sales with revenues guarantees (EU Commission & HERA, 2023).

Subscription models for antimicrobial development are also being considered in the US, with a bill authorizing the implementation of subscription contracts for antimicrobials drugs proposed in 2020 and reintroduced to Congress in April 2023. The Pioneering Antimicrobial Subscriptions To End Up surging Resistance Act of 2021 (PASTEUR Act) put forward the establishment of a Committee on Critical Need Antimicrobials, granting a 10-year subscription to developers of new drugs addressing the most significant unmet needs. The Department of Health and Human Services has initiated the necessary steps to promote a similar payment scheme should the PASTEUR Act not be ratified (Global AMR R&D Hub & WHO, 2023; Outterson et al., 2022; Clancy & Hong Nguyen, 2020).

The accessibility of new antibacterials in the G7 and seven other high-income European countries has been assessed, focusing on antimicrobials approved from 2010 onwards (Outterson et al., 2022). Most of the drugs considered were accessible only in the US, UK, and Sweden. Given issues related to access of antimicrobials, Japan and Canada are also planning the use of subscription models in this area anytime soon (Anderson et al., 2023a). Vu et al. (2020) proposes a subscription model for high-income countries to purchase vaccine portfolios for emerging infectious diseases, showing its financial feasibility and potential economic benefits. Cherla et al. (2021) suggest the implementation of subscription models for the treatment of rare diseases, through the implementation of multiple tenders with patented therapeutic alternatives.

**SUBSCRIPTION MODEL**

- De-linkage of reward from quantity
- Enhanced access



- Difficulty in setting the value ex-ante
- Difficulty in defining each Member State contribution in the EU context

### 3.8. Innovation prizes

The concept of innovation prizes (also known as 'inducement prizes') involves awarding monetary rewards or recognition to individuals or organizations that successfully develop groundbreaking products or solutions. Unlike patents, **innovation prizes focus on rewarding the outcome rather than granting exclusive rights.**

The first instance of an innovation prize can probably be traced back to the 1714, with the establishment of the Longitude Prize by the British government. Over time, there have been several applications in diverse fields, including agriculture, aerospace studies and applications, energy solutions. **The natural area of application of innovation prizes is one where the policy-maker has sufficient information to clearly define the properties of a solution** but does not know who has sufficient knowledge and skills to successfully address the challenge (Wright, 1983).

A risk to be avoided is that prizes are assigned to innovations that do not become available to patients. This issue may be addressed using other tools that exploit similar incentive mechanism such as **market-entry rewards** or **Advance Market Commitment (AMC)** (Kremer & Williams, 2009). In these cases, the availability of the technology is a condition for reward payments to be made. **Milestone-R&D payments** also share some key characteristics of prizes. In this case, however, payments are made when pre-defined development stages are completed, typically in the later stages of the R&D process.

With reference to health-related innovation, prizes attract attention thanks to two main characteristics: i) their **ability to reward R&D efforts toward areas characterized by UMN and / or ground-breaking innovation**, ii) their **potential to reduce prices in comparison to situations where patents grant monopoly power**. While the former advantage exists no matter whether prizes are used as substitutes or complements with respect to existing forms of IP protection, the latter **relies on the fact that prizes replace patents**. An ongoing process related to the introduction of an innovation prize is the Longitude Prize 2014 that will reward a team of innovators who develop a point-of-care diagnostic test that will conserve antibiotics for future generations. An interesting feature of this example is that AMR was selected by the British public within a wide set of topics, thus showing awareness of the public of the seriousness of the related threat.

Concerning the **implementation** of innovation prizes, a key, sometimes overlooked decision, is whether prizes should be used **in addition to patents or to replace them**. Theoretical contributions tend to look at prizes as substitutes of patents, whereas in real world applications they are conceived to exist alongside patents (Murray et al., 2012).

Also crucial at the implementation stage is a **clear definition of specific objectives and victory conditions** (Kalil, 2006). The respect of a condition based on a best-in-class judgement may be difficult to be assessed at the time of launch (Boluarte & Schulze, 2022). As further discussed below,

the **definition of the efficient size of the prize** is also crucial (Kay, 2011). The complexity of governance is often overlooked but crucial (Murray et al., 2012), especially in the context of EU pharmaceutical legislation, where coordination issues may arise within the EU and with incentives from other countries. **Intra-EU challenges include defining country-level contributions to prize funding.**

**The lack of systematic application of this tool makes it difficult to draw solid evidence-based conclusions regarding its effect on innovation.** The sparsity of applications implies that existing evidence is essentially based on case-study analyses, with limited external validity. Overall, however, existing experiences seem to suggest that **prizes are effective in attracting R&D effort**, they tend to **attract** interest of **diverse developers** and provide an opportunity for **collaboration among several players**, even among those not previously established in the field (Kay, 2011). Finally, prizes may provide incentives beyond the pure monetary value received, because competitors may also attribute a significant value to the implications in terms of **reputation** (Brunt et al., 2012). However, their impact depends on the attractiveness of the prize size and associated benefits to investors. The perception of excessive competition affects the investors' R&D decision, with **excessive competition discouraging some investors** (Fullerton & McAfee, 1999). Rewarding multiple participants according to well-defined rules can mitigate this effect. Another aspect, sometimes overlooked, is whether prizes efficiently allocate societal resources. Depending on the number of participants a **risk of over-investment may exist**, i.e. a level of investment such that costs exceed marginal expected societal benefit (Murray et al., 2012) as well as a **risk of R&D costs duplication** (Maurer & Scotchmer, 2004).

Limited real-world applications hinder clear conclusions on the effectiveness of innovation prizes as incentives for addressing unmet needs. However, their characteristics and limited evidence suggest that innovation prizes are potentially interesting incentive tools, provided certain conditions are satisfied. Systematically replacing patents with prizes is hardly feasible and risky. **Introducing prizes as additions to existing incentives is a more feasible approach, allowing for real-world insights and limiting regulatory risk** (Kremer & Williams, 2009). A further possibility would be to provide manufacturers with the option to choose between prize and IPR (Shavell & Van Ypersele, 2001). Defining precise objectives, particularly in terms of patient outcome, can be challenging. For **antimicrobials** target identification is relatively straightforward and current R&D investments are deemed largely insufficient. This makes this therapeutic area particularly appealing for the introduction of prizes. In this case, they should **serve as supplementary incentives alongside patents**, especially considering the potential drawbacks of price reductions for antimicrobials. More generally, in the area of antimicrobials, prizes, as any other policy aimed at stimulating innovation, should be part of a broader strategy to ensure appropriate use of the therapeutic options available.<sup>37</sup>

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<sup>37</sup> In a UK government commissioned report, Jim O'Neill made a proposal aimed at reconciling these two objectives. See, <https://amr-review.org/>.

## INNOVATION PRIZES



- Innovation directed to eligible products
- De-linkage of reward from quantity and enhanced access, if used to replace exclusivities
- Additional incentive if used alongside other tools
- Ability to target ground-breaking innovation
- Possibility of conditioning payment on successfully bringing the product to the market



- Difficulty in defining each Member State contribution in the EU context
- Difficulty in setting the value ex-ante
- Risk of overinvestment and duplication of R&D efforts

### 3.9. Tax credits

Tax credits are a specific type of tax relief or depletion granted by governments, according to which **a designated percentage of eligible R&D costs incurred by the pharmaceutical company is deducted against its tax liability** (OECD, 2023). Tax credits typically work as **push incentives** as they are provided alongside the development process, irrespectively of the attainment of a successful product (Harris, 2018; Anderson, 2009).

Tax credits are part of broader R&D incentive programmes for orphan medicine development adopted by several countries (see Table 2). Apart from rare diseases, tax credits have been used to boost R&D in multiple clinical areas. The Biotech and New Pharmaceutical Development Act (Biopharmaceutical Act) promulgated in 2007 in Taiwan is an incentive programme aiming at stimulating innovation activities in the biotech and new pharmaceutical industry, heavily relying on tax credits Liang & Liu, 2021; Hsieh et al., 2009). Biopharmaceutical companies benefitting from the Biopharmaceutical Act considerably improved innovation activities (Liang & Liu, 2021). Several EU countries (e.g., Belgium, France, Italy, Spain) offer R&D tax credits for companies engaging in specific R&D activities, including those in the pharmaceutical sector. The features of tax credits may vary from one country to another, since **EU Member States retain control over their individual fiscal policies** (OECD, 2023). These supply side tax incentives are sometimes supplemented by more specific tax benefits policies. For instance, the Netherlands provide tax credits for high-tech startups investing in R&D for rare diseases; similarly, in France manufacturers of treatments for rare diseases are exempted from some taxes (Health and Safety, 2015). In April 2002 the UK Government introduced tax credits for all pharmaceutical manufacturers engaging in R&D, with the provision of additional tax benefits granted to pharmaceutical companies performing R&D into vaccines and drugs targeting tuberculosis, malaria and HIV/AIDS (Health and Safety, 2002).

By their very nature of push incentives, **tax credits might be extremely effective in supporting sponsors in the early-stage development phases**. Indeed, these tax benefits reduce the marginal cost of R&D activities, enabling and stimulating manufacturers to engage and afford innovation processes (Grabowski & Moe, 2008; Yin, 2008). In addition, tax credits are more likely to influence sponsors' decision to engage in R&D activities than direct subsidies. Firstly, this funding mechanism operates in a decentralized way, **reducing the chance of moral hazard (since the manufacturer**

**ought to invest in R&D to obtain the tax benefits) and free riding (as the sponsor still bears part of the R&D costs)** (Liang & Liu, 2021; Grabowski & Moe, 2008; Grabowski, 2005). Furthermore, since tax credits are **less exposed to budget revisions than grant programs**, they tend to be more stable over time (Harris, 2018).

As other form of incentives, **tax credits provide limited incentives for ultra-rare diseases** (Harris, 2018; Yin, 2008). **Push incentives, including tax credits, are less likely than pull incentives to lead to a concentration of R&D efforts toward diseases with comparatively high prevalence within the class of rare diseases** (Gamba et al., 2021; see Box 3).

