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European pharmaceutical research and development.
Could a public infrastructure overcome market failures?

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European Pharmaceutical Research and Development. Could a public infrastructure overcome market failures?

Massimo Florio and Chiara Pancotti

Abstract

With a focus on research and development in innovative medicines, this working paper discusses a new European approach to pharmaceutical policy. After examining the European pharmaceutical sector's features, and the strengths and weaknesses of the current research and business model, the study explores the need for and the concept of a European infrastructure with a long-term transboundary mission.

Any European medicines infrastructure should focus on threats and research and development areas underinvested under the current business model. More specifically, the study uses an extensive literature review to investigate the feasibility of different options in terms of the scope of the mission and legal, organisational and financial arrangements for establishing such a European infrastructure.

Based on their research, the authors present a range of policy options. The most ambitious of these considers a Europe-wide public infrastructure with budgetary autonomy and home-grown research and development capacity. This organisation would be tasked with building a portfolio of new medicines and related biomedical technologies up to the delivery stage over 30 years, in partnership with third-party research centres at the national or European level and with companies. It would be the world's most important global player in biomedical innovation.

Keywords: coronavirus disease, epidemic, medical research, pharmaceutical expenses, pharmaceutical industry, pharmacy, public health, technology assessment

JEL codes: H51, H54, I18

This working paper draws from selected parts of a study that was originally published by the Panel for the Future of Science and Technology (STOA), managed by the Scientific Foresight Unit of the Directorate for Impact Assessment and European Added Value, within the Directorate-General for Parliamentary Research Services (EPRS) of the European Parliament, with M. Florio as principal investigator.

The Working Paper aims to disseminate some findings. The study includes additional findings based on an expert survey led by D.A. Prockazka, University of Economics, Prague, see

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1 Introduction

1.1 Background

Europe's pharmaceutical sector and related biomedical activities are major contributors to the European Union (EU) economy in terms of overall added value, highly skilled jobs, research and development investment, and innovation. The functioning of the industry is of essence for European citizens' public health, the overall productivity of the EU economy, and the global role of the EU in addressing current and future health challenges.

However, the COVID-19 pandemic has spotlighted some critical issues in how governments have designed and managed their health policies, the priorities of pharmaceutical research, and market regulation. In particular, it has shown the importance of preparedness and ensuring the availability of appropriate medicines under any circumstances. At the same time, the COVID-19 pandemic has highlighted the value of collaborative R&D to develop new approaches for the detection, diagnosis and treatment of some challenges to human health and showed the importance of cross-EU and global collaborations against a country-by-country approach (Radin and Eleftheriades, 2021).

On 1 June 2020, the European Commission (EC) published a roadmap for a pharmaceutical strategy for Europe, which was then adopted on 24 November 2020. It aims to ensure Europe's supply of safe and affordable medicines and support the European pharmaceutical industry's innovation efforts. The strategy is a key component of building a stronger European Health Union, as advocated by the EC president Ursula von der Leyen in her September 2020 State of the Union Speech.

In such a context of rethinking a European approach to pharmaceutical policy, the STOA Panel of the European Parliament (EP) has launched a study to assess the desirability and feasibility of setting up a large-scale European public infrastructure aimed at addressing long-term market and policy failures in the pharmaceutical sector throughout the whole drug life cycle (research, development, production and distribution). The underpinning rationale for such a concept is to address failures that other existing remedies cannot effectively correct, such as regulatory reforms of the medicines authorisation framework, reconsideration of public subsidies to industry R&D, changes in tax and competition law, revision of protection of intellectual property (IP), demand-driven policies by payers of medicines. These issues are mostly outside the scope of the study.

Europe has a wealth of excellent research capacity at the national level, an international organisation body such as the EMBL, other valuable pan-European research infrastructures, and several competitive pharmaceutical companies. However, the EU is far from having achieved a critical mass of public institutions for biomedical R&D comparable to what is available in the United States (US). Indeed, the US has since long built their federal institutions in this area, such as the National Institutes of Health (NIH) and the Biomedical Advanced Research Authority (BARDA), with respectively a yearly budget (2020) of USD 41.7 billion and 1.6 billion. The NIH is mainly a funding organisation, but its Intramural Research Program (IRP), with around USD 4 billion per year, about 1,200 principal investigators and 5,000 Postdoctoral Fellows, is the largest biomedical research institute in the world (see details at https://irp.nih.gov/about-us). Other US federal agencies interested in biomedical research include DARPA (Defence Advanced Research Projects Agency), the DoE (Department of Energy), some National Laboratories, and other entities with federal funding. Overall, the US government is the top global player in public support for biomedical R&D.

As done so far, the existing EU system of direct and indirect support to R&D health projects has intrinsic limits, which cannot be solved with a mix of regulatory and marginal policy adjustments. Such limits cannot even be solved by creating additional authorities or agencies with limited budgets, possibly with some coordination powers, but without their world-class R&D pipeline,

objectively verifiable delivery mechanisms, with a public mission that commands the respect of the scientific communities, the national health systems, and European citizens

1.2 Objective & structure

This working paper aims to disseminate some findings from the study mentioned above. More specifically, the paper discusses the strengths and weaknesses of the current pharmaceutical R&D and business model and explores options for a European R&D infrastructure to address some market failures and other issues of concern from the public health perspective. Moreover, it assesses the feasibility of different options in terms of mission, legal, organisational and financial arrangements for establishing a new European infrastructure, a broad term covering, in principle, an R&D infrastructure and a delivery organisation with a transboundary public health mission. A terminological issue: the paper mentions pharmaceutical R&D for conciseness, but several issues dealt with here are also applicable to biological products, testing technologies and diagnostic innovations, and other fields of biomedical research.

This working paper is structured as follows:

- Section 2 presents the results of the desk-based research, i.e. it provides stylised facts on the pharmaceutical industry, an overview of the European pharmaceutical sector and its market failures, an overview of the European policy framework and the European health R&D panorama.
- Section 3 discusses the concept of the new European infrastructure, including an initial discussion of its mission, legal basis, financing, and IP management.
- Section 4 presents the policy options.
- Additional details, including workstrands and implementation issues, are given in the Annexes.

2 Literature review

2.1 Methodology and resources used

The methodology employed to draft the document at hand combines the finding from a selective literature/documentary review and a survey of expert stakeholders. The latter targeted over 50 experts and was conducted by Dr David Anthony Prochazka (Prague University of Economics and Business). For more details in this respect, see the STOA study[1]. The method for the literature review is presented below.

To guarantee that the literature we identify covers the most relevant issues, we employ a systematic approach and rigorous methodology combining different strategies, which are laid out in the following.

- A list of the relevant key-words for searching the scholarly literature was defined. We refine this list in an iterative process, where the results obtained from applying the search terms to the literature in scholarly databases such as REPEC and PUBMED decide whether it is necessary to adjust the terms or include additional ones.
- Publications by the most relevant stakeholders for contents relevant to the study topic were screened. This includes publications by the EC, the EP and other 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 consider selected publications by relevant think-tanks and consultancies. To ensure we include official statements and innovative viewpoints, we also scan blog posts and conference proceedings relevant to the subject.
- Once the relevant body of literature was collected, the documents/publications were classified by topics and keywords.

We read and assess the classified body of literature; hence we tried to identify commonalities and patterns within the statements made on each topic. From this, we derive an overview of the most relevant issues and viewpoints and a calibrated summary regarding both the current state and the (expected) future trends. This last step also allows us to substantiate the reliability of our findings by triangulation, meaning that different and independent sources support a statement. In addition, we take care that a good balance between sources is guaranteed.

2.2 Results

2.2.1 Background on pharmaceutical industry

The pharmaceutical industry can be defined as a complex system of processes, operations, and organisations involved in the discovery, development, and manufacturing of medical products (Moniz et al. 2015), including therapeutics drugs and vaccines. Note that the words ‘medicine’, and ‘drug’ are often used interchangeably, and the word ‘drugs’ can also include vaccines, depending on the context. In this document, the word ‘drug’ is arbitrarily assigned to the end-products of the pharmaceutical industry. The pharmaceutical industry, like many other contemporary industries,

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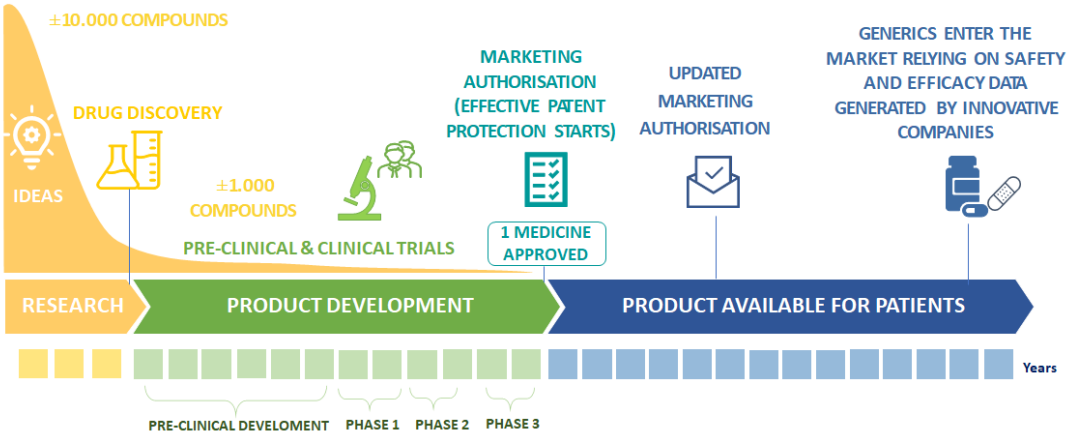
is organised along a global value chain (cf. EP, 2021; Kedron and Bagchi-Sen, 2012; Zeller and Van-Hametner, 2018), including the following stages:

- the discovery of new drugs through research;
- the pre-clinical development;
- the design and execution of clinical trials (3 phases);
- the approval of new drugs by public health authorities;
- the manufacturing of approved drugs, including:
- the supply/sourcing of key starting materials;
- the production of intermediates and active pharmaceutical ingredients (APIs);
- the production of the finished dosage forms (e.g., pills or capsules) through the combination of APIs with excipients.
- the marketing and distribution of drugs;
- post-marketing surveillance.

The cycle for new drug development is schematically represented in Figure 1. It clearly shows the importance of R&D in the lifecycle of pharmaceutical products.

Figure 1: Drug cycle



Source: Authors adapted from https://www.efpia.eu/about-medicines/development-of-medicines/intellectual-property/.