Among the limitations of tax credits, it must be noted that, by their own nature, they **work as an incentive exclusively for companies making profits**. Hence, their impact may be limited for manufacturers not yielding revenue-generating products, e.g. small biotechnology companies. As a consequence, **tax credits are more convenient for established pharmaceutical companies** (Harris, 2018; Valverde et al., 2012; Yin, 2008). Moreover, supply-side tax incentives **may turn extremely expensive for governments and taxpayers since they are not capped by a pre-determined spending limit** (Harris, 2018).

#### TAX CREDIT



- Limited correlation between size of the incentive and market size



- Limited or no impact for manufacturers making no or limited profits
- Budget impact harder to predict than with direct subsidies

### 3.10. Open science framework

There is no formal definition of open science, but this can be seen as the **effort of making the primary output of the research freely and publicly accessible** (OECD, 2015).

The results of **basic research**, primarily financed by the public sector, though public universities and research centres, and by philanthropic organizations (Panteli & Edwards, 2018; Institute of Medicine (US) Forum on Drug Discovery, 2009) are **often freely accessible** (Florio et al., 2023). Some public-private partnerships, such as Open Source Drug Discovery, Open Source Malaria, the Structural Genomics Consortium, Sage Bionetworks, and the Agora Open Science Trust, also follow an open science model.

In an open science model, **IPR may be used to prevent others from seeking patent protection and make innovations freely accessible. Alternatively, researchers may rely on contract and social norms**: this mechanism results in lower costs, as there's no need to support patenting expenses (OECD, 2011) While Open Source Drug Discovery and the Drugs for Neglected Diseases initiative (DNDi) employ IPR to ensure free access to innovations, with patented innovations licensed non-exclusively (Sugumaran, 2012),<sup>38</sup> the Structural Genomics Consortium, focusing mainly on early-

<sup>38</sup> <https://dndi.org/advocacy/pro-access-policies-intellectual-property-licensing/>.

stage R&D, does not patent the research output nor permit its affiliates to do so (Stevens et al., 2016). The same holds for the Agora Open Science Trust, whose research outputs, however, still benefit from market exclusivity granted to orphan medicinal products in many countries as well as from data exclusivity. These exclusivities provide commercial incentives for manufacturing and distribution of successful products.<sup>39</sup>

The open science framework was firstly adopted in bioinformatics, the best-known initiative of which being the Human Genome Project (Munos, 2006), and is more commonly adopted for databases, models, research tools, and platform technologies. For these IP assets expenses are low (Balasegaram et al., 2017), while patenting costs represent an obstacle (Stevens et al., 2016); moreover, these assets contribute to drug development but with unclear scope. The open science framework has also been **adopted for those clinical areas characterised by a very limited market size, where exclusivity has a limited role in fostering innovation and the profit-driven model struggles to produce significant innovation** (Todd et al., 2021; Sugumaran, 2012). An exception is represented by the Istituto di Ricerche Farmacologiche Mario Negri, an Italian nonprofit organization focusing on several therapeutic areas, both profitable and unprofitable. While the open science model is mainly adopted for basic research (UN, 2016), it was also **successfully used for late R&D stages** by the Istituto di Ricerche Farmacologiche Mario Negri, the Agora Open Science Trust, and the Drugs for Neglected Diseases initiative. Another area where the open science framework may be particularly productive is **drug repurposing** (Balasegaram et al., 2017), as highlighted by the case of fexinidazole (Wyllie et al., 2012; Torreele et al., 2010). Many open science initiatives during the COVID-19 pandemic focused on repurposing.<sup>40</sup>

By making innovation immediately available to all, **open science speeds up the accumulation and application of knowledge** (Munos, 2006) **and the pace of development** (UN, 2016). This was the case during the COVID-19 pandemic, when the proteins' structure of the virus was made publicly available through the RCSB Protein Data Bank, making it possible for scientists throughout the world to analyse which molecules could interact with it. As highlighted by the natural experiment constituted by NIH agreements providing open access to methods for engineering mice with specific characteristics, open science also **stimulates new researchers' participation, increased R&D, diversified follow-on R&D, and new results** (Murray et al., 2016). It also encourages **patients' participation** (Balasegaram et al., 2017).

**Open science also increases the efficiency of the R&D process, by limiting duplicative R&D investments:** new studies can leverage previous ones, including those that were unsuccessful (Balasegaram et al., 2017; Moon et al., 2012). Open science could also **reduce the risk for patients to be exposed to undue risks** related to clinical trials, caused by selective reporting of favourable research (Gøtzsche, 2011).



By lowering the cost of innovation, **pooling mechanisms, such as open science and public-private partnerships, enable more affordable pricing** (Suleman et al., 2020). Finally, **by relying on incentives different from financial returns, open science realigns R&D choices and public health priorities** (Balasegaram et al., 2017).

<sup>39</sup> <https://www.agoraopensciencetrust.org/our-drug-development-business-model>.

<sup>40</sup> <https://www.ospfound.org/open-research-platform.html>.

Current open science initiatives heavily rely on **public funds and donor financing** (Moon et al., 2012). Innovative financing mechanism can be evaluated for the future as more projects are developed following an open science approach (Balasegaram et al., 2017).

#### OPEN SCIENCE FRAMEWORK

	<ul style="list-style-type: none"> <li>• Increased R&amp;D efficiency, due to the limited duplication of R&amp;D efforts</li> <li>• Better exploitation of knowledge spillovers</li> <li>• Better affordability</li> <li>• Better alignment of R&amp;D investment decisions and public health priorities</li> </ul>
	<ul style="list-style-type: none"> <li>• Reliance on public funds and donor financing</li> </ul>

### 3.11. Public-private partnerships

The challenging economic and regulatory forces and the increased complexity of targeted pathologies, as well as the decline in R&D productivity and in the number of new products launched during the first decade of the century (de la Torre & Albericio, 2023) stimulated, since the 2000s, the creation of a new business model, based on public-private partnerships (PPPs) (Vertinsky, 2022; de Vruh & Crommelin, 2017).

PPPs are **long term agreements between one or more public institutions (including academia and regulators) and private partners. They may also include other stakeholders**, such as charities and foundations (who provide funds, but also act as a trusted intermediary or broker for IP assets) (de Vruh & Crommelin, 2017), representatives of public and private payers as well as patients' associations (which may be helpful in connecting their members with clinical trials, and in ensuring that patients' needs are taken into account (de Vruh & Crommelin, 2017; Sebelius, 2011). **By sharing capital and costs, PPPs distribute the risk over a diversified portfolio of subjects, becoming attractive for both governments and the private sector** (Vertinsky, 2022). Since partnerships involve existing entities, they can be organised within a tight time frame (Garattini et al., 2022).

PPPs put together actors who traditionally play different roles in the R&D continuum (Drolet & Lorenzi, 2011) and they join two different systems of knowledge creation (de Vruh & Crommelin, 2017). Partners can share data, expertise, and resources, as well as leverage resources spread across different entities. This **integration** allows overcoming knowledge undersharing and fragmentation (Goldman et al., 2013), and exploiting complementary competences, leading to **improved research efficacy** and to **significant achievements** in terms of models, databases and tools (de Vruh & Crommelin, 2017; Goldman et al., 2013). Moreover, cooperation among different partners allows **more medicines to move along the research process**, from lab bench to medical bedside (Sebelius, 2011). Treatments may also be developed in a **shorter time span**, as shown by the rapid development of vaccines by PPPs for COVID-19.

PPPs may adopt different IP strategies for the management of partners' previous knowledge assets (background IP) and downstream knowledge generated by the PPP (foreground IP). **Several PPPs have embraced an open science approach** (de Vruh & Crommelin, 2017), enabling them to



pursue research independently of immediate economic gains. However, for partnership to work, **clear IP strategies are needed** (Stevens et al., 2016).

Moreover, **it is crucial to align missions and establish clear reward agreements, to ensure that the sharing of public-private benefit reflects the sharing of risks and costs** (Vertinsky, 2022; de Vruh & Crommelin, 2017). To this end, conditions related to affordability and accessibility can be included in the agreement. For example, until 1995 a fair pricing clause regulated NIH collaborations and licensing agreements. However, the clause was then dismissed to stimulate collaborations and commercialisation (Mazzucato & Li, 2021). The ex-ante definition of rewards may also pose challenges, due to the difficulty of predicting R&D outcomes (Vertinsky, 2022).

Most PPPs focus on areas that are barely attractive to pharmaceutical companies, that is **pre-competitive research topics**. These include novel scientific concepts (e.g., new tools for drug discovery, models to predict potential side effects, and new approaches for patient stratification) and infrastructures (e.g., databases). The results of this research are important for the industry, patients and regulatory agencies (de Vruh & Crommelin, 2017; Goldman et al., 2013). These partnerships can also **boost the competitiveness of the pharmaceutical sector**, as in the case of the Innovative Medicines Initiative (IMI), a partnership between the EC and the European Federation of Pharmaceutical Industries and Associations (EFPIA) (Goldman et al., 2013).

Another form of PPPs is represented by **product development partnerships**, which focus on product development (although manufacturing may be outsourced) and **accessibility** (de Vruh & Crommelin, 2017; Stevens et al., 2016), with parties agreeing in advance upon acceptable profits.<sup>41</sup> These partnerships **focus on UMN**, as in the case of the Drugs for Neglected Disease initiative (DNDi), the Medicines for Malaria Venture and the Global Alliance for Tuberculosis Drug Development. These partnerships have demonstrated their ability to swiftly bring new products to market (Bompart et al., 2011) **while operating within tight budget constraints** (Ploumen & Schippers, 2017), **facing no marketing costs, and often relying on open science models to reduce R&D costs**.<sup>42</sup> **Accessibility is achieved through the use of non-exclusive licences** (see Box 1), as for DNDi;<sup>43</sup> **through the transfer of drugs to the private sector with price caps**, as for M4K Pharma (Wong et al., 2019);<sup>44</sup> **or through the application of a 'delinkage' model**, in which the price of drugs and the R&D costs are uncorrelated (Suleman et al., 2020) and medicines are sold at prices close to the production cost (Moon et al., 2012). The delinkage model is facilitated by the lower development costs (Suleman et al., 2020) and by specific partners' agreements on profitability. Product development partnerships also present the advantage of providing **transparent information on R&D costs** (Garattini et al., 2022; Ploumen & Schippers, 2017), which may be useful for the public sector to define other incentive schemes (such as prizes). Finally, the presence of non-profit players in an oligopolistic market populated by private companies may **increase social welfare**, since collusion is made more difficult and companies' profit-maximizing behaviour is influenced by non-profit organisations (Willner et al., 2018; Matsumura & Kanda, 2005; De Fraja & Delbono, 1990).

To grant research independence, and that the agenda is not profit-driven, product development partnership may rely on donations, often with a limit to each donor's contribution (as in the case of DNDi) or on public funds. The allocation of these funds may be periodically reviewed in order to

<sup>41</sup> <https://www.fairmedicine.eu/en/our-approach/how-does-fair-medicine-work/>.

<sup>42</sup> <https://dndi.org/advocacy/transparency-rd-costs/>; <https://m4kpharma.com/>.

<sup>43</sup> <https://dndi.org/advocacy/pro-access-policies-intellectual-property-licensing/>.

<sup>44</sup> <https://fortune.com/2020/03/26/coronavirus-vaccine-drug-development-open-science-COVID-19-treatment/>.

assess the partnership results (Garattini et al., 2022) but enough time should be left to let the partnership engage in long-term missions (Florio et al., 2021).

#### PUBLIC-PRIVATE PARTNERSHIP



- Better alignment between public health needs and R&D investments
- Increased R&D efficacy thanks to public-private synergies
- Increased competitiveness of the pharmaceutical sector
- Ability to develop new products with a limited budget
- Enhanced access to innovation
- Transparency of R&D costs
- Feasibility within a short timespan



- Need for a clear alignment of missions, as well as clear IP and reward agreements

### 3.12. Public infrastructures for pharmaceutical R&D

The current system is characterised by **huge public investments, either for basic research or in the form of incentives to companies**, while **returns are privatised**, with drugs for hepatitis C virus and COVID-19 vaccines representing notable examples (Florio et al., 2023; Garattini et al., 2022; Barenie et al., 2021). Indeed, while academia and public institutions have a significant role in promoting innovation and enriching the industry's pipeline, the process of bringing new products to market is predominantly controlled by large companies (de Vruueh & Crommelin, 2017). Moreover, while public sector mainly relies on open science practices, this is not the case for the private sector (Florio, 2023; Florio et al., 2021). Consequently, **taxpayers pay twice for the same innovation: the first time by financing public basic research, or through subsidies or incentives for private firms; the second time through drug prices** (Florio et al., 2023). **A stronger implementation of public interest provisions** throughout the pharmaceuticals' life cycle, encompassing fair investment returns and products' accessibility, **is required** (Barenie et al., 2021; Panteli & Edwards, 2018).

**One way of doing so would be to include fair pricing clauses in collaborations involving public funds** (as was the case for NIH-funded projects until 1995); **to impose conditionalities on private profit reinvestment, on knowledge sharing, on the transparency of R&D costs; or to adopt a more proactive public management of IPR of publicly funded innovations** (Mazzucato & Li, 2021; UCL Institute for Innovation and Public Purpose, 2018). In the US, before 1980, inventions arising from government-funded research belonged to the federal government. Given that many government-owned patents went unused, and many innovations remained uncommercialised, the Bayh-Dole act was introduced in 1980 to assign ownership of inventions arising from federally-funded research to collaborating partners. However, to safeguard the public interest, federal agencies that have provided funding for innovation development can retain the patent licence themselves or grant it to others if the contractor fails to take effective steps toward practical application of the invention. This can be done to address health or safety needs or to fulfil public use requirements stipulated by federal regulations ('march-in clause'). Nevertheless, there is an ongoing debate about whether the march-in clause can be used to address accessibility concerns.

The literature on the effect of the Bayh-Dole Act on basic and applied academic research provides mixed evidence (Thursby & Thursby, 2011; Kenney & Patton, 2009). Since the march-in clause has never been exercised, it is only potentially helpful in balancing risk sharing and benefit sharing in the pharmaceutical sector (Treasure et al., 2015; Vertinsky, 2022). Moreover, the uncertainty on the possibility to use the clause to address accessibility generates unpredictability for both patients and companies (Treasure et al., 2015; Stevenson, 1998).

**To confer the public sector decision-making power over development choices, prices and distribution of publicly funded innovations, another possibility is that governments assume a more active position**, investing throughout the entire innovation chain (Mazzucato & Li, 2021). **This could be achieved by creating public research infrastructures active throughout the whole R&D and production process** (in-house, or through outsourcing). These infrastructures can be open to collaborations, in partnership with third-party research centres and with pharmaceutical companies, based on transparent contractual arrangements (Florio et al., 2021).

A public infrastructure may **grant products' accessibility and lead to better alignment between R&D choices and public health needs**, by defining research targets based on public health priorities (Florio et al., 2021; Mazzucato & Li, 2021). **Governments, in consultation with experts and stakeholders, can define key problems and define the research agenda, with a long-term vision**. According to the budget, the mission-oriented infrastructure **can intervene in all therapeutic areas not sufficiently addressed by the private sector, where the private industry charges exorbitant prices or where there are shortages; alternatively, it may focus only on the most critical clinical area**. The public infrastructure may also focus, as a complementary mission, on comparative studies (Garattini et al., 2022; Florio et al., 2021). Through a long-term vision, the public infrastructure could also **ensure preparedness in case of emergencies**.

The infrastructure should **take public ownership of the results of the undertaken R&D projects**. It can adopt different approaches with respect to IPR, such as an open science, or a socially responsible IP approach, in which profits coming from non-exclusive licensing are reinvested, and licensing agreements specify drug price conditionalities to grant accessibility (Garattini et al., 2022; Florio et al., 2021). In addition to licensing, other fundings could come from voluntary contributions by participating countries, grants and donations and revenues from the commercialised products.

Several examples of direct involvement of the public sector or mission-oriented public infrastructures exist in other fields, such as space policy and defence. Concerning health, the Intramural Research Program of the NIH, in the US, represents the largest biomedical research institute in the world;<sup>45</sup> other federal agencies include the NIH (National Institutes of Health) itself, mainly a funding organisation,<sup>46</sup> and BARDA (Biomedical Advanced Research Authority), whose goal is to ensure preparedness in case of a health threat, and to support the transition of medical countermeasures from research to approval.<sup>47</sup> Also Europe is characterised by a multitude of bodies dealing with health matters, such as the ECDC (European Centre for Disease Prevention and Control), whose goal is to identify and assess risks related to infectious diseases,<sup>48</sup> and HERA (Health Emergency Preparedness and Response Authority), whose mission is to strengthen Europe's ability

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<sup>45</sup> <https://irp.nih.gov/about-us>.

<sup>46</sup> [www.nih.gov](http://www.nih.gov).

<sup>47</sup> <https://aspr.hhs.gov/AboutASPR/ProgramOffices/BARDA/Pages/default.aspx>.

<sup>48</sup> <https://www.ecdc.europa.eu/en>

to prevent, detect, and rapidly respond to cross-border health emergencies.<sup>49</sup> However, European agencies benefit from a very limited budget compared to similar entities in the US, and funded projects do not have the critical mass and the continuity needed to achieve programmatic objectives (Florio et al., 2021). Moreover, no agency deals with the entire product life cycle.

According to the scope of its mission, and of its internal R&D capacity, the required budget for a large-scale European R&D and innovation infrastructure would be between 3.5 billion euro and 6.5 billion euro per year. The expected benefits for society are related to improved accessibility, health gains and reduced economic impact of severe pathologies. In the case of Europe, the preparedness in front of epidemic and pandemic risks would bring a large benefit-cost ratio (Florio et al., 2021). In a 30 years timespan, such an infrastructure would be able to launch a significant portfolio of R&D projects (Florio et al., 2021).

In 2023, also the European Parliament adopted a [resolution](#) asking the Commission and Member States to assess the need for a large-scale, mission-oriented, public European health R&D infrastructure.<sup>50</sup>

#### PUBLIC-INFRASTRUCTURE FOR PHARMACEUTICAL R&D



- Better alignment between public health needs and R&D investments
- Attention to repurposing and superiority trials
- Enhanced access to innovation
- Better opportunities for knowledge integration and dissemination
- Transparency on R&D costs
- Preparedness in case of emergencies



- Long-term implementation
- Limited evidence on ability to manage innovation throughout the whole product life cycle due to limited use to date
- Large upfront payment from the public sector required

<sup>49</sup> [https://health.ec.europa.eu/health-emergency-preparedness-and-response-hera\\_en](https://health.ec.europa.eu/health-emergency-preparedness-and-response-hera_en)

<sup>50</sup> [https://www.europarl.europa.eu/doceo/document/TA-9-2023-0282\\_EN.html](https://www.europarl.europa.eu/doceo/document/TA-9-2023-0282_EN.html)

## 4. Results from the interviews

This section presents the findings based on the answers to each question asked during the interviews with stakeholders (see Annex 1).

We thank all the interviewees for participating in the survey and sharing their views and opinions.

### 4.1. Main hurdles

*Question 1. Given the current regulatory and incentive framework in Europe, could you rate from 1 (irrelevant) to 4 (highly relevant) each hurdle for each market? (The same level of relevance may be assigned to different hurdles)*

	<i>Antimicrobials</i>	<i>Orphan diseases</i>	<i>Paediatric drugs</i>
<i>Low expected revenues</i>			
<i>Perceived risk of failure in R&amp;D</i>			
<i>Difficulty in running trials</i>			
<i>Uncertainty/complexity of the current regulatory framework (European and/or national)</i>			
<i>Other: ...</i>			

Response rates to Question 1 vary across markets, and they are higher in the case of antimicrobials, with 19 respondents rating at least one dimension in the case of antimicrobials, as compared to 16 and 15 in the case of, respectively, orphan medicinal products and paediatrics.