However, beyond new drugs (often called new concept drugs, i.e. a branded product that represents a first attempt to treat chemical and biological reactions that cure diseases.) there are also other types of drugs (EP, 2021), namely:

- Precedented: a branded product that builds on existing drug concepts and requires less innovation and thus lower investment.
- Generic: is the same as a branded name drug in dosage, safety, strength, quality, performance, and intended use. By skipping the R&D stages of product development, a generic incurs the lowest cost.
- Biosimilar: biological medicine highly similar to another already approved biological medicine. A biosimilar can rely on the safety and efficacy experience gained with the reference medicine. Differently from generics, biosimilars require long development and usually have significant R&D costs.

Other definitions are reported in the Glossary at the beginning of the document.

2.2.2 Characteristics of the pharmaceutical R&D process

Pharmaceutical R&D is conventionally broken down into stages: basic research, pre-clinical or translational research, and clinical development, which typically comprises three phases of trials. Phase I tests the safety of the product in humans, Phase II provides an initial assessment of its efficacy, and Phase III aims at definitively assessing the efficacy and dosage in a large number of patients. To meet post-marketing surveillance requirements, some R&D continues while the new drug is on the market. As a whole, pharmaceutical R&D is risky, costly and time-consuming (UNCTAD, 2015, Schuhmacher et al., 2016). According to a recent OECD report, the successful development of a new medicine takes an average of 10 to 15 years, and the probability of obtaining marketing approval for a drug entering Phase I clinical trials ranges from 7% to 45%, depending on the type of drug and approval process (OECD, 2018). The recent experience with some vaccines for COVID-19 shows that the duration of the process is not independent of specific circumstances, including the pressure from a public health emergency, government subsidies to R&D, and/or other forms of public intervention.

These characteristics of the pharmaceutical R&D process have many implications.

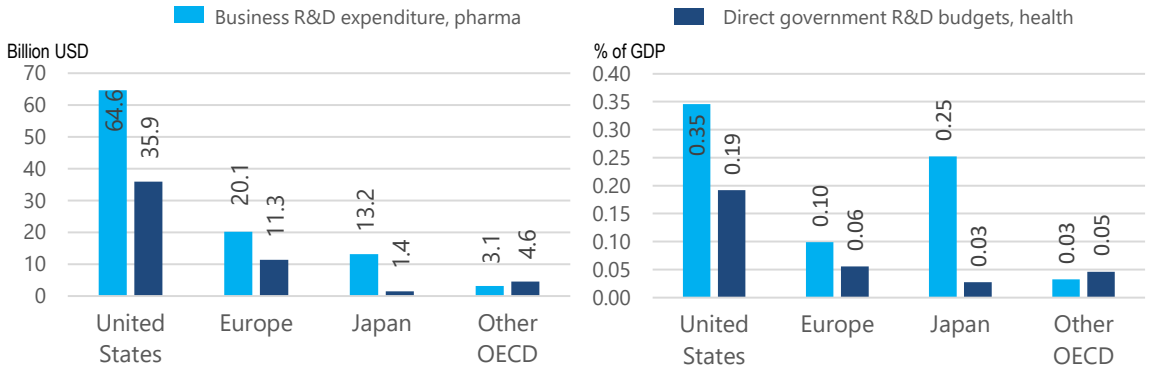
- First, with such a long investment (and economic return) gestation lag, it is optimal for investors to exploit the economies of scope, which requires building up heterogeneous portfolios of patents and R&D projects, which in turn requires a considerable amount of capital. Indeed the long journey leading to marketing authorisation is usually not sustainable for a small company that intends to enter the market with a single innovation or a family of interconnected pharmaceutical innovations. The capital needed to go beyond the early stages would not be easy to find, even in contexts where venture capital helps inventors.
- Second, to guarantee R&D investment and innovation in the pharmaceutical sector, it is claimed that some legal protection for investors is needed according to the traditional Schumpeterian argument that concentration spurs innovation (see, e.g., Mc Kenzie and Lee, 2008). Therefore, intellectual property rights (patents) and exclusive authorisation regimes for placing a new drug on the market (granted by the public agencies in charge of marketing approval) exist. See further in section 3.3.
- Third, pharmaceutical R&D is funded from a complementary and complex mix of private and public sources. Governments mainly support basic and pre-clinical research through various tools, including direct budget allocations, research grants, publicly owned research institutions and higher education institutions, which are also critical to disseminate R&D capacity. Moreover, many countries provide direct R&D subsidies or tax credits to pharmaceutical companies. The industry largely funds clinical trials (Chopra, 2003; Ehrhardt et al., 2015), often through service providers, such as Contract Research Organisations (CRO). Several studies attempt to map the contributions of public funding to pharmaceutical/health R&D. For instance, Viergever and Hendriks (2016) identified 55 major public and philanthropic funders of health research globally that together spent in one year USD 93 billion, of which USD 26.1 billion was spent by the United States NIH, followed by the EC (USD 3.7 billion), and the United Kingdom Medical Research Council (USD 1.3 billion). See Vieira (2019) for a review of literature documenting the contributions of public funding to drug development. In this regard, Kourouklis (2021) concluded that government funding is an important determinant of the pharmaceutical innovation process across different stages and products for all the twenty-four EU countries involved in the study.

2.2.3 Trends in R&D expenditure, productivity and profitability

According to OECD data, the expenditure on R&D in the pharmaceutical industry in OECD countries grew by 14% in real terms between 2010 and 2016. In 2016, the pharmaceutical industry spent approximately USD 20.1 billion on R&D across EU countries (figure 2, light blue bars), while

governments of EU countries from which data are available collectively budgeted about USD 11.3 billion for health-related R&D (see blue bars in Figure 2). The latter is a broader category than pharmaceuticals; therefore, the figure understates total government support because it excludes most tax incentives and funding for higher education and publicly-owned corporations (OECD, 2018).

Figure 2: Business enterprise expenditure for pharmaceutical R&D (BERD) and government outlays for health-related R&D (GBARD), 2016 (or nearest year)



Note : BERD, i.e. business enterprise expenditure on R&D, covers R&D carried out by corporations, regardless of the origin of the funding, which can include government subsidies. GBARD, i.e. Government budgets for R&D, captures R&D performed directly by government and amounts paid to other institutions for R&D. It does not cover spending by public corporations or general university funding that is subsequently allocated to health.
Note: Europe includes 21 EU member states that are also OECD countries, Iceland, Norway and Switzerland. No data available for Lithuania, Luxembourg and New Zealand.
Source: Authors based on OECD Health Statistics 2019 data available at :
https://doi.org/10.1787/888934018203

Also, the R&D amount spent per approved medicine has increased over the years. The most cited studies, DiMasi et al. (2003, 2016), estimated the average development cost to be USD 802 million (the study covered new drugs that had first entered clinical testing anywhere in the world from 1983 to 1994); in 2016 the same researchers pegged this at USD 2,8 billion (in 2013 dollars) referring at period 1995-2007, with capitalised costs growing at 8.5% per year (DiMasi et al. 2016). This is a very high estimate, one of the highest we have seen. In fact, despite three decades of research on the cost of drug development, no published estimate can be considered a gold standard (Morgan et al., 2011) and studies show a wide variation in estimates. Restricting the focus to Europe, the investigation carried out by the EC (2009) found out that originator companies claim that the cost of a new medicine, from basic research to launch, amounts to between USD 800 million and USD 1 billion (this figure includes the costs of failed projects). However, for biopharmaceuticals, the costs of R&D are generally reported to be higher than those of traditional pharmaceuticals. A recent study on the cost of developing a new drug in the US (Wouters et al., 2020) investigates the R&D costs for 360 drugs (of 50 companies) approved by the FDA over a decade. It finds a median value for a new drug (out of a sample of 65 products placed on the market between 2009-2018) of USD 985 million and an average value of USD 1,3 billion, but with great variability across therapeutic fields: costs are about double the average for oncology and immunology, on average for infectious diseases and gastrointestinal diseases, below the average for the nervous system and dermatology. The values are adjusted to take into account the frequent failure of projects.

The decreasing productivity of the pharmaceutical industry in terms of approved medicines per R&D expenditure (Pammolli et al., 2011; Scannell et al., 2012; OECD, 2018) in the last two decades is caused by a complex combination of factors. These include i) growing requirements to obtain market approval, which have increased clinical trial costs; ii) an ever-increasing base of effective drugs that have shifted efforts towards innovative drugs or drugs for more complex diseases such as neurodegenerative diseases and mental disorders, which require more complex trials and involves and higher failure rate (Bhatt, 2011; Scannell et al., 2012). Recently, signals have started to emerge of a change of tendency (Pammolli et al., 2020), but it is still unclear if there will be a reversal of the past trend of decreasing productivity.

Notwithstanding decreasing productivity, the OECD report (2018) recognises that the high profitability of the pharmaceutical industry has remained stable, though returns are concentrated on a relatively small number of products. Among pharmaceutical companies, the largest ones by sales and market value also show higher profit margins. A recent cross-sectional study (Ledley et al., 2020), which compared the annual profits of 35 large pharmaceutical companies with 357 companies in the Standard and Poor's 500 Index from 2000 to 2018, found a statistically significant differential profit margin favouring pharmaceutical companies. In bivariable regression models controlling for company size and year, the difference in gross profit margin is 30.5%, the difference in EBITDA margin is 9.2%, and the net income margin difference is 3.6%. Other studies find similar conclusions. According to an analysis by Professor Aswath Damodaran, the average yearly profit margin for the top 151 pharmaceutical companies world-wide is more than 24%, higher than most other sectors (The Economist, 2019). Also, official sources like the General Accounting Office of the US (GAO, 2017) estimate that the profitability of large pharmaceutical firms is often twice that of the large top 500 companies worldwide. While the industry may dispute such findings, the evidence seems overwhelming and points to market power as the driver of relatively high margins compared to other sectors.

2.2.4 Overview of the European pharmaceutical sector

2.2.4.1 Demand side

The demand side of the pharmaceutical sector is unique as it is characterised by a complex ecosystem of agents, including patients, doctors, public and private hospitals, insurance providers and reimbursement systems (EC, 2009). For prescription medicines, the final consumer (i.e., the patient) systematically differs from the decision maker (generally the prescribing doctor) and very often also from the payer (generally in the EU, the national health system, and ultimately the taxpayers).

In 2019, pharmaceutical revenues worldwide totalled USD 1.25 trillion (Statista, 2020). According to data from IQVIA MIDAS, Europe (including the UK, Russia, Turkey and Switzerland) represented the second largest market globally, accounting for 22.9% of world pharmaceutical sales, compared with 48.7% for North America. The European pharmaceutical market in 2018 was worth Euro 213 billion at ex-factory prices, with Germany, France, Italy, the United Kingdom and Spain, the top five EU markets, accounting for 60% of this market (EFPIA, 2020). However, during the period 2014-2019, the average growth rate (5.4%) of the top five EU markets has been lower than in the US (6.1%) - partly because of the cost-containment policies adopted by regulators and because of market dynamics, including generic and biosimilar competition (Belloni et al., 2016) - and significantly lower than the Brazilian, the Chinese and the Indian markets rate (respectively, 11.2%, 6.9% and 11.1%) (IQVIA MIDAS, 2020).

According to OECD (2020), around 80% of retail expenditure is due to prescription medicines, while most of the remaining part is due to over-the-counter medicines, whose cost is generally fully borne by patients. On average, government and compulsory schemes cover around 56.1% of all retail pharmaceutical spending, followed by out-of-pocket expenditure (41.6%) and voluntary

private insurance (2.3%). Importantly, while in Germany and France, the government and compulsory schemes finance more than 80% of the expenditure, this share is less than 50% in eight countries (Hungary, Malta, Denmark, Lithuania, Latvia, Poland, Bulgaria, Cyprus), being as low as 17% in Cyprus.

Another difference among European countries concerns the generics' market share. Wouters et al. (2017) compared generic drug prices and market shares in 13 European countries (DE, FR, UK, ES, IT, PL, CH, NL, EL, PT, BE, SE, and DK). They found that generics' market shares (i.e. share of reimbursed generics in hospital and retail pharmacies) vary widely across countries: in 2013, the share in value terms ranged from 42% in Poland to 11% in Italy, while the share in terms of volume ranged from 83% in the UK to 17% in Switzerland. Such variation is also observed by EFPIA publications. According to their latest publication, the share accounted for by generics in the pharmaceutical market sales value ranged from 67.3% in Italy to 14% in Switzerland in 2019 (EFPIA, 2021). Note that differences among estimates provided by the two sources may depend on new policies but also on the data considered. For example, Wouters et al. (2017) consider ex-manufacturer and retail prices, while EFPIA (2021) considers ex-factory prices. Moreover, the first source excludes biosimilar products, parallel-traded generic drugs, off-patent brand-name drugs and generics sold in hospital pharmacies, while in the second source, the share is computed with different criteria for the different countries. So, for example, in Italy, the share of generics in reimbursable pharmacy market sales is reported.

Pharmaceutical sales are driven by drugs for the nervous system (13.2% of total sales), followed by drugs for the alimentary tract and metabolism (12.3% of total sales), and by drugs for the cardiovascular system (roughly 10.8% of total sales) (OECD, 2020). Instead, pharmaceutical consumption, as measured by Defined Daily Doses (DDDs) per 1,000 inhabitants- a fixed unit of measurement independent of price, currencies, package size and strength- is mainly driven by drugs for the cardiovascular system (470 DDD per 1,000 inhabitants), followed by drugs for the alimentary tract and metabolism (248 DDD per 1,000 inhabitants) and by drugs for the nervous system (173 DDD per 1,000 inhabitants). The figures in this paragraph are the authors' elaboration of OECD data referring to main groups of drugs as defined by the Anatomic Therapeutic Classification (year 2018). Note that DDDs are not established for antineoplastic agents, for which data are not available. Countries included: Austria, Belgium, the Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Italy, Luxembourg, Netherlands, Portugal, Slovak Republic, Slovenia, Spain, and Sweden.

Important differences emerge among countries. For example, in 2017, in the UK, the consumption of cholesterol-lowering drugs (belonging to drugs for the cardiovascular system) was almost four times as in Lithuania; the consumption of anti-diabetic drugs (belonging to drugs for the alimentary tract and metabolism) in Finland was two times as in Latvia; consumption for anti-depressant drugs (belonging to drugs for the nervous system) in the UK was more than seven times as in Latvia (OECD, 2019). Differences in consumption among countries may depend on the different prevalence of illness but also on specific market features.

In Europe overall, the most important purchasers are national health services or insurance schemes. Indeed, governments, different from other regions of the world, are extensively responsible for healthcare and for deciding which medicines should be provided to patients at the expense of the health service or insurance scheme. For this reason, once a new product has received marketing authorization from the authority of a country, the patent-holder or manufacturer enters into negotiations with the potential purchasers of that country; indeed, drug pricing remains a national competence.

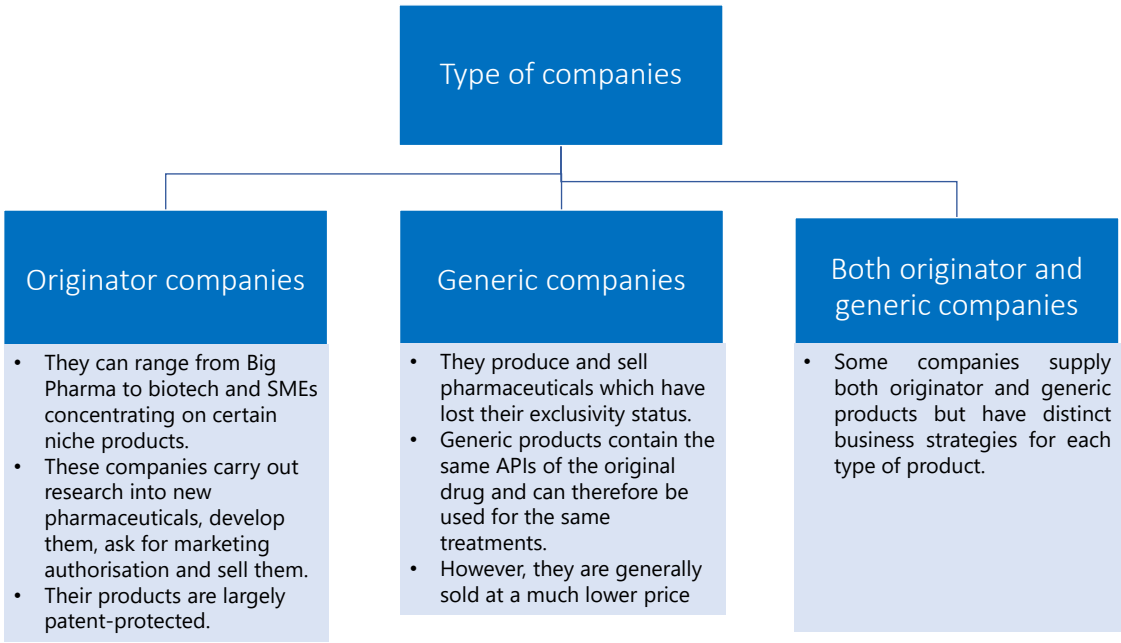
2.2.4.2 Supply side

On the supply side, the pharmaceutical sector is characterised primarily by three types of companies (EC, 2009). See Figure 3 below.

According to Eurostat Structural Business Statistics, the overall pharmaceuticals manufacturing sector (NACE Code 21) in the EU-28 (i.e., including the UK) is characterised by a relatively small number of large, capital-intensive enterprises. In total, there were 4.7 thousand enterprises in the pharmaceutical manufacturing sector in 2016. Together they employed 568 thousand persons (in 2018, they were raised to 652) and generated EUR 96.4 billion of value added (in 2018, it was raised to EUR 119.2 billion). Most of the value-added generated in the EU-28's pharmaceuticals manufacturing sector in 2017 was contributed by Germany (23%), ahead of France (14%) and Italy (11%). These countries are key players in the global pharmaceutical trade (EFPIA, 2020). France, Germany, Italy and Spain have the largest number of APIs manufacturers in the EU (Progenerika, 2020).

Overall, the pharmaceutical industry is one of the most dynamic, growing and profitable sectors in the EU. In 2017, the total turnover amounted to EUR 284 billion in the EU-28, representing an increase of 24% compared to 2011. In the same year, the pharmaceuticals manufacturing sector's gross operating rate (in structural business statistics from Eurostat, the gross operating rate is the ratio of gross operating surplus to turnover) was 22%, more than twice as high as the manufacturing average (10.1%). The gross operating rate remained quite stable over the years. In 2011, it stood at 23%.

Figure 3: Types of companies



Source: Authors.

The pharmaceutical sector's investments in R&D are substantial compared to other industries. Based on the EU R&D Scoreboard data, the 'Pharmaceuticals & biotechnology' sector in Europe shows the highest ratio of R&D investment to net sales (16%), more than one-third as high as the 'Software & computer services' sector (12%), which is in the second position. Moreover, according to EFPIA (2020) estimate based on Eurostat data, the pharmaceutical industry in the EU-28 invested EUR 37.5 billion in R&D in 2019, representing an increase of 25% from 2010 (we discuss

later some issues of R&D expenditure measurement). The detailed breakdown of R&D expenditures declared by firms is not a piece of information available in the public domain, and there are several issues of definition of such items, such as amortisation, depreciation, market research, and others (The Economist, 2019).

Overall, the European pharmaceutical industry is not in a dominant position. There has been a steady shifting of R&D investment out of Europe to the US. According to EFPIA (2016, 2020), in 1990, the total pharmaceutical R&D expenditure in the US was slightly lower than in Europe, but ten years later, R&D expenditure in the US has overtaken that in Europe. From 2015 to 2019, the annual growth rate of pharmaceutical R&D expenditure in Europe has been less than half that of the US. In addition, the European industry is currently facing increasing competition from emerging economies, especially Brazil and China. For instance, in 2016, China's industry spent USD 14 billion on R&D, which represents a more than 2.5-fold increase since 2010 (in real terms) (OECD, 2019).

On top of that, extensive outsourcing of much of Europe's drug supply chain in the last decade has created a situation where the European pharmaceutical industry is particularly dependent on Asia. According to the European Fine Chemicals Group, whilst the APIs for innovative drugs are mainly sourced from Europe, more than two-thirds of APIs for generic drugs are sourced from Asia. According to an EFPIA survey conducted in February 2020, 77% of all APIs needed for innovative medicines production in the EU come from the EU itself; 12% of APIs come from the United States and only 9% from Asia (including Japan and South Korea). According to a recent report from the EP, in 2019, the EU imported EUR 11.1 billion and exported EUR 7.4 billion APIs, generating a trade deficit of EUR 3.7 billion for APIs (EP, 2021). Also, most starting materials or critical process chemicals are sourced from Asia.