In some cases, respondents offered a broad perspective related to the discussed hurdle rather than a numerical answer. Therefore, also the following presentation is based on overall assessment rather than on a statistical analysis.

#### **Antimicrobials:**

- There is wide consensus in rating '**low expected revenues**' as **highly relevant**. Various explanations are provided related to pricing and quantity concerns. Antibiotics currently in use are effective (absent resistance) and have very low prices. Once developed, any new antibiotics will not be used extensively to limit the emergence of resistance, rather it will be kept as a reserve to be used when available therapies are no longer effective. This reduces expected profits, especially in the short-medium term;
- With respect to the **perceived risk of failure in R&D**, we record some **heterogeneity** in responses; however, the majority indicate this hurdle as relevant or highly relevant. A distinction needs to be made between incremental and radical innovation: (i) the risk of failure is perceived as **small for incremental innovation, which are associated with higher risk of resistance in the short term**; (ii) the risk of failure is perceived as **high for disruptive innovation, which is more promising in terms of reduced risk of resistance**.

The development of new antimicrobials is described as a scientific challenge as it is very difficult to identify new molecules (no new class has been identified since the '80);

- The issue of drug resistance is growing but it is difficult to predict for which kind of bug or bacteria it will emerge;
- Assessment of the difficulty in running trials is also heterogenous. It may be **difficult to find patients with resistance** and the **time for enrolment in trials is very short**. Moreover, clinicians may be reluctant to enrol patients into clinical trials when there is uncertainty on patient's response to existing drugs. Another issue is the collection of informed consent from patients in intensive care units;
- Other **organizational hurdles** are identified **in clinical trials** related to pharmacological regulations, the trial design and the definition of clinical endpoints, as well as issues related to data privacy and protection, and differences in hospital protocols and regulation. To this end, **harmonization of regulation** might be useful as well as the creation of a European platform to automatically share and retrieve clinical data collected during trials;
- Under the current regulatory framework, eligibility rules to access incentives are considered sufficiently clear and it is not perceived as a relevant hurdle. Uncertainty related to the implementation of the pharmaceutical reform is mentioned by some interviewees in relation to the present situation.

#### Rare diseases:

- As regards the issue of low expected revenues two contrasting views emerge: on the one hand, the market is characterized by a **small population** (implying low expected revenues). On the other hand, several participants recognize that the **current set of incentives** grants very strong protection and is **effective** in increasing expected revenues. They also note that prices can be extraordinarily high, and orphan medicinal products can reach the blockbuster status. It is also mentioned that some products that have benefited from orphan legislation incentives would have been developed also without them. However, the hurdle represented by low expected revenues depends on the type of indication and its prevalence, with **revenues not perceived as attracting for ultra-rare indications** (even if also for this segment, the possibility of high prices and interesting discovery opportunities still exist);
- On the side of the generic industry, **development of biosimilar products is not perceived as economically sustainable** given the costs related to the authorization process and the predicted reduction with respect to the originator's price;
- With regards to the perceived risk of failure in R&D, different views are reported. **Assistance in the design of clinical trials** is important in reducing the risk of failure. The important role of academic research is also highlighted;
- **Difficulty in running trials is mostly perceived as relevant or highly relevant** (unanimously among patients and pharmaceutical industry representative that responded to this item). Various issues are mentioned including the difficulty in defining clinical endpoints, finding a control, finding patients to enroll due to the small population involved (even if families of rare disease patients are keen to be included in clinical trials). New (innovative) ways of running trials are mentioned as a possible solution;
- In most cases the uncertainty/complexity of the current regulatory framework does not represent a major hurdle for the development of orphan medicinal products. Exceptions may be due to the **strategic use of the market exclusivity provision to extend protection** from competition (but the proposal for a new EU pharmaceutical legislation seems to

address this issue). Moreover, the current regulation is perceived as complex in the case of biosimilar products.

#### Paediatrics:

- **Different opinions** emerge regarding the issue of **low expected revenues**. On the one hand, the population is small and when talking about 'children' different age classes deserve different treatment. On the other hand, paediatric trials are rewarded in the EU, but sometimes the reward is not perceived as sufficient;
- As for the **perceived risk of failure** in R&D, answers are **highly heterogenous**: 50% of respondents declare the perceived risk of failure as not relevant (score of 1 or 2) and 50% declare it to be relevant (score of 3 or 4). Those respondents considering R&D as challenging mention scientific and trial hurdles, the need for dedicated centres to run and manage the trials (private-public partnership may be useful in this context, as it is the case of C4C-*connect4children*). Other respondents considered R&D as not challenging, because **drugs that have already proven effective in adults are usually exploited**. However, difficulties with drug optimization for children may arise;
- In most cases, the experts report that **difficulty in running trials is a relevant or highly relevant hurdle**. Various difficulties have been mentioned related to the small population involved and ethical considerations. Parents are reluctant to involve children in clinical trials. Moreover, children are often treated off-label, so that even doctors do not perceive the need to include their patients in trials. Finally, 'children's diseases' is a broad category: at the regulatory level, it comprises different definitions according to different age groups so that it is difficult to define the population involved;
- In general, the uncertainty/complexity of the current regulatory framework is not considered an issue;
- It is mentioned that the system generally works well to run paediatric trials for adult-approved compounds, but more should be done to foster trials in paediatric-specific diseases.

#### Additional comments provided by participants:

The list of hurdles provided is mostly considered as complete, but other issues are also mentioned:

- The EU level regulations are clear. However, **market access** (health technology assessment, the negotiation of prices and reimbursement procedures) within single countries **can be complicated**;
- The **lack of cooperation** among countries may be an important hurdle in areas characterised by a small market size;
- There is an issue with **transparency** of R&D costs and profits in pharmaceuticals.

## 4.2. The role of incentives

Question 2. Consider the following list of incentives:

- *supplementary patent protection certificates,*
- *data exclusivity,*
- *market protection (protection from marketing the same molecule),*
- *market exclusivity (protection from marketing similar molecule(s) with analogous characteristics),*

- *transferable exclusivity vouchers,*
- *priority review vouchers,*
- *advance purchase agreements,*
- *subscription models,*
- *innovation prizes (milestone R&D payments or market entry rewards)*
- *tax credits*

Could you identify one or more among them that you believe is most effective/efficient in striking the balance between the following objectives?

- *Stimulus for innovation, specifically for antimicrobials, orphan diseases, paediatric drugs;*
- *Availability and affordability;*
- *Predictability for generic companies and competitors.*

In the following, we highlight the main advantages or shortcomings that are identified by the different stakeholders. Each interviewee focused on different incentive(s), and larger attention was devoted to the first listed objective, i.e. to stimulate innovation. It was noticed that there is not a single recipe that can be applied, but **different solutions should be identified for different therapeutic areas.**

#### **SPC, market protection, market exclusivity, and data exclusivity**

- SPC, market protection, market exclusivity and data exclusivity are generally commented together (and sometimes also commented together with transferable vouchers), claiming that they all have the objective of strengthening exclusivity;
- As it is the case with the literature, these tools are either **described as important or detrimental to enable innovative R&D;**
- On the one side, having **'too long' exclusivities may produce strong obstacles to follow-on development** also counterbalancing the positive effect in terms of stimulus to innovation;
- **Prolonged exclusivity does not act as a stimulus for directing R&D to less profitable areas and UMN**, and can make drugs prohibitively expensive, thus limiting access and drug availability;
- The length of exclusivities is not discounted to take into account **public funding** received;
- **In the case of rare diseases**, a distinction needs to be made. There is consensus that orphan regulations have fostered developed in this area. However, most rare diseases are **ultra-rare**, and specific incentives are needed in this area. A suggestion in this direction is the creation of a **dedicated European R&D infrastructure**. In this context anything that prolongs the protection has limited interest because of limited competition at the end of the protection period (except for few profitable compounds). In some cases, there are no generic products for orphan medicinal products even ten years after the exclusivity has expired. Competition is even more limited in the case of biosimilars;
- In the case of **antimicrobials**, a **different framework** is generally invoked because of the limited market revenues that can be 'pulled' by these mechanisms;
- **Data exclusivity** was introduced in a moment in which patent protection was limited in most European countries and acted efficiently to provide a balance among the three objectives. It is still perceived as **useful because of the impact it can have on further development of the existing product** and may be very important for small companies;



- It is very important that the protection framework is **predictable** because of the long investment horizon that characterizes pharmaceutical R&D;
- **Transparency** on the length and the scope of these measures **is invoked** to have predictability for generic entry.

#### **Transferable exclusivity vouchers (TEVs):**

- Respondents that are against the use of TEVs (most public health experts and researchers/clinicians) noticed how, in the current framework, the price of drugs can be very high, and **granting a TEV is risky** because it is very uncertain on which product it will be used and who is going to pay (it can shift the burden of paying for the innovation onto a certain group of patients and also across Member States); there is also a concern related to the **increased uncertainty around the expiry of (data) exclusivity**. The voucher can potentially be used for high-priced drugs, leading to serious financial consequences. Also, it tends to be perceived as an incentive mainly for large companies;
- Some respondents perceive TEVs (and transferable data exclusivity voucher that have been proposed in the proposal for the new European Pharmaceutical Regulation) as a valuable option, especially in the context of antimicrobials. As an advantage, TEVs are extremely **easy to implement**, and they **do not require a coordination effort** among EU Member States;
- In order to grant predictability, **clear and timely information must be available on where the voucher will be used** (the proposed EU reform goes in this direction);
- The voucher **should be conditioned on availability, therapeutic value, level of innovativeness of the drug** for which it is granted.

#### **Priority review vouchers (PRVs):**

- Most respondents are **against the use of PRVs** in a European context either because useless or even detrimental;
- PRVs **do not stimulate R&D investments and do not ensure access**, so that conditions on access to the new medicine should also be considered;
- The perception is that they have **stressed the review system** in the US (and this might also be a problem in the European framework), and there is a **risk of inaccurate reviews**;
- Only one respondent is extremely supportive of this measure, described as already successfully tested in the US. However, to optimise the impact of this incentive, the scheme should be introduced in Europe as a **complement** to the US program,

#### **Advance purchase agreements (APAs) and subscription models (SMs):**

- APAs and SMs are often commented together;
- In most cases, they are perceived as **valuable options for fostering research, particularly when directed to support research around AMR**;
- They can produce **adequate and certain revenues over time, while ensuring access**. Indeed, APAs can be flexibly designed to include access constraints or licensing options of the new compound;
- The **challenge** is to **set the right price**;
- In the antimicrobial setting (characterised by a high risk of failure and bankruptcy) the price should allow the innovator to ensure that the product is regularly supplied, and its use monitored (including aspects related to resistance) as well as to carry on additional research efforts;

- The application of **SMs** can be more **problematic** as compared to **TEVs in the EU context due to the need to define the contribution of each Member State**. However, the possibility of overcoming the phase of negotiation of the reimbursement price in each Member State is an advantage;
- **SMs** have the advantage of **de-linking** the revenue stream from the quantity sold, which is important in the case of antimicrobials;
- Any effort related to AMR should also address the problem under a cultural perspective to enhance appropriateness in the use of antimicrobials;
- One respondent points to the fact that APAs may work, but they cannot be 'stand-alone' and **need to be properly balanced with other measures**.

#### **Innovation prizes** (milestone R&D payments or market entry rewards):

- Sometimes commented together with APAs and SMs, but some specificities are identified;
- Generally ranked as **effective and efficient in stimulating R&D** with the advantage of providing a clear direction to the innovation process (e.g., with objectives defined by independent scientists), and value may also be **linked to the therapeutic value of the drug**;
- They would be **critical for small/medium enterprises**, because they **can grant support in the early stages of development**;
- **If prizes are used in addition to patents, access conditions should be considered**;
- Market entry rewards may be superior with respect to milestone payments, because they reward a product that has proven therapeutic effects. Relatedly, milestone payments entail a high risk for the payer and **their value is difficult to be determined**, especially when rewarding early-stage achievements;
- One respondent challenges the idea behind innovation prizes, as pharmaceutical innovation and **drug development is not a 'one-shot' experiment**, rather the process is cumulative with different waves of innovation, **making it difficult to identify 'the one invention' to be rewarded**.

#### **Tax credits:**

- This incentive received the least attention in the interviews. Those mentioning it notice that tax credits are **not currently feasible at the EU level**, so they are not worth investigating. However, coupled with other tools, tax credits would help generating a sustainable innovation system at the EU level;
- Tax credits would be **irrelevant for companies that make no profits**. This situation is more common for small companies.

#### **Other:**

- In the context of rare diseases, scientific support (e.g., protocol assistance; intelligence support) is perceived as extremely important;
- **A mix of incentives is considered superior** to the use of only one of them to ensure an inflow of financial resources throughout the product life cycle.

### 4.3. Alternative frameworks

*Question 3. Do you envisage any more radical reform of the current system of incentives (mostly based on patents and exclusivity) to achieve these objectives?*

When answering to Question 3, most interviewees commented upon the pharmaceutical sector; however, some respondents also answered focusing on UMN and AMR. Two participants did not respond to this question.

**Three main positions** can be identified: **(i) the system works**; **(ii) the system may work but should be adjusted to find a better balance between the three objectives** (prevailing view); **(iii) the system does not work, and some radical reforms should be put in place**. New approaches were often invoked in the context of for UMN and AMR.

The different views are detailed in the following:

- It is **difficult to strike a balance between the three objectives**, and a **political decision** is needed. This choice has **implications for the competitiveness and innovativeness of the European pharmaceutical industry**, that is **declining as compared to the US** (that, together with China, provides greater support to the industry to attract investments). Relatedly, concerns are raised about the impact of the reform on the European pharmaceutical industry;
- **The EU innovation system should be reinforced using also other tools in addition to exclusivities**, such as tax incentives and the development of a strong and virtuous research system (bridging universities, public research and the private sector). Public financing may also have a role by selecting areas of excellence;
- In pharmaceuticals, **predictability and stability are essential** because of the investments' long horizon (15-20 years);
- The **current system of incentives** has proven to be **effective in stimulating research efforts in the pharmaceutical domain**. However, there is **room for 'experimentation'**, e.g., change the length and breadth of available provisions to better understand their functioning and limitations. Limited areas, such as antimicrobials, may be a useful laboratory for experimentation.

Different concerns arise in relation to the functioning of the current system:

- The **patent system** was originally designed to reward innovation and provide a balance between the different objectives, but it has then been **misused** so that now it is **not clear whether it is still serving its original purpose**. Reforms of the current framework should be more focused on patients, access, and affordability. As a first step, Europe should recognize that the **current system is imbalanced** as signaled by the presence of excessively high prices, with **new innovative therapies strongly impacting national budgets**;
- **Stimulus to support repurposing of drugs is envisaged**, e.g. by introducing additional protection to new therapeutic indications;
- One limitation of the current system is that patent grant is not necessarily linked to the therapeutic value of the protected compound. An effort should be made to better **direct innovation efforts toward drugs with therapeutic advantage**, and to drive investment **towards the areas with higher societal value**;

- A **stronger involvement of the EC** in the different stages of the process is invoked by different respondents. The EC does not have power on reimbursement and price setting, but it should enter this discussion for the innovations that it decides to push more. It is suggested to create a European Compassionate Use Program, which builds on the EMA PRIME scheme to facilitate negotiation with payers or to accelerate access to these priority medicines. Another proposal is the creation of an **EU fund for centralized procurement**;
- A new framework would be needed that encourages **reasonable prices, without being detrimental to company profits**, taking also into account the amount of public financing already received. A '**sufficiency principle**', whose objective is to avoid over-protecting the investments, may be considered.

Some interviewees invoked **radical reforms**, with different interviewees providing **different alternative models**, as detailed in the following;

- **Increase the involvement of public research in all development stages** (including clinical trials). Two possibilities: (1) public organizations patent their findings, and the private sector is involved in the production of compounds via licensing agreements; (2) public organizations are not allowed to patent their findings, and knowledge is disseminated through scientific publications;
- **Increase the role of PPPs and other actors to improve health**. Europe should set its medical priorities and then select the best project to be financed as to actively manage the innovation ecosystem;
- Substitute, at least in some clinical areas such as antimicrobials, the current monopoly-based model with a model in which collaboration is first established between the industry, the academia and public institutions (that could fund part of the research) and then competition should be in the latest development stages and in manufacturing the product (**collaboration and competition model, to replace the current competition-monopoly model**);
- Replace the monopoly incentive system with **innovation prizes**. The advantage of market entry rewards with respect to R&D payments is in the fact that only successful development is rewarded.

A new framework is invoked in the context of **UMN**, especially for the development of antimicrobials, as **innovation rewards based on patents and exclusivities are not able to foster research effort in this area**:

- Different solutions are proposed including an **open-source model** and **PPPs**;
- In the case of antimicrobials, it is essential to **delink** revenues from volumes of sales;
- Finance **antimicrobial** development using a '**play or pay model**' under which those pharmaceutical companies that do not have an infectious disease department should contribute to a fund that may be used to reward the 'player' in infectious disease research;
- **The issue of AMR should be addressed centrally** given the 'public good' nature of innovation in this context.

## 4.4. A comment on the proposal for a new EU pharmaceutical legislation

*Question 4. If you had the chance to gain information on the current EU legislation proposal, could you mention what you believe it is its main weakness and main strength?*

As for previous questions, not all interviewees answered, and the rate of response varies also between strengths and weaknesses, with a clear prevalence of the latter.

Most respondents recognise the proposal is a step in the right direction, especially in **shedding light on the issues of affordability and access**. At the same time, many interviewees are sceptical about the timing and the instruments chosen. **The introduction of TEVs appears to be particularly controversial.**

### Strengths

- The legislation proposal is considered by many interviewees a **good start** that potentially moves in the right direction **in addressing the issues of access** to pharmaceuticals in Europe;
- The requirement of **broader transparency regarding R&D public funds** received is positively evaluated;
- The introduction of **Union compulsory licence mechanism** in case of health crises is welcomed by some interviewees (mainly, public health experts) who claim that this mechanism should not be limited to crises situation;
- Representatives of the generic industry positively value the **reaffirmation of the validity of the 'Bolar exemption'**. Indeed, Article 85 provides the list of exceptions to patent rights and SPCs that do not constitute a patent infringement. It also clarifies that price and reimbursement are included under the 'Bolar exemption';
- One respondent highlights that there is a positive attempt to apply a 'sufficiency principle' in relation to orphan medicinal products.

### Weaknesses

- Many stakeholders, mainly public health experts, claim that the proposal brings forward many little changes without actually modifying the current system. In particular, one respondent underlines that the **complexity of the proposed system** could result in a potential lack of internal consistency;
- Some interviewees are critical about the perspective embraced in the proposal, pointing out that **the legislation seems to favour competition instead of cooperation**, also when cooperation could be more appropriate (e.g., open access platforms for insulin infusion pumps);
- The proposal of introducing **TEVs is highly debated**. From the perspective of the pharmaceutical industry, this incentive scheme is considered a **good stimulus for innovation**, even though some skepticism is expressed regarding the excessively demanding requirements to be met. Conversely, other respondents are drastically against it. Among the arguments provided, some claim that TEVs would introduce **more uncertainty for generic companies** and further complicate the system since the additional protection is not tied to the product for which the voucher is initially granted. Therefore, TEVs could encourage strategic behaviours by big producers and consolidate monopolies.