Worldwide, the pharmaceutical sector is changing rapidly not only in terms of the geographical distribution of markets but also in terms of players. Big Pharma, i.e., the multinational companies which dominate the industry sales and that were traditionally responsible for all aspects of the drug discovery pipeline, are increasingly outsourcing functions and are focusing investment on a limited number of therapeutic areas (Nickisch et al., 2009) while disinvesting from others. New players, especially emerging biopharmaceutical companies, have entered the market. These companies are driving a large portion of innovation and development in the life sciences. According to IQVIA (2019), emerging biopharmaceutical companies accounted for about 80% of the research pipeline in 2018. In a similar vein, PharmaProjects (2020) reports that the share of the total R&D pipeline to which top pharma companies contribute has been shrinking over the last decade. Conversely, the percentage of drugs in the entire pipeline that originates from companies with just one or two drugs in their portfolios increased up to 19% in 2020.

The review of the literature suggests that Big Pharma are increasingly disinvesting in riskier upstream research and increasingly accessing products that are already in later clinical trial stages through acquisitions of small biotech companies or start-ups with promising portfolios of patents. This trend dates back to the 1980s when large companies began to look to universities and small start-ups as sources of ideas and new products, using a mix of contracts, licenses, alliances, and outright acquisitions. According to Richman et al. (2017), the number of annual merger and acquisition (M&A) deals at the global level grew from approximately 100 deals in the late 1980s to almost 800 deals in 2015. Also, some recent analyses show that between 1995 and 2015, 60 pharmaceutical companies around the world merged into just 10 (Visnji, 2019).

As an alternative to mergers, licensing is used extensively in the pharmaceutical sector. According to Kyle (2020), small firms and start-ups rely not only on licensing revenues to finance their R&D but especially, on venture capital, including corporate venture capital. In response to decreasing productivity of R&D investment (see section 2.2.3), M&A, licensing, and corporate venture capital are said to have emerged as strategies that pharmaceutical companies adopt to tap into innovative

sources outside their organisational boundaries to access new ideas, technologies, and even talents (Felix and Iversen, 2020; Schuhmacher et al., 2016; Comanor and Scherer, 2013). Several authors studied the relationship between M&A and innovation (for instance, Morgan, 2001; Comanor and Scherer, 2013; Haucap et al., 2019; Cunningham et al., 2019). Two recent empirical articles are worth citing. Haucap et al. (2019) find a decline in R&D output following European pharmaceutical mergers. Cunningham et al. (2021) show that acquired drug projects are less likely to be developed when they overlap with the acquirer's existing product portfolio, especially when the acquirer's market power is large because of weak competition or distant patent expiration. According to Cunningham et al. (2021), 5.3%–7.4% of acquisitions (including some large ones by the value of the deal) in their study sample are "killer acquisitions", i.e. dictated by the incumbent firms' desire to discontinue the target's innovation projects and pre-empt future competition.

For clinical trials, big Pharma often relies on CRO. These companies offer a wide range of services from pre-clinical research up to post-marketing surveillance, although clinical trial services dominate the CRO services market. According to estimates by Fortune Business Insights (2019), the global CRO services market size was over US$ 38 billion in 2018, and it is expected to exceed US$ 90 billion in 2026. Although currently, there is a large number of firms operating in the CRO market, the top ten are multinational companies that hold over 50% of the market, and the trend is towards further concentration. The realisation of clinical trials involves hospitals and other organisations in direct contact with patients. CROs offer contracts to hospitals to enrol patients. Contracts for clinical trials can take various forms, but they essentially involve the recruitment of a patient at a price up to several thousand euros (typically, only a small share of such price or nothing at all goes to the patient herself/himself). One major reason to recur to CROs is that clinical trial protocols have become increasingly complex, involving multi-country, and thus costly (Getz, 2008).

Big Pharma's tendency to outsource functions is not limited to R&D but also to manufacturing, which is no longer a profit centre for Big Pharma companies. In the last decade, the Contract Manufacturing Organisation (CMO) has grown considerably. According to estimates by Fortune Business Insights (2020), the global CMO services market size was over US 92 billion in 2018, and it is expected to exceed US$ 188 billion in 2026. CMO offers pharma companies services which range from manufacturing of APIs to packaging and sometimes even distribution. More recently, Contract Development and Manufacturing Organisations (CDMO) emerged with the concept of providing pharma companies with a comprehensive single-source of services from drug development through commercial manufacture. Similarly to CRO and CMO, even the CDMO market is fast growing. According to estimates by Fortune Business Insights (2020), the global CDMO services market size was over US$ 130 billion in 2018, and it is expected to exceed US$ 278 billion in 2026.

In sum, the pharmaceutical supply chains are complex, increasingly globalised, and driven by lead firms, which are, in most cases, big pharmaceutical companies. Outsourcing is an increasingly common feature of the industry, with lead firms outsourcing testing and validation services, clinical trials management, manufacturing and distribution operations to an increasingly global supply base. There is a concern among experts that the observed rush to M&A deals tends to increase market power and weaken competition. After the COVID-19 pandemic, the industry has shown a new evolution towards increasing collaborations among lead firms. Firms have established agreements to carry out joint research or have joined their complementary assets, such as R&D and manufacturing. Such new approaches may not necessarily survive after the end of the pandemic, but they certainly denote the industry's continuous flexibility.

2.2.4.3 Drugs' prices regulation in EU

Governments of the EU Member States follow different price regulations and reimbursement policies (Stargardt and Vandoros, 2014), and the pharmaceutical markets remain very fragmented

by country (for a review of pricing policies, see (WHO, 2020)). The External Reference Pricing (ERP) policy, for which the price set for the same product in one or several countries is used as a benchmark for setting or negotiating the product's price in a given country, is the most frequently used pricing policy in Europe. However, it is not adopted in all Member States, and even the methodology of adoption varies from one country to another (Leopold et al., 2012, 2013; Vogler et al., 2015). Also, internal reference pricing, i.e. pricing drugs by reference to therapeutic comparators within the same country, and value-based pricing based on health technology assessment, i.e. the evaluation of properties, effects, and/or impacts of health care technology, are not uniformly adopted (OECD, 2008; WHO, 2020). Similarly, only a few European countries adopt Managed Entry Agreements to limit pharmaceutical expenditure while ensuring the largest number of patients access to innovative medicines (Ferrario, et al., 2017; Pauwels et al., 2017). EU countries also differ in the adoption of patient co-payment policies, both for healthcare providers and for pharmaceuticals (Drummond and Towse, 2012).

Despite the fragmentation of the market, the presence of a European single market and the process of EU monetary convergence led to price convergence for many products (Stargardt and Vandoros, 2014) - although with some exceptions concerning some countries and specific periods of time (Leopold, et al., 2013). This convergence might depend on the ERP policy adopted by several EU countries, even if the evidence on the extent of ERP impact on price convergence is mixed (Leopold et al., 2012; Tuomi et al., 2013; Kaló, et al., 2015; Kanavos et al., 2017). Another possible factor playing, in theory, an important role in price convergence is parallel trade (Vogler et al., 2015), estimated at EUR 5.5 billion in 2018 (EFPIA, 2020). In practice, however, evidence for the EU seems to suggest that parallel trade for prescription drugs does not automatically reduce price differences (Kyle et al., 2008).

The pharmaceutical prices by country do not depend only on government regulation (such as price controls and reimbursement decisions) but also on several other factors, such as income per capita, exchange rates, the size of the market, the characteristics of the product (such as how innovative it is, how old it is, and its therapeutic advantages), the patent status, the characteristics of the firm and the presence of competitors (Kanavos and Vandoros, 2011; Von der Schulenburg et al., 2011; Cabrales and Jiménez-Martín, 2013; Kyle and Qian, 2014; Puig-Junoy & González López-Valcárcel, 2014).

Box 1. European Integrated Price Information Database Collaboration

To facilitate the application of the ERP policy, the European Integrated Price Information Database Collaboration (EURIPID), a voluntary non-profit initiative grouping many authorities in charge of pricing and reimbursement in different member States, operates to enhance price control while providing appropriate access medicines. The EURIPID database contains data on official prices of publicly reimbursed medicines and it is available to the authorities which joined the collaboration. Currently, 24 European countries plus the European Commission participate in EURIPID.

As a consequence of differences in expected prices, the use of ERP and parallel import, and differences in market size, the availability and entry date of drugs in European countries strongly differ (Kyle, 2007; Danzon et al., 2005). For example, the average time to market from marketing approval in Europe for cancer drugs, in the period 2011-2018, ranged from 17 to 1,187 days, with drugs from Germany, the UK and Austria benefiting from the shortest delay (less than 31 days) and with drugs in Greece and Estonia suffering from the longest delays (more than 950 days) (Uyl-de Groot et al., 2020). An illustrative example of five drugs, (Vogler et al., 2019) finds that availability in Central and Eastern Europe occurred only several years after marketing approval. Similarly, (Maini and Pammolli, 2017) document the presence of launch delays up to three years on average in Central-Eastern Europe. A delay in patient access to new drugs may result in diminished patient

benefits and an increase in potential life loss (Uyl-de Groot et al., 2020). Beyond delay, there are availability issues (see next section).

According to OECD (2020), the spending for retail pharmaceuticals averaged Euro 380 per person (adjusted for differences in purchasing power) in EU-28 (i.e. including the UK) in 2018. The maximum expenditure per capita was observed in Germany (Euro 615, i.e. 60% above the EU average), followed by Belgium, France and Austria (they spent about 20-40% more than the EU average), the minimum expenditure was observed in Denmark (Euro 236). Importantly, these variations may reflect differences in the basket of available medicines, health conditions, pharmaceutical prices, market penetration of generics and hospitals' relative role in dispensing pharmaceuticals.

The average list price of new drugs is fast increasing, especially in oncology and orphan drugs (OECD, 2018). For instance, the price of cancer treatments has increased tenfold between 1995 and 2010, with still an acceleration in recent years (AIM, 2019). As mentioned above, companies often explain increasing drug prices by raising R&D costs (OECD, 2018). However, as pharmaceutical companies make investment decisions based on expected return, expectations of higher prices can, in a sense, make increasingly expensive R&D projects more viable (OECD, 2018), creating a reverse causality from future prices to planned R&D costs. In turn, high R&D costs can justify high prices. This cost spiral is further amplified by the increasing rate of acquisitions, resulting from the industry evolution towards a division of innovation effort between smaller and larger firms. Indeed, large firms that acquire either technology in the R&D process or promising start-ups pay premiums over them, which must be recouped by subsequent revenues (see e.g., Bonaime and Wang, 2019).

The consequences of high drug prices are affordability problems for patients and sustainability of health care systems (Box 2).

According to OECD (2019), expenditure on retail pharmaceuticals accounts for a variable share of current total health expenditure in the EU countries, ranging from 7% in Denmark and Norway to 41% in Bulgaria. Most of this expenditure is public spending (see Figure 4).

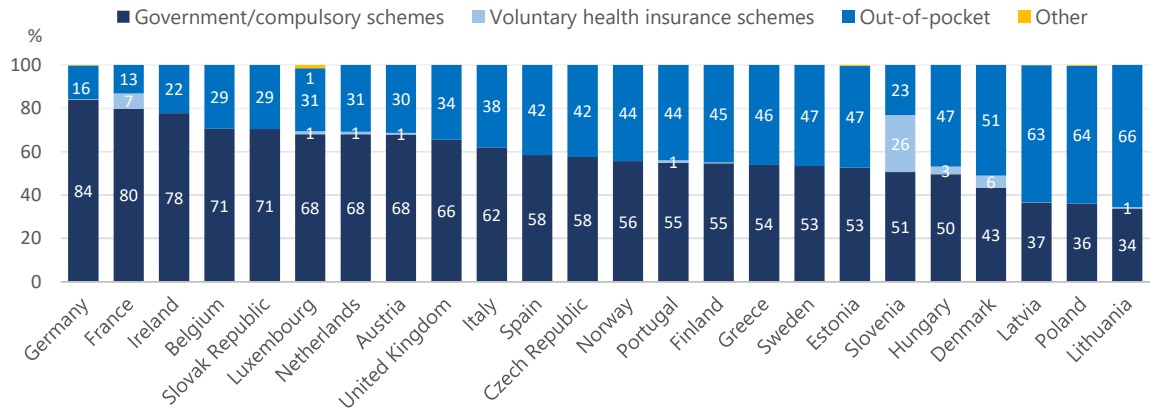
Box 2. Concerns on out-of-reach prices

In April 2016, at the EU informal meeting of Ministers of Health in Amsterdam on "Innovative and Affordable Medicines", the challenges in the pharmaceutical system were noted. In this context, several MS expressed the wish to cooperate and take action on a voluntary basis to face common challenges to the sustainability of national healthcare systems, which may be linked to a number of potential factors, e.g. the affordability of medicinal products related to high prices, possible unintended or adverse consequences of incentives and the lack of leverage of individual Member States in negotiations with industry.

Later in the same year, the Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States also noted with concerns an increasing number of examples where patients access to effective and affordable essential medicines in the MS is endangered, among others, by unaffordable price levels. The Council also noted with concern that companies may seek very high prices while the added value of some of these products is not always clear. In 2017, the European Parliament adopted a resolution on EU options for improving access to medicines which calls, among other things, for a new Transparency Directive to ensure full transparency on price-setting and reimbursement procedures used for medicines in the Member States.

Source : EP (2017) and https://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-balance-pharmaceutical-system/

Figure 4: Expenditure on retail pharmaceuticals* by type of financing, 2017 (or nearest year)



Note: "Other" includes financing from non-profit-schemes, enterprises and the rest of the world. *Includes medical non-durables.
Source: authors based on OECD Health Statistics 2019 data available at :
https://doi.org/10.1787/888934017994

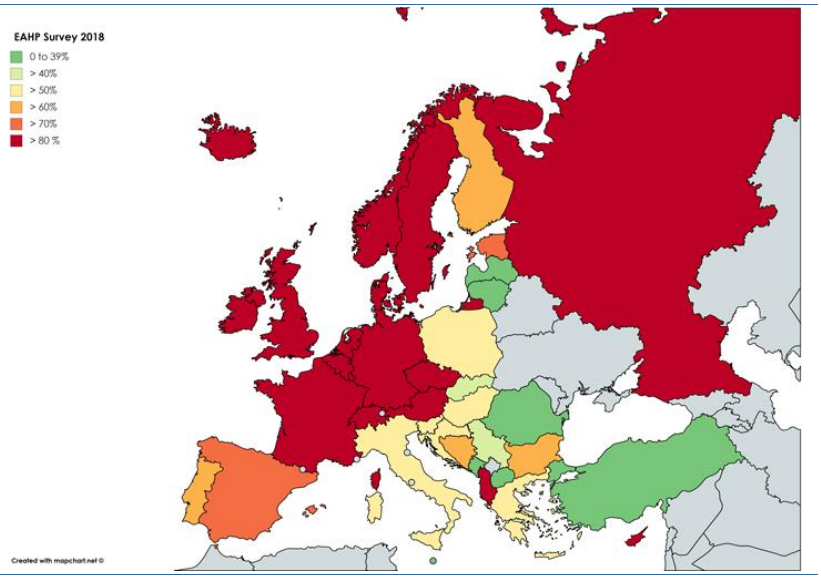
Yet analysing expenditure on retail pharmaceuticals only gives a partial picture of spending since it does not includes the costs of pharmaceuticals used for hospital inpatient care. While retail pharmaceutical spending grew at a slower pace or even declined since 2008 due to austerity measures (Belloni et al., 2016), hospital pharmaceutical spending has tended to expand in a number of countries, including the Czech Republic, Denmark, Germany, Spain and Finland. In these countries, the annual average growth in hospital pharmaceutical expenditure, in real terms, in the period 2008-2018 is respectively 4.9%, 4.9%, 3.1%, 1.8% and 1.4% (OECD Health Statistics, 2019).

2.2.4.4 Drugs' availability in EU

The availability of authorised drugs is strictly linked to producer choices and pricing policies. Medicine shortages have been a global healthcare issue for some time. According to the Heads of Medicines Agencies (i.e., the network of medicines agencies of the European Economic Area) website, drugs' availability is an increasing problem within Europe. In the last decade, shortage episodes have become increasingly frequent in European countries, and COVID-19 has served to put this existing phenomenon under the spotlight.

In 2018, the European Association of Hospital Pharmacists conducted a survey (see Miljković et al., 2019) to hospital pharmacists throughout Europe (including the UK, Russia, Turkey and Switzerland) and found that 90% out of 1666 respondents answered 'Yes' when asked if shortages of medicines are a current problem in delivering the best care to patients (see figure 5, which present data on frequency by country). The share has increased compared to the 2014 survey (EAHP, 2014). In 2018, antimicrobials were the area most commonly affected by medicine shortages (77%) like in 2014, followed by preventive medicines (43%), and anaesthetics (39%). Instead, shortages in oncology medicine decreased compared to 2014 (39% in 2018, 54% in 2014). The 2014 survey also pointed out that the shortages affect both generic and innovative medicines.

Figure 5: The frequency of medicine shortages in Europe



Source: https://www.eiu.com/topic/medicine-shortages based on European Association of Hospital Pharmacists, 2018

Also the Pharmaceutical Group of the EU, which is the European association representing more than 400,000 community pharmacists, conducts an annual survey among its members to map the impact of medicine shortages from the community pharmacists' perspective. The results of the 2019 survey not only show that the vast majority of respondents (87% out of 24 member organisations) indicated that the situation got worse compared to 2018 but also point to the existing gap in needed information, tools and legal options available to community pharmacists in many European countries for providing solutions to patients in case of a shortage (PGEU, 2019).

The trends highlighted by these two surveys are in line with recent reports prepared respectively by the European Parliament's Committee on the Environment, Public Health and Food Safety and by the OECD. The EP report estimated that the number of shortages increased 20-fold between 2000 and 2018 and have increased 12-fold since 2008 (EP, 2020). The OECD study on shortage notifications in 14 OECD countries between 2017 and 2019 shows that notifications of expected or actual shortages increased by more than 60% (forthcoming).

The root cause of shortages is multifaceted (The Economist Intelligence Unit, 2017) and includes:

- **Economic causes.** As mentioned above, in Europe, the sustainability of healthcare budgets, which is pressured by multiple factors such as a growing and ageing population and the increased cost of new innovative medicines, has been put under scrutiny in the aftermath of the 2008 crisis (OECD, 2015; Belloni et al., 2016). Several national authorities have adopted austerity measures and applied short-term cost-containment measures such as ad-hoc price cuts, external reference pricing, payback to pharmaceuticals. Such actions have driven some generics price, which was already low, to unsustainably low levels from generic manufacturers' standpoint. As a result, some of them withdrew from the market, thereby increasing the risk of medicine shortages. Generally, the combination of low volume use of medicines and cutting

prices reduces the market's attractiveness to manufacturers. To be noted that generic medicines represent around 4% of total healthcare expenditure in Europe while their relevance for care is very high (62% of medicines dispensed today in Europe are generic medicines).

- **Supply chain causes.** Manufacturers of medicines are dependent on APIs, and so changes in supply, quality and regulation of APIs could cause disruptions in the supply of medicines. The EU's increasing dependence on third countries may further exacerbate the risk of supply chain disruptions. According to the EMA, 40% of medicinal end products marketed in the EU originate in third countries, while 80% of active pharmaceutical ingredients are produced in China and India (EP, 2020).
- **Manufacturing and quality factors**. In some cases, the supply cannot meet the need for a medicinal product because many national markets across Europe rely on too few suppliers or because of limitations of the production output of a certain manufacturer. In some cases, shortages are also due to quality-related problems of medicines, that is they no longer comply with good manufacturing practices established by EMA. According to a review carried out by the European Healthcare Distribution Association, manufacturing and quality-related issues account for greater than 60% of cases of shortages (Clews, 2019).
- **Regulatory factors**. All drugs sold in Europe must be subject to a valid marketing authorisation (either via EMA and/or competent national authorities) within the EU. The fulfilment of regulatory requirements can create shortages in two cases. First, when the marketing authorisation of a previously approved medicine on the market is invalidated for administrative or other reasons, the drug must wait for new approval/renewal from the competent authority. Second, when a competent national authority requires to fulfil a specific requirement from that country.

To address the shortage problem, different actions have been taken over the years and various stakeholders have advocated different solutions. In 2013, the EMA held a meeting to develop a proactive approach to addressing such an issue (see EMA (2016) for meeting proceedings). As a result, a task force was established by the EMA and the Heads of Medicines Agencies to develop tools that could support the medicines' supply chain and prevent future disruptions to it. Since 2016, EMA also manages a public catalogue for shortages that affect or are likely to affect more than one Member State. Although regulatory authorities within and outside the EU are increasingly working together to prevent shortages and to limit their impact whenever they occur, most medicine shortages were dealt with at national level before COVID-19. The COVID-19 pandemic has underlined that access to medicines is a global concern that requires pan-European coordination (see EP, 2020). Indeed, the topic is addressed by the new Pharmaceutical Strategy (see section 2.2.6), in particular, by the pillar "Enhancing the resilience of the pharmaceutical supply chains". The latter aims to build the EU's *open strategic autonomy* in the pharmaceutical sector by diversifying production and supply chains, promoting strategic stockpiling, and increasing production and investment in Europe (EP, 2021).