**PRVs and SMs are suggested by two different public health experts as viable alternatives;**

- Some respondents are concerned with the **modulated duration of data and market protection**. In particular, combining the reduction of market exclusivity from 8 to 6 years with the possibility to extend it under some circumstances (e.g., market authorization in all 27 Member States, paediatric trials, and trials against a relevant and evidence-based comparator) creates **uncertainty for generic products**, especially with regard to the timing of entrance;
- Some interviewees highlight the **difficulty in receiving approval in all EU Member States within two years from EMA approval**, and the proposed waivers do not solve this issue. One respondent proposes to **consider application** within one year rather than actual approval within two years;
- Some interviewees note how the legislation, when dealing with several issues such as AMR, should not **ignore the global perspective**;
- The proposal may add complexity for rare diseases because 'high UMN' are vaguely defined;
- Some respondents notice that the proposal does **not place sufficient emphasis on the creation of added-therapeutic value**.

## 5. Discussion

The **pharmaceutical framework is highly complex**. This is due to a number of factors, including the length and uncertainty of pharmaceutical R&D processes, the global nature of the playing field, and the size of the investments required. The two **key objectives – innovation and access – can be difficult to reconcile** when the incentive for private investors is linked to market revenues, which in turn depend on prices.

In recent decades several pharmaceutical innovations have contributed to increased life expectancy and better quality of life for patients. Nevertheless, some significant challenges still lack adequate solutions. **Access** to new products is **not always granted** to patients, even in cases in which public investments play a crucial role in the R&D process. Furthermore, some therapeutic areas suffer from scarcity of private investment, leading to the existence of **UMN**. These areas are scarcely attractive, because of the **small market size** or the **low** level of **expected prices**. Finally, a large proportion of new medicines offer **limited therapeutic advancement** in comparison to existing ones and the **number of superiority trials is lower than desirable**. **Direct involvement of the public sector is mainly limited to basic research**, and synergies with the private sector are underexploited.

We use the combination of results from our extensive overview of the literature, complemented by interviews with expert stakeholders, to assess the strengths and weaknesses of several tools and frameworks that can be used to promote pharmaceutical innovation, direct innovation towards specific therapeutic areas, grant patient access and predictability for producers of generic and biosimilar drugs. Results are presented in Table 3.

The **current framework mainly relies on exclusivities** (including patents, SPCs, and regulatory exclusivities) to provide incentives to innovate. Exclusivities, however, struggle to find a balance between the stimulus to innovation and access, because of possibly high prices due to limited competition.

There are several reasons to believe that the provision of **incentives to private R&D investment based on exclusivities will continue to play a major role** in the future. Firstly, the TRIPs agreements pose constraints to the reform of IPR policies. Moreover, by relying on the market as the main source of incentive, exclusivities reduce the regulatory burden and the risk of allocating R&D investments to projects with limited likelihood of serving patients. Additionally, they do not require an upfront payment from the health system. Finally, under the current framework, **remarkable results in terms of ability to improve patient outcomes have been achieved**. A related question is **whether the extent to which investments are protected by exclusivities is appropriate**. Existing comparisons between the profitability of the pharmaceutical industry and other sectors tend to indicate that the former does better, even when accounting for risk, although the estimated differences vary considerably depending on the study considered. Moreover, this is not necessarily true for all companies, and results seem to be significantly less favourable, on average, for small biotech companies. The public sector often plays an important role, e.g., by undertaking basic research on which several innovations are grounded, or by providing financial support to private companies. Some contributions from the literature, as well as some interviewees, suggest that this role should be considered in setting prices.

Once an appropriate length of exclusivities is determined, **ensuring transparency on the timing of expiry** is essential to allow timely entry into the market for the producers of generics and biosimilar products. This condition is not always ensured, because the current system leaves room for strategic use of exclusivities to extend their length (evergreening strategies). The problem is

exacerbated by the fact that the protection provided by the combination of patents and SPCs varies across countries.

Another limitation of **exclusivities** is that, by relying on the market as a source of incentive, they **are unable to direct R&D investments towards areas where the size of the market is particularly small**, or uncertainty on future profits is particularly relevant as, for example, in the case of **future health emergencies**. Addressing these challenges requires identifying the most appropriate incentive tool on a case-by-case basis.

When the size of the market is the main reason why a therapeutic area is not appealing for R&D investment it is essential to **de-link the amount of the reward received by the company from the size of the market**. The fact that the current orphan legislation is mainly based on reinforced exclusivities is probably one of the reasons why its impact on R&D targeting diseases with particularly low prevalence was limited (Gamba et al., 2021). De-linkage may be obtained by relying on tools that involve an ex-ante commitment (APAs, SMs and innovation prizes). The use of these incentives could be particularly interesting to address UMN related to **diseases with extremely low prevalence and, in particular, for antimicrobials**. In the field of antimicrobials, incentives towards innovation should be part of a broader strategy meant to ensure appropriateness in the use of these products. This strategy could also include new pricing schemes, suitable to reduce the risk of overuse and misuse. Ex-ante commitment agreements also ensure access. From the perspective of the industry, they reduce market-related risks. Potential issues related to the introduction of ex-ante commitment agreements include the need to define the amount of the upfront payment and the conditions under which it is awarded. Moreover, the use of these instruments has been limited so far, providing limited evidence on their impact as a stimulus to innovation. Implementing prizes and SMs at the EU level would also require defining the size of individual countries' contributions to finance them. The opportunity to de-link revenues from sales is greater for SMs and innovation prizes compared to APAs. Additionally, when compared to innovation prizes, SMs reduce the risk of shortages.

Ex-ante commitment agreements, and in particular SMs, seem more promising than vouchers (PRVs and TEVs) that also allow for the de-linking of revenues from sales. An advantage of vouchers is not requiring an upfront payment from the health system. However, for PRVs, evidence on the impact on innovation is controversial, whereas the impact of TEVs is potentially positive (but this instrument has not yet been implemented). With vouchers, access to the incentivised product is not guaranteed, and specific conditions need to be defined. Because vouchers are granted for one product, but may be used on a different product, these tools may adversely impact access in the market where the voucher is used. In particular, TEVs limit access by extending an exclusivity, while PRVs have a positive, though limited, effect because of faster authorisation. Other implications of transferability are that the size of the reward is decoupled from the value of the innovation, and, in the case of TEVs, the actual cost of the incentive is hard to predict. This is one of the reasons why TEVs do not receive strong support either in the literature or in the interviews.

Is a well-designed system of incentives sufficient to successfully address all the challenges highlighted above? Some R&D projects entail **risks that private investors are unlikely to be willing to face**. This is true, for example, for future **health emergencies**, for which uncertainty is huge, as are the related health threats. Another threat we are not yet prepared for is **AMR**. On this point, the existing literature and most stakeholders interviewed call for **urgent action**. In this framework, **public-oriented approaches** can act as a **complement to a strong and competitive private industry**, by focusing on areas that are particularly unattractive for private investors. These



initiatives would also bring benefits related to patient access, which is another motivation for their introduction. The creation of an **open science framework** can contribute to the diffusion of **knowledge spillovers** and, along with well-designed PPPs, to the creation of **synergies between private and public initiatives**. For some initiatives, such as open science and PPPs, results may be expected reasonably soon. On the other hand, the creation of a **pharmaceutical R&D infrastructure must be seen as a long-term investment**, involving a **substantial upfront payment**.

In addition to the specific incentives discussed so far, other aspects of the regulatory framework play an important role. Within the EU, the fact that Member States are responsible for market access procedures, including reimbursement and pricing decisions, leads to large disparities in access: launches may be delayed by several years (Büssgen & Stargardt, 2022) especially in some, often small countries, or new products may not be launched at all. Interestingly, the view that pricing and reimbursement decisions at country-level are crucial determinants of missed or delayed access is shared by all categories of respondents, including patients, the industry and experts from different backgrounds. These difficulties have led some countries to set up joint purchasing initiatives, such as the Beneluxa, involving Belgium, the Netherlands, Luxembourg, Austria and Ireland. Joint procurement at EU level is possible for medical countermeasures for serious cross-border health threats (Decision 1082/2013/EU), and was implemented during the COVID-19 pandemic.

Table 3 – Summary of results: impact of incentives on different dimensions

	Impact on:			
	innovation	direction of R&D (e.g. UMN)	access	predictability for generics, biosimilars, competitors
<b>Exclusivities</b>				
<b>Patents</b>	Prevailing view: positive	Very limited (market-based incentive)	Negative (high prices from limited competition)	Negative (strategic behaviour)
<b>SPCs</b>	Controversial	Very limited (market-based incentive)	Negative (high prices from limited competition)	Negative (differences among countries)
<b>Data exclusivity</b>	Positive but limited	Limited (market-based incentive)	Negative (barely relevant if shorter than market protection)	Negative (strategic behaviour)
<b>Market protection</b>	Positive (in absence of patents)	Very limited (market-based incentive)	Negative (high prices from limited competition)	Negative (strategic behaviour)
<b>Market exclusivity</b>	Positive	Very limited (market-based incentive): weak incentives for ultra-rare diseases	Negative (high prices from limited competition)	Negative (strategic behaviour)
<b>Vouchers</b>				
<b>TEVs</b>	Potentially positive (never implemented)	Positive (incentive delinked from market size)	Null in the market of targeted product; negative in the market where it is used	Negative in the market where it is used (provisions to limit this drawback need to be included)
<b>PRVs</b>	Controversial	Positive (incentive delinked from market size)	Null in the market of targeted product; positive but limited in the market where it is used	Null

	Impact on:			
	innovation	direction of R&D (e.g. UMN)	access	predictability for generics, biosimilars, competitors
<b>Ex-ante commitment</b>				
<b>APAs</b>	Positive (reduced market risk for manufacturers)	Positive (incentive partially delinked from market size)	Positive (if prices and quantities are appropriately defined)	Null
<b>SMs</b>	Potentially positive (reduced market risk for manufacturers; limited evidence)	Positive (incentive delinked from market size)	Positive	Null
<b>Innovation prizes</b>	Potentially positive (limited evidence)	Positive (incentive delinked from market size)	Positive (if patents are replaced)	Positive (if patents are replaced)
<b>Push incentives</b>				
<b>Tax credits</b>	Positive (reduced costs for manufacturers)	Limited (weak incentives for ultra-rare diseases)	Null	Null
<b>Public oriented approaches</b>				
<b>Open science</b>	Positive	Positive (no profit objectives)	Positive	Positive
<b>PPPs</b>	Positive	Positive (dedicated effort)	Positive (many product-development PPPs focus on this aspect)	Positive (most PPPs adopt an open science approach)
<b>Public R&amp;D infrastructures</b>	Potentially positive (limited evidence)	Positive (dedicated effort)	Positive	Positive

## 6. Policy options

The study identifies five policy options (POs) that could be considered to address the main issues arising from the overview of the literature and the interviews. A baseline case (PO0), reflecting the current situation, is used as a benchmark for the assessment of the alternatives.

### **PO0 Current regulatory framework**

The current regulatory framework is mainly based on the following instruments: patents, SPCs, market protection, data exclusivity, market exclusivity and some other push incentives (e.g., priority review vouchers, tax credits defined at the national level). The combination of instruments is tailored to the specific characteristics of the medical condition addressed. For example, in the EU, orphan drugs are granted market exclusivity, while SPCs are extended in cases where clinical trials include paediatric populations.

Decisions on patents to be taken at the EU level are constrained by the existence of the TRIPS agreement at the WTO level. On the other hand, decisions on other instruments (e.g. tax credits, SPCs) are taken at national level. Member States are also responsible for pricing and reimbursement decisions. For public health emergencies, strategic coordination for the development of medical countermeasures is entrusted to HERA, which is also responsible for joint procurement under these circumstances.

#### **Strengths:**

- Innovations achieved with important impacts on patient outcomes;
- Attention paid to rare diseases under the Orphan legislation;
- Prevalence of market-based incentives reduces the risk of over-investment in projects with limited likelihood to reach the patient;
- Limited need to seek coordination at the EU level for decisions with financial implications.

#### **Weaknesses:**

- Different tools often overlap, thus reducing clarity on the actual extension of protection, especially when relevant decisions are made at the national level;
- Inequality in access to innovation related to the relevance of the national level in pricing and reimbursement decisions;
- Negative impact on access, due to high prices for some innovations;
- Relevance of UMN, such as the large number of orphan diseases with no therapeutic option;
- Weak incentives for the private sector to address future emergencies subject to substantial uncertainty;
- Prevalence of incremental versus disruptive innovation;
- Substantial uncertainty on the actual extension of exclusivity faced by competitors and generics;
- Possibility for manufacturers to exploit evergreening strategies.

The highlighted weaknesses suggest that a reform of the current regulatory framework should be considered.

## PO1 Strengthening EU coordination in IPR and procurement

The option to strengthen coordination in IPR would essentially reinforce initiatives that have already been undertaken. A milestone in this direction is the recent creation of the '**unitary patent**', and the proposal to create a '**unitary SPC**', the implementation of which is already under discussion.

Article 5 of Decision 1082/2013/EU provides that the institutions of the Union and any Member States wishing to do so may engage in a **joint procurement procedure** for medical countermeasures for serious cross-border health threats. This also provided the legal basis for joint procurement of COVID-19 vaccines. This policy option would involve a significant extension of the use of this instrument beyond emergency situations. An **EU procurement authority** could be established alongside an **EU pharmaceutical fund**. The role of the EU procurement authority could be similar to that of HERA in case of public health emergencies, but extended beyond these circumstances. Once products have received EMA authorisation, the EU procurement authority could be responsible for negotiations with manufacturers. This could also lead to the definition of a **transparent EU price**, hopefully grounded on explicit evidence-based criteria (e.g. cost-effectiveness). The coordination of HTA initiatives under Regulation (EU) 2021/2282 could contribute significantly to this achievement. The EU price could be the amount received by the manufacturer for each unit sold and be paid through the EU Pharmaceutical Fund. Each country could contribute to the fund by paying, for each unit used within the country, a given amount, which could be defined considering the country's ability to pay (proxied by appropriate measures such as, e.g., per-capita GDP). This country-specific contribution may be higher or lower than the EU price. To ensure **financial sustainability** of the fund, country-specific contributions should be such as to ensure balance between the total expected amount to be paid to the manufacturer and the expected total amount of contributions made by Member States. As part of a risk management strategy, an experimental phase of the policy could be envisaged, limiting centralised procurement to a relevant number of products. Importantly, to increase the chances of reaching a consensus, Member States could be given the **option to opt out** of coordinated procurement, even for a single product, as also permitted under the Joint Procurement Act. In this case, pricing and reimbursement decisions would be taken as under the current system.

This policy would require a significant initial investment and reaching a broad consensus among Member States. However, it could lead to a 'win-win-win' situation for patients, the industry and national regulators/payers. Patients could benefit from earlier access to new products, with reduced disparities between countries. The pharmaceutical industry could enhance efficiency, by significantly reducing explicit and implicit costs (primarily due to launch delays) associated with national market access procedures. National regulators/payers could also see a significant reduction in the transaction costs related to pricing and reimbursement decisions, for which they would be able to rely on a highly qualified EU authority.

Some of the problems associated with parallel trade could also be alleviated by the existence of an EU price. The advantages of this policy option are greater the larger the number of participating countries.

**Advantages** with respect to PO0:

- Earlier access and enhanced availability for patients;
- Reduced disparities in availability between countries;
- Quick timeframe for product launches for industry;

- Reduced transaction costs;
- Greater transparency on prices.

#### **Disadvantages** with respect to PO0:

- Need to establish a new EU authority (or assign additional competences to an existing one) and financial mechanism;
- Need to define each Member State contribution to the fund;
- Need to reach a wide consensus among Member States.

#### **PO2 Adjusting current incentives to limit excess profits**

The current framework provides a number of incentives for innovation. However, these are still insufficient to stimulate R&D in some areas, while in other cases R&D investments are overpaid. PO2 would aim **to reduce the risk of overpaying for R&D**, by adjusting the length of exclusivities granted, according to circumstances such as whether the revenues generated are sufficient to **compensate for the R&D costs** or the amount of **public funding received**. To the extent that this policy could reduce prices, by reducing the length of exclusivity period, it could also provide benefits in terms of patient access.

#### **Advantages** with respect to PO0:

- Savings for public financial resources that could be reinvested in R&D (e.g. to address UMN);
- Greater transparency in the use of public funds;
- Enhanced patient access.

#### **Disadvantages** with respect to PO0:

- Difficulty in estimating profitability of single products (only revenue could be reasonably estimated);
- Reduced incentive to improve efficiency for industry due to profit caps;
- Difficulty in defining a fair level of profits;
- Complications related to the association between public funds received and specific products.

#### **PO3: Redesigning incentives**

This policy option would involve a revision of the way in which some of the incentives are currently deployed and the adoption of some new solutions. One issue characterising the current system is its complexity. One reason for this is that different forms of exclusivity often overlap, and their expiration date may vary from one country to another. The complexity of the framework provides a greater scope for industry to take strategic action aimed at extending exclusivities beyond the original expiration date, which may adversely affect access and predictability for competitors. Another issue is the existence of UMN.

This policy option would involve the following changes:

- **Simplification** of the system of exclusivities. This could be achieved by relying **mainly on patents and SPCs**, both of which could benefit from simplification thanks to the ongoing initiatives on the unitary patent and the proposal for a unitary SPC. The duration of the **other**

**forms of protection** (data and market protection) **could be reduced** with respect to PO0. In particular, **data exclusivity should be used cautiously**, as it can pose an important barrier to knowledge spillovers. Even better, data exclusivity could be replaced with data compensation, i.e., the possibility for other actors to access data against payment. However, the extent to which exclusivities are reduced should be carefully defined so as not to weaken the incentive for the private sector to invest in innovative projects.

- Studies aimed at extending the use of medicines to **new indications** could be supported (repurposing). In this case, the most appropriate instrument would seem to be an extension of the length of market protection.
- There is a reasonable consensus that the existing **Orphan** legislation has stimulated R&D in this area, although the impact has been limited or absent for diseases with extremely low prevalence. In light of the results achieved, the combination of market exclusivity with other incentives currently provided (e.g. assistance in trial design) could be confirmed. **Additional instruments** whose impact is de-linked from the size of the market could be dedicated to diseases with **very low prevalence**. In particular, medicines targeting these diseases could be eligible for **subscription models** under certain conditions, such as the ability to treat a disease for which no medicine with a specific indication exists and/or the availability of evidence of relevant added therapeutic value. This is in line with the definition of high UMN in the proposed new EU pharmaceutical legislation. A risk associated with the introduction of subscription models is that the evidence of the impact on innovation remains limited.
- **Antimicrobials** present unique challenges. Standard market-based instruments are clearly inappropriate to incentivise private R&D while tackling resistance through appropriate use. Under this policy option the key tool to stimulate private R&D would be **subscription models** managed at the EU level. However, it would be essential to incentivise a parsimonious use of new antimicrobials by also using prices as a tool. To this end, following a scheme similar to the one described under PO1 for joint procurement, **Member States** could be required to **contribute to an EU fund** according to the quantities used. In this case, the price could be non-constant. In particular, the **unit price** paid by the Member State could **increase with the level of consumption per capita at the country level**, as an incentive to avoid overuse and misuse. Subscription models could also help in **addressing the problems of shortages** that sometimes arise at the country level.

**Advantages** with respect to PO0:

- Explicit targeting of (high) UMN to create new therapeutic opportunities where they are still lacking;
- De-linkage of revenues from volumes for antimicrobials (reduces risk of AMR);
- Reduced risk of shortage of antimicrobials with the use of subscription models;
- Reduced uncertainty for the industry in the market of antimicrobials and ultra-rare diseases.