2.2.4.5 Unmet medical needs

Beyond the unavailability of authorised drugs, the pharmaceutical market is, to some extent, characterised by unmet demand in certain therapeutic areas (i.e. unmet medical needs). This is due to different factors. First, the lack of pharmaceutical companies' incentive to allocate resources in areas where the expected return on investment is low. Being private companies, some of them listed on the stock exchange, pharma companies are driven by profit (or returns) maximisation to deliver financial value to their shareholders (Perkins, 2001; UCL Institute for Innovation and Public Purpose, 2018). In choosing R&D investments, they seek to maximise future profits considering different variables: the probability of achieving marketing authorisation, the potential sales volume (i.e., the market size), and the prices that the new product(s) can command in different countries.

In other words, they tend to direct their research and innovation (R&I) effort towards less risky and highly profitable areas or to suitably combine risk and return. As already mentioned, there is a visible tendency of Big Pharma in disinvesting from riskier upstream research and accessing products that are already in later clinical trial stages through licensing or acquisitions. This is not surprising, and it is also understandable from a business point of view. However, the results of such strategy are not always necessarily aligned with the public goal of directing efforts towards the greatest health needs, which may imply high risk and low financial returns, with possibly high social benefits as an externality (vaccines and antibiotics were often in this category in the past according to the literature).

An analysis carried out by Taghreed et al. (2019) helps shed light on the priorities of the pharmaceutical industry. These authors discuss the findings of the WHO Global Observatory on Health Research and Development, established in 2017. It is an analysis of 86,000 products developed since 1995, including medicines, vaccines, and diagnostics. Among these, those still in use are 14,999, of which 87% concern non-communicable diseases (48% of these concern cancer), and only 9% infectious diseases. Less than 0.5% of all the products in use concern the WHO list of neglected tropical diseases, and only 0.4% concern pathogens that are included in the list of those considered by the WHO as a priority.

The dominance of cancer in the industry R&D pipeline is remarkable if one looks at the top 10 pharma companies. According to PharmaProjects (2020), cancer candidates comprise 36.7% of all pharma R&D pipeline (considering both pre-clinical and clinical-stage candidates), and the total oncology franchise has grown by 14.2% as compared to 2019, continuing the upward trend that has been recorded for all of the past decade. For the second year, among cancer R&D projects, the largest share is represented by anticancer immunologicals. The same study also reports that in 2020 anti-infectives was the only therapeutic area to record an actual decline (-1.7%) in a context where the overall R&D pipeline growth rate is nearly 10%. This shrinkage represents a significant and concerning move away from this area.

Beyond cancer, high-incidence chronic or life-long treatments (such as diabetes) are generally prioritised by the industry over disease prevention and vaccines because the former offer wider and more stable prospects for medicines sales. Pharmaceutical firms have little incentive to develop vaccines (Lo et al., 2020; Glennerster *et al.*, 2006). Different from drugs, vaccines prevent diseases. Hence their expected use and revenues are limited, especially if vaccines concern infectious diseases that give rise to local epidemics in areas with low spending power.

It is worth noting that the clinical research for developing SARS and MERS vaccines was interrupted in most places a few years ago due to lack of interest and funds and this, as declared by the OECD General Secretary, Angel Gurrìa, in a letter to the G20 and by Dr Peter Hotez, to the US Congress, was a missed opportunity to develop vaccines in anticipation of future epidemics (OECD, 2020a; Hixenbaugh, 2020; Invivo, 2020). A similar situation applies to antibiotics, where the lack of market incentives has led to underinvestment in new compounds (Medicine Foundation 2018a; Morton et al., 2019), although antimicrobial resistance is an increasing global problem. It appears that some of Big Pharma are no longer even researching new antibiotics (Rizvi, 2020) despite the expectation that, by around 2050, bacteria that are resistant to current drugs could kill 10 million people a year (O'Neill, 2016).

However, the literature (Barrenho et al., 2019) and the industry experts acknowledge that the misalignment between R&D investment and unmet health needs is not only the result of firms' lack of incentive to allocate resources in areas where the expected return on investment is low, but it can also be explained by:

- **Lack of scientific progress**. There are areas such as neurodegenerative diseases that are attractive from market perspectives (i.e. with a potentially large market) but very challenging

given the state of scientific knowledge. On the contrary, in the last decade, scientific opportunities and the development of personalised medicine (coupled with public incentives) has pushed firms to focus on innovative medicines for niches of population. According to OECD (2017), worldwide, the share of orphan drugs in the total sale of branded drugs has increased from 6% in 2000 to over 16% in 2016, and it is expected to reach 21% in 2022. Between 2001 and 2015, EMA approved 117 orphan drugs compared to 339 approved by the FDA (OECD, 2017). However, data from Orphanet show that even in Europe the approval of orphan drugs has improved over the years (an increase of 268% from 2013 to 2019 versus the 2007 to 2012 period).

- **Wrong signals from the public sectors**. Through direct research grants to academic researchers in certain areas, and to a lesser extent also with indirect support, governments signal pharmaceutical companies on priority areas. A problem arises when public contributions and direct support to basic research are not allocated according to public health needs, as this conveys a wrong signal to the industry. Li (2017), Hegde (2009), Jones (2011), and Azoulay et al. (2013), suggest that government allocation of public funding across institutions and R&D fields is unlikely to be just a function of public health need and utterly efficient. In a similar vein, the healthcare sector's purchase choices may convey wrong signals to the pharmaceutical industry. For instance, if hospitals continue to buy older and more expensive products despite alternatives, this reduces firms' incentive to invest in that area.
- **Career-oriented publication incentives.** In universities and public research institutions, researchers need to publish, possibly in the most prestigious peer-reviewed journals (generally those with the highest impact factor). A researcher's career essentially depends on how much and where she or he publishes, more than if the results published are relevant to public health. Quality, quantity and relevance of the publications might coincide, but sometimes they do not. Firstly, some research themes and investigation methods are less fashionable than others in academia. Researchers' preferences inevitably follow the currents of scientific thought because of reputational reasons. There is nothing wrong with that, but this system may not necessarily be the best one for the health agenda. Second, to publish something influential in the medical area, it is usually essential to have been involved in double-blind studies with randomized samples of treated patients and control groups. This, in turn, requires a high number of patients with specific characteristics and, above all, an accurate and standardized data detection mechanism. This is notoriously the most expensive step in research and requires funding that can be offered by pharmaceutical companies only, at least for large-scale trials. In other words, researchers at universities and public institutes often end up being attracted to the orbit of industry-sponsored research (Fugh-Berman, 2013).

While some critical medical needs remain unmet, a large share of new medicines developed are 'me-too' drugs, i.e. drugs that offer little or no therapeutic advance in comparison to existing ones, but which are sufficiently different to get a patent (this is the most used definition of me-too drugs. However different definitions exist, see Aronson and Green (2020). According to an analysis of 1345 new medicine approvals in Europe between 2000 and 2014 by Année du médicament (2015), 51% of newly approved medicines were modified versions of existing medicines and did not offer any additional health benefits. In a similar vein, a study published in 2020 (Hwang et al., 2020) finds that only a third of new drugs approved by the US FDA and the EMA from 2007-2017 have high therapeutic value, according to appraisal by independent organisations.

2.2.5 Market failures in the pharmaceutical sector

Following the discussion in the previous sections, three main issues, possibly related to market failure, have been identified by the literature, namely:

- The misalignment between R&D priorities of the industry and public health needs;
- Out-of-reach drug prices;

- Drug shortages.

However, these are the symptoms, not the causes of problems. To understand the roots of these problems, it is worth recalling what a market failure is from an economic standpoint, some peculiar features of the market structure of the pharmaceutical sector, and which failures are observable in it.

In standard welfare economics, a market failure is defined as a situation in which the allocation of goods and services by a free market, where agents' pursuit of pure self-interest, leads to results that are not Pareto efficient (i.e., a situation where no individual can be better off without making at least one individual worse off or without any loss thereof) and thus leads to a net loss from the societal point of view. In other words, the market equilibrium is such that re-allocations of economic goods (input and outputs) are possible with a net benefit for society.

Market failures are associated with various situations, and different economists have different views about what events are the sources of market failure. It is widely accepted that a market failure can occur for three main reasons, respectively linked to 1) the nature of the market (monopoly, oligopoly, monopsony, monopolistic competition), 2) the nature of the good (public good, common goods, externalities), and 3) the nature of the exchanges within the market (transaction costs, information asymmetry) (Atkinson and Stiglitz, 2015; Hindriks and Myles, 2013).

As seen, the pharmaceutical sector structure is a highly skewed distribution: an oligopolistic core with a fringe of companies acting in different submarkets or therapeutic areas (Di Iorio and Giorgetti, 2020). Such a situation originates for different reasons, including the high fixed costs of pharmaceutical investment and related externalities, patent protection, the market authorisation system, the asymmetry of information between drug companies and consumers. All these create barriers to competition.

2.2.5.1 "Natural monopoly" arising from investment

A natural barrier is the relevant initial investment cost to enter the pharma market, which means that average production costs fall over a large range of output quantities. R&D costs – especially in the last decades - can be considered fixed costs for pharmaceutical firms, more precisely large sunk costs (Sutton, 1991; Sutton 1998; EC, 2014; Kyle, 2020). When the fixed costs of an industry are large, a natural monopoly or a natural oligopoly could arise because few firms are able to afford these large initial fixed investment costs. Therefore, an essential characteristic of a natural monopoly/oligopoly is that it enjoys economies of scale and scope. The effect of scale economies is widely debated in the literature (see DiMasi et al., 1995; Henderson and Cockburn 1996, 2001; Plotnikova, 2010).

Plotnikova (2010) claims that scale economies might have lower importance and even become irrelevant in the development stage of drugs. This claim is supported by the fact that drug development can be outsourced to a CRO, which specialises in the organisation of clinical trials. Nevertheless, it is worth noting that most CROs are themselves large multinational companies which in turn enjoy economies of scale. The level of scope economies in R&D is also debated in the literature (Henderson and Cockburn 1996, 2001; Giorgetti, 2006; Plotnikova, 2010). Notwithstanding, large pharmaceutical companies' tendency to focus on a carefully selected portfolio of drugs is undeniable. Indeed, given the long and risky R&D process, the optimal choice for large companies is building a portfolio of patents (see below) and development projects, each at a different stage of the cycle, so that already proven and profitable projects finance new and riskier ones. If a diverse array of R&D projects is conducted in one firm, economies of scope can arise due to positive internal spillovers.