**Disadvantages** with respect to PO0:

- Risk of lower incentive for private companies to invest in R&D in cases where market and data exclusivity are reduced;
- Difficulty in defining the fair value of subscription payments;
- Risks related to the use of relatively new incentive tools (e.g. subscription models);

- Need to find an agreement on the rules defining contributions at the country level to fund subscription payments.

#### PO4 A European infrastructure for pharmaceutical R&D

The policy options presented so far rely on the fact that an appropriate system of incentives may stimulate private sector R&D investment in areas where it remains insufficient to address patient needs, whilst addressing the other existing challenges, such as access. PO4 suggests a **more active role for the public sector**, with the objective of directly addressing some remaining challenges and creating an opportunity to better exploit the synergies with private initiatives, including relying on PPPs. In particular, this option involves creating a European infrastructure for pharmaceutical R&D in the public interest, with a well-defined research agenda **focusing on areas where private sector investment falls short**. Natural areas of interest would be those characterised by the presence of UMN, but attention could also be paid to mitigate the consequences of health emergencies, such as pandemics and epidemics, which have additional relevant economic implications. The European infrastructure could also play an active role in conducting **independent superiority trials and repurposing studies**.

The European infrastructure would have its own dedicated budget, conducting R&D activities in its own laboratories and/or through R&D contracts with selected third parties. The activity of the new infrastructure could cover the whole product life cycle, by extending the existing capacity of public institutions to undertake late-stage phases. The infrastructure could adopt an original approach with respect to IPRs, such as open science, or a socially responsible IP approach. As part of this strategy, profits from non-exclusive licensing would be reinvested, and licensing agreements should specify drug price conditionalities to grant patient access.

Further details on the characteristics of the public R&D infrastructure are provided in Florio et al. (2021). Moreover, the European Parliament has already adopted a resolution asking the European Commission and Member States to assess the need for a large-scale, mission-oriented, public European health R&D infrastructure.

#### **Advantages** with respect to PO0:

- Better alignment between public health needs and R&D investment;
- Attention paid to repurposing and superiority trials;
- Enhanced access to innovation;
- Better opportunities for knowledge integration and dissemination;
- Transparency of R&D costs.

#### **Disadvantages** with respect to PO0:

- Long-term implementation;
- Limited evidence on ability to manage innovation throughout the whole product life cycle, due to limited application thus far;
- Large upfront payment from the public sector required.



## PO5 A comprehensive approach

This policy option is based on a **combination of PO1, PO3 and PO4**.<sup>51</sup> The EU coordination of IPR policies and procurement could be substantially strengthened, as detailed in the description of PO1, which might ensure more timely and equitable access to innovation for patients. The current system of incentives could be revised in accordance with PO3. This revision would involve a decrease in the duration of market protection and data exclusivity, and the implementation of specific incentives (including SMs) for UMN, carefully selected to account for the underlying R&D challenges. Even a well-designed system of incentives is unlikely to provide solutions in those areas where the incentive for private investors is particularly weak, such as emergency preparedness and particularly small markets. The role of a European infrastructure for pharmaceutical R&D (PO4) would be an essential complement to private initiatives and could bring additional benefits, such as greater focus on repurposing and superiority trials and the creation of knowledge spillovers.

The **value of this combination of policies would exceed the sum of its components, by creating additional synergies**. For example, the impact for the industry of reduced market protection and data exclusivity (PO3) could be compensated by a substantial reduction in the time needed to enter national markets and the costs related to these costly and uncertain processes, as a result of greater EU coordination (PO1). The creation of an EU pharmaceutical fund (PO1) could facilitate the implementation of subscription models (PO3). The redesign of incentives to fulfil UMN (PO3) could produce immediate results, thus also covering the lengthy implementation of a complex project such as introducing an European R&D infrastructure (PO4). Over time, this infrastructure could contribute to reducing the knowledge gap on actual R&D costs through a deeper EU involvement in these activities. Finally, PO5 could result in a more efficient allocation of R&D priorities between private and public infrastructures, based on specialisation and cost efficiency, as well as in an improved ability to establish public-private partnerships.

**Advantages** with respect to PO0:

- Exploitation of synergies among PO1, PO3, PO4;
- Mitigation of risk through the diversification of actors (private and public) involved throughout the whole R&D chain;
- Earlier access and enhanced availability for patients;
- Reduced disparities in availability between countries;
- Quick timeframe for product launches for industry;
- Reduced transaction costs of market access;
- Greater transparency on prices and R&D costs;
- Explicit targeting of (high) UMN to create new therapeutic opportunities and preparedness for emergencies;
- Advantages of the use of SMs for antimicrobials: de-linkage of revenues from volumes, reduced risk of shortage, reduced uncertainty for industry;
- Better alignment between public health needs and R&D investment;
- Attention to repurposing and superiority trials;

<sup>51</sup> PO2 shows important implementation hurdles and some of its objectives could be more efficiently achieved through some of the provisions of PO3 (e.g., the reduced length of existing exclusivities).

- Better opportunities for knowledge integration and dissemination.

**Disadvantages** with respect to PO0:

- Need to reach a wide consensus among Member States to establish a new EU authority (or assign additional competences to an existing one) and a financial mechanism;
- Large upfront payment from the public sector required;
- Risks related to the use of relatively new incentive tools and frameworks (e.g. subscription models, public infrastructure active throughout the whole R&D chain).

## 7. Conclusions

This study examines the impact of regulatory mechanisms and alternative frameworks on access to and innovation in pharmaceuticals. The study combines an extensive review of the scientific literature and technical reports, involving more than 230 different sources, and 24 semi-structured interviews with selected international stakeholders (researchers and clinicians, public health experts, public officers, representatives of the pharmaceutical industry and patient organisations). The strengths and weaknesses of the current system are identified, and five policy options are considered. These options aim to ensure the development of accessible medicines in all clinical areas, improve availability, increase price and R&D cost transparency, and ensure preparedness for emergencies. To achieve these goals, **a combination of policies is suggested**, given the specificities of clinical areas, the relevant heterogeneity of diseases and the diversity of actors in the field with different ethos and capabilities.

The preferred policy option combination would include: **strengthening EU coordination on IPR and procurement; revising existing incentives** by reducing the length of exclusivities granted to all products **and introducing specific incentives** (subscription models), independent of market size, **for specific UMN** (antimicrobials and ultra-rare diseases); and **creating a public R&D infrastructure active throughout the whole R&D process** to address areas that may remain insufficiently attractive for private investors. Efforts could be made to significantly strengthen EU coordination in the areas of intellectual property rights and procurement to ensure patients have earlier access to new medicines and to reduce transaction costs for both payers and industry (including generic and biosimilar manufacturers). Within this framework, the current system of incentives could be redesigned, combining a reduction in the length of exclusivities granted to all products and the use of new (e.g. subscription models) and more targeted incentives to address UMN. Finally, a European infrastructure for pharmaceutical R&D could be established to complement private R&D initiatives, especially in areas where private investment is likely to remain insufficient. Such an infrastructure could also play a role in facilitating collaborations with private actors and in generating knowledge spillovers.

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## Annex – Questionnaire

*In what follows, we will ask you some questions related to different types of incentives that are used or may be used to incentivise R&D targeting unmet medical needs, in particular antimicrobials, orphan diseases and paediatric diseases.*

*You will be free to stop the interview at any time, and, if you do not feel comfortable in answering a question (or part of it), you can decide to skip it.*

**Question 1.** Given the current regulatory and incentive framework in Europe, could you rate from 1 (irrelevant) to 4 (highly relevant) each hurdle for each market? (The same level of relevance may be assigned to different hurdles)

	Antimicrobials	Orphan diseases	Paediatric drugs
Low expected revenues			
Perceived risk of failure in R&D			
Difficulty in running trials			
Uncertainty/complexity of the current regulatory framework (European and/or national)			
Other: ...			

**Question 2.** Consider the following list of incentives:

- supplementary patent protection certificates,
- data exclusivity,
- market protection (protection from marketing the same molecule),
- market exclusivity (protection from marketing similar molecule(s) with analogous characteristics),
- transferable exclusivity vouchers,
- priority review vouchers,
- advance purchase agreements,
- subscription models,
- innovation prizes (milestone R&D payments or market entry rewards)
- tax credits

Could you identify one or more among them that you believe is most effective/efficient in striking the balance between the following objectives?

- Stimulus for innovation, specifically for antimicrobials, orphan diseases, paediatric drugs;
- Availability and affordability;
- Predictability for generic companies and competitors.

*Question 3.* Do you envisage any more radical reform of the current system of incentives (mostly based on patents and exclusivity) to achieve these objectives?

*Question 4.* If you had the chance to gain information on the current EU legislation proposal, could you mention what you believe it is its main weakness and main strength?

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Health is a fundamental human right, and achieving equality in access to medicines is crucial for ensuring public health. The current system of innovation strongly relies on the private sector, while remuneration of innovation is mainly based on exclusivities. This system presents several issues, such as innovation being driven by market size, the partial misalignment between industry's research and development (R&D) priorities and public health goals, access constraints, and the scarcity of disruptive innovations. In this context, this study analyses the impact of different R&D incentive mechanisms and alternative frameworks that may contribute to pharmaceutical innovation and public health. In particular, the study analyses the implications for innovation and accessibility, in terms both of prices and of availability.

Based on an extensive review of the literature combined with interviews with expert stakeholders, the study offers a range of policy options. These seek to ensure the development of accessible drugs in all clinical areas, improve availability, price and research and development cost transparency, and ensure preparedness in the event of emergencies. Policy options suggested include strengthening EU coordination on intellectual property rights and medicine procurement, reducing the length of exclusivities, and introducing specific incentives (subscription models) de-linked from market size for specific unmet medical needs (antimicrobials and rare diseases with extremely low prevalence). A further suggestion is the creation of a public infrastructure active throughout the whole drug research and development process. A combination of policies would exceed the sum of its components, by generating additional synergies.

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