2.2.5.2 Legal barriers

Another cause of reduced competition is when legislation grants originator companies exclusive civil rights to the commercial exploitation of an invention. A patent, which is by far the most exploited tool for protecting R&D investments in pharmaceuticals (Garattini and Padula, 2018), is a property right to a product or a process with a length of 20 years from application. In the case of the pharmaceutical sector, patents usually protect chemical formulas in order to avoid duplication by any rival company. However, patenting is increasingly moving upstream in the research process, so not only are products being patented but the tools and processes for research that might lead to those discoveries are being patented as well (Wang, 2008). Patents for drugs are considered by the industry vital to safeguard the innovative approaches used by pharma companies (EC, 2009); they allow companies to recoup investments that are incurred during the R&D stage.

Also, drug patents can secure against infringement cases, as competitors can easily duplicate the manufacturing of a drug. In fact, replicability is the main source of externalities in any industry leading to underinvestment (Romer, 1990). While patents grant the inventor a legal monopoly, this legal protection is theoretically designed to incentivise innovation given the characteristics of R&D: highly risky, highly uncertain, highly expensive, leading to imitation and appropriation. After patent expiry, any manufacturer is allowed to copy the originator product. This creates the market of off-patent medicines, which are very likely to be sold at much lower prices than the originators since their manufacturing and marketing approval normally require very limited investments (Garattini and Padula, 2018). Notwithstanding the rise of generic companies, which increased competition in off-patent medicines, there has been no significant change in the ranking of the leading pharmaceutical companies (UNCTAD, 2015).

While the rationale behind patents is clear, as they may create incentives to guarantee innovation, the way such legal protection has been strategically abused through the use of multiple patents is also worth mentioning (Gurgula, 2020). The fact that a single drug may be protected by a primary patent (typically covering a new active ingredient or a new formulation) as well as many secondary patents with much smaller inventive steps, but each adding a full 20 years of protection, creates a problem of patent thickets (Di Iorio and Giorgetti, 2020). According to Shapiro (2001), the definition of a thicket is "a dense web of overlapping intellectual property rights (IPR) that a company must hack its way through in order to actually commercialize new technology". Moreover, the fact that the patent system doesn't differentiate between breakthroughs and minor innovations pushes companies to focus the efforts, very often, on minor modifications of existing medicines.

In most OECD countries, including the EU Member States, regulatory frameworks also provide other forms of protection from competition, usually for a period beginning at the time of marketing authorisation. For example, in the EU, original drug manufacturers generally enjoy 8 years of data exclusivity and 10 years of market exclusivity as of the date of approval of their medicine (Article 14(11) of Regulation (EC) No 726/2004). For orphan medicinal products, (Article 8(1) of the Orphan Regulation (EC) No 141/1200 sets a market exclusivity of ten years where EMA and National Competent Authorities cannot accept another marketing authorisation application, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product. Differently from patents, which are granted by the patent offices, exclusive marketing rights are granted by the marketing authorisation competent authorities upon approval of a drug and can run concurrently with a patent or not.

2.2.5.3 Regulatory authorisations

Regulatory barriers are requirements set by a national agency to market a drug in a country. In the EEA countries (i.e., EU-27 plus the UK, Norway, Iceland and Liechtenstein), medicinal products

may only be placed on the market after obtaining marketing authorisation. The EU pharmaceutical system builds on a dual system where the EC authorises innovative medicines for the entire EU on the basis of a positive scientific evaluation from the EMA (this is the so-called centralised procedure) and competent national authorities in the Member States authorise generic and other essential medicines (this is the so-called decentralised procedure which follows a mutual-recognition procedure). Each marketing authorisation decision is taken based on scientific criteria concerning the quality, safety and efficacy of the medicinal product concerned in view of protecting public health (EC, 2009). However, marketing authorisation is a long and expensive process, particularly for new and small companies (Amaouche et al., 2018).

2.2.5.4 Information barriers

The issue of asymmetric information in public procurement and regulation is a core concept of industrial economics (Laffont, Tirole 1993; Tirole 2014) that has been largely explored for such sectors as energy and telecommunications, but not so extensively for the pharmaceutical industry. The pharmaceutical market is characterised by information and incentive asymmetry between providers (pharmacists/hospitals), patients, third-party payers (public health system/ insurers), and pharmaceutical companies (Campbell and Kaló, 2018). The latter are the only ones with complete information about the cost, price, quantity, and quality of the sold drugs. Asymmetric information may be due to different factors, ranging from patent protection without full disclosure of relevant information to a lack of knowledge to understand and interpret available information publicly. Information asymmetry increases producer surplus and reduces consumer surplus and, at the same time, it may create a deadweight loss. For example, the asymmetric information on the R&D costs affects the pricing of drugs regardless of the schemes used. It is worth noting that asymmetric information also causes consumers, and to a certain extent physician, to not always choose the best options even when competition and a proper regulatory framework are in place. The case of generics is illustrative in this respect.

2.2.6 The European policy framework

Following the Maastricht Treaty of 1992, creating the EU, public health was introduced into the founding treaty. While the primary competence for health matters remains with the Member States, the EU's role has become more prominent over the years. Article 168 of the Treaty of Lisbon states that:

> *"Union action, which shall complement national policies, shall be directed towards improving public health, preventing physical and mental illness and diseases, and obviating sources of danger to physical and mental health. Such action shall cover the fight against the major health scourges, by promoting research into their causes, their transmission and their prevention, as well as health information and education, and monitoring, early warning of and combating serious cross-border threats to health".*

Hence, EU health policy serves to complement national health policies and to ensure health protection in all EU policies by pursuing strategic objectives such as the prevention and control of diseases, the harmonisation of health strategies and standards between Member States, the modernisation of health infrastructure, the efficiency of Europe's health systems (Quaglio, 2020).

The EC's Directorate for Health and Food Safety (DG SANTE) supports the efforts of EU countries in the field of health policy through various means, including by proposing new or amended

legislation[2], providing financial support, coordinating and facilitating the exchange of best practices between EU countries, ensuring collaboration with relevant international partners, and promoting health promotion activities.

Concerning specifically the EU pharmaceutical sector, it is extensively regulated (see table 1) in the dual interest of protecting public health while ensuring the single market for pharmaceuticals and it is characterised by a division of competencies between the Member States and the EU level. The EU has exclusive competence concerning the competition rules necessary for the internal market's functioning for medicinal products. The EU pharmaceutical legislation provides harmonised regulatory standards for the authorisation and supervision of medicinal products as well as incentives (including supplementary protection certificates, data exclusivity or market exclusivity, and protocol assistance) for promoting the development and marketing authorisation of medicinal products targeting orphan medicinal products (i.e. products to treat patients suffering from rare diseases), paediatric medicinal products and advanced therapy medicinal products. In turn, health technology assessment (HTA), pricing and reimbursement of medicinal products are within the competence of Member States. Each country decides which medicinal products are reimbursed by the national public health system and at what price. Also, any voluntary cooperation on pricing and reimbursement between countries remains their own prerogative.

Table 1: – Key EU legislation in the area of medicinal products for human use

Directive/regulation	Topic(s)
Directive 2001/83/EC Regulation (EC) No 726/2004	Requirements and procedures for marketing authorisation and for monitoring authorised products
Directive 2001/20/EC Regulation EU No 536/2014	Common rules for the conduct of clinical trials in the EU
Regulation (EC) No 141/2000	Medicinal products for rare diseases (orphan medicines)
Regulation (EC) No 1901/2006	Medicinal products for children
Regulation (EC) No 1394/2007	Advanced therapy medicinal products

Source: authors

In June 2020, the Commission proposed a new pharmaceutical strategy for Europe (henceforth the Strategy). It is a key pillar of the Commission's vision to build a stronger European Health Union (the European Health Union package include COM(2020) 724, COM(2020) 725, COM(2020) 726, COM (2020) 727), which President von der Leyen set out in her 2020 State of the Union speech. The new Strategy is meant to lead to a review of the existing regulatory framework and policy, and a subsequent review of the basic pharmaceutical legislation. According to the text published on 25 November 2020, the new strategy pursues a twofold aim. On the one hand, it is stated to be patient-centred and to ensure the quality and safety of medicines at affordable prices. On the other hand, it also desires to boost the EU's pharmaceutical industry's global competitiveness.

2 The EU can adopt health legislation under the Treaty on the Functioning of the EU: Article 168 (protection of public health), Article 114 (approximation of laws) and Article 153 (social policy). Areas where the EU has adopted legislation include: patients' rights in cross-border healthcare; pharmaceuticals and medical devices (pharmacovigilance, falsified medicines, clinical trials); serious cross border health threats; tobacco; organs, blood, tissues and cells.

The strategy has four work strands that flow from these general objectives and a detailed analysis of flaws affecting the pharmaceutical market: (i) fulfilling unmet medical needs and ensuring accessibility and affordability of medicines for patients; (ii) promoting a competitive and innovative European pharmaceutical industry; and (iii) enhancing the resilience of the pharmaceutical supply chains; and (iv) ensuring a strong EU voice globally. Each strand contains flagship initiatives (see annex 2 for more details) and other proposed actions. A close look at the Strategy reveals that it acknowledges most of the market and policy failures discussed in section 2.2.5.

The main concrete initiatives and the implementation timeline identified in the Strategy are summaried in the table below.

Table 2: – Main initiatives and target year of the Strategy

Area		2021	2022	2023
HTA	Adopt the European HTA Regulation	✓		
Health data	Legislative proposal for a European Health Data Space	✓		
Clinical trials	Implementation of a regulatory framework for clinical trials	✓		
Authorisation of medicinal products	Revision of the legal framework for authorisation conditions to make life-cycle management more efficient	✓	✓	✓
Artificial intelligence	Support for the development of high-performance computing and artificial intelligence for innovation in the R&D of medicines	✓	✓	
Personalised medicine, genomics and digital tools	Review of pharmaceutical legislation to promote cutting-edge products, scientific developments and technological change		✓	
Electronic product information (EPI)	Development and implementation of EPI legislation applicable to all EU pharmaceuticals		✓	
Competition law	Review of pharmaceutical legislation to ensure that markets function competitively		✓	
Intellectual property	Review of the incentive system to promote innovation, access and affordability of medicines across the EU		✓	
Patents, Supplementary Protection Certificates	Optimising the system for greater transparency and efficiency		✓	
Generic drugs and biosimilars	Revision of pharmaceutical legislation to address competition and improve access to generic and biosimilars		✓	
Medicines for children and rare diseases	Revision of legislation to improve the treatment landscape and address needs through tailored incentives		✓	
Production and supply chain	Review of pharmaceutical legislation to improve the security of supplies and remove bottlenecks through specific measures		✓	
Supply chain and sustainability	Revision of manufacturing and supply provisions in pharmaceutical legislation to improve supply-chain transparency and environmental sustainability		✓	

Source: authors based on the new Pharmaceutical Strategy

2.2.6.1 The EU bodies dealing with health matters

The panorama of institutional actors dealing with health issues in the EU is wide and fragmented. Restricting the focus on EU agencies, the main actors are the EMA, the European Centre for Disease Prevention and Control (ECDC), and the newly established Health and Digital Executive Agency (HaDEA).

The European Medicines Agency (EMA) is a decentralised agency of the EU responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU and

for ensuring that medicines are safe and that they work as expected after they have been authorised. As such, it works in close collaboration with the national authorities of the 27 EU Member States as well as the UK, Iceland, Norway and Lichtenstein. Although most new medicines in Europe are approved through the centralised procedure, the only medicines which are mandatory for evaluation at EMA are those for rare diseases, HIV/AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases, as well as all biotechnology products and other innovative products. In addition, EMA also provides guidance and support to medicine developers, including scientific and regulatory information on how to design and run clinical trials. The Agency charges fees for the services it renders. Indeed, the largest part of the EMA budget derives from fees and charges paid by companies. In 2021, the total budget amounts to EUR 385.9 million, of which 86% derives from fees and charges and 14% from the EU contribution and less than 1% from other sources (source: EMA website). According to some experts, one of the most significant limits of the current EMA mandate is that the Agency does not systematically evaluate a new drug's added therapeutic value, which is then entirely devolved to each EU State's regulatory authority. As explained by Padula and Garattini (2020) once preliminary efficacy and safety have been assessed for market approval, EMA passes the buck to national authorities for relative effectiveness analysis, including comparative and risk-benefits and cost-effectiveness profiles.

The European Centre for Disease Prevention and Control (ECDC) is a decentralised agency of the EU responsible for identifying, assessing and communicating threats to human health posed by infectious diseases. It was established after the 2002 SARS outbreak, when EU countries and the Commission realised the needed for a more coordinated response to viral outbreaks. ECDC was created looking at the US Centres for Disease Control and Prevention (CDC). However, with around EUR 55 million (OJ C 107, 31.3.2020, p 23), the ECDC annual budget is a small fraction of the CDC one, that amounted to USD 12 billion in 2020. Also, the ECDC mandate (identifying and assessing risks related to infectious diseases only) is narrower than the CDC mission. While ECDC is supposed to work in partnership with national health protection bodies across Europe to strengthen and develop EU-wide disease surveillance and early warning systems, the COVID-19 pandemic showed that it has limited coordination power indeed. It is acknowledged by various parties that ECDC has struggled to oversee COVID-19 surveillance and assess the virus' impact in Europe because it heavily relies on countries for information (Deutsch, 2020). In contrast, governments are often poorly collaborative, and they provide ECDC with incomplete data (reporting methods are differed among countries or within a single country).

Following the first stage of the COVID-19 pandemic, the EC presented a Communication on Building a European Health Union: Reinforcing the EU's resilience for cross-border health threats (see COM(2020) 724 final). The Communication was accompanied by three legislative proposals: an upgrading of Decision 1082/2013/EU on serious cross-border threats to health, a strengthening of the mandate of the ECDC to provide hands-on support to Member States and the EC to deal with health crises, and an extension of the mandate of the EMA to serve as a central hub for scientific excellence.

Beyond that, the EC also announced the creation of a completely new authority: HERA, an EU Health Emergency Preparedness and Response Authority. Along the lines of the existing US Biomedical Advanced Research and Development Authority (BARDA, see more in section 2.2.7), the goal of HERA, as for the EU Communication (see COM(2021) 576 final), is to strengthen Europe's ability to prevent, detect, and rapidly respond to cross-border health emergencies, by ensuring the development, manufacturing, procurement, and equitable distribution of key medical countermeasures (including vaccines, antibiotics, medical equipment, chemical antidotes, therapeutics, diagnostic tests and personal protective equipment).

According to EC Decision (see C(2021) 6712 final), HERA is established within the Commission as a shared resource for Member States and EU alike and will have different modes of operation during

preparedness and crisis times. In the "preparedness phase", it will steer investments and actions in strengthening prevention, preparedness and readiness for new public health emergencies. HERA's tasks during the "preparedness phase" are briefly illustrated in the Table 3. While task 2 concerns the promotion of advanced R&D of medical countermeasures and related technologies, HERA will not be directly responsible for managing a pipeline of research projects for developing medicines in the citizens' interest.

Table 3: – HERA's tasks

Task	Objective	Key actions
1. Threat assessments and intelligence gathering	To detect biological and other health threats soon after they emerge, evaluate their impacts and identify potential counter measures.	- Threat detection - Threat modelling - Threat prioritisation (by early 2022, identify and act on at least 3 specific high impact threats - Threat awareness - Epidemic surveillance
2. Promoting advanced R&D of medical countermeasures and related technologies	Promote research and innovation to develop effective, safe and affordable medical countermeasures	- Create a common strategic EU research and innovation agenda for pandemic preparedness - Pool fragmented pandemic preparedness research capacities across the EU. - Create a long-term and large-scale EU platform for multi-centre clinical trials and corresponding data platforms.
3. Addressing market challenges and failures and boosting the Union's open strategic autonomy	Identify and ensure the availability of critical technologies and production sites for medical countermeasures in the EU capable of increasing their production in times of need, including through support of breakthrough innovation.	- Mapping and monitoring supply chains, manufacturing capacities and ever-warm production sites. - Work with industry to address bottlenecks and supply chain dependencies within and outside the EU. - Set up new industrial partnerships and organise pan-European matchmaking events across the EU. - Establish close linkages with and build on the outcomes of relevant initiatives such as IPCEI Health and EU FAB.
4. Ensuring the provision of medical countermeasures	Use stockpiling and EU procurement to ensure provision of countermeasures	- Promote wider use of joint EU-level procurement. - Tackle possible challenges related to the transportation, storage and distribution of medical countermeasures across the EU. - Assess existing stockpiling capacity in the EU and develop a strategy to ensure effective geographical coverage and timely deployment across the EU. - Provide operational recommendations to the Union Civil Protection Mechanism
5. Strengthening knowledge and skills	Improve MS's capacities in preparedness and response related to medical countermeasures	- Organise training programmes to improve knowledge and skills related to all aspects of access to medical countermeasures.

Source: authors based on EC (2021).

In the “crisis phase”, HERA will be able to draw on stronger powers for swift decision-making and implementation of emergency measures. During the preparedness phase, HERA will have a budget of EUR 6 billion over a 6-year time period. In the event of a “crisis phase”, the Council could also trigger financing through the Emergency Support Instrument.

Under the new EU programming period 2021-2027, the Health and Digital Executive Agency (HaDEA) is also being established by Commission Implementing Decision (EU) 2021/173 of 12 February 2021. The Agency will be responsible for implementing all the programmes for health (the EU4Health programme, the Pillar II, Cluster 1: Health of Horizon Europe, the health components of the Single Market Programme (i.e. Food safety: health for humans, animals and plants along the food chain and better training for safer food), and digital (the Digital Europe Programme, the digital components of Connecting Europe Facility, and the digital research strand of Horizon Europe) purposes. Accordingly, the total budget managed by HaDEA will amount to around EUR 20 billion over the 7 years period of the 2021-2027 MFF. At the beginning, the Agency will have around 380 Staff and it will grow to more than 500 FTE.

2.2.6.2 The main funds for health projects and initiatives

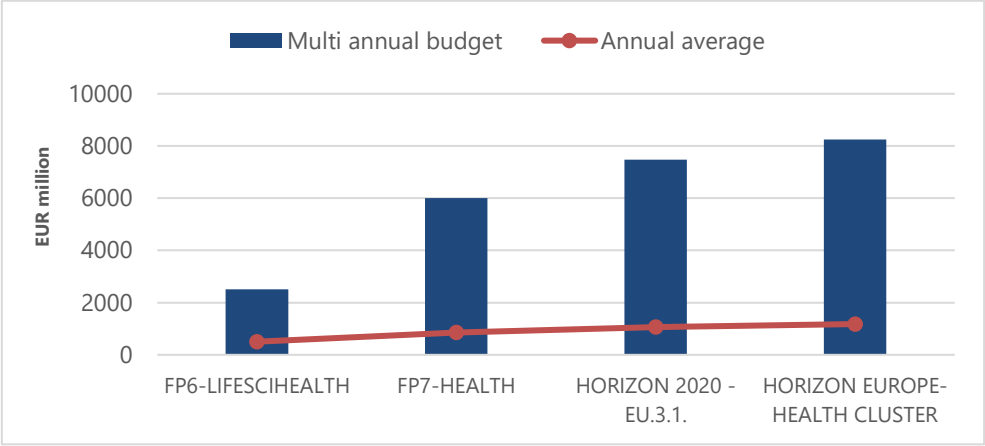
The financial support for the EU’s health policy comes from the EU health programme, which finances a range of collaborative projects on health promotion, health security and health information across Europe. The first comprehensive EU Public Health Programme (Decision No 1786/2002/EC of the European Parliament and of the Council) dates back to 2003 and covered the period 2003-2008. After that, the Second (Decision No 1350/2007/EC of the European Parliament and of the Council) and the Third (Regulation (EU) No 282/2014 of the European Parliament and of the Council) Health Programmes were adopted respectively in 2008 and 2013 to cover the period 2009-2013 and 2014-2020. The financial envelope of such programmes has constantly increased over time (EUR 312 million in 2003-2007; EUR 321.5 million in 2008-2013; EUR 449.4 million in 2014-2020). However, the big leap arrived only with the fourth Health Programme (2021-2027), which is EU’s response to COVID-19. By investing EUR 5.1 billion, EU4Health will become the largest EU health programme ever in monetary terms.

The EU4Health programme has three general objectives:

1. protecting people in the EU from serious cross-border health threats and improving crisis management capacity;
2. making medicines, medical devices and other crisis relevant products, available and affordable and supporting innovation;
3. strengthen health systems and the health care workforce, including by investing in public health, for instance through health promotion and disease prevention programmes and improving access to healthcare.

The EU4Health programme will also be a key element of support to the new Pharmaceutical Strategy.

Figure 6: Budget allocated to health priority from EU Framework programmes on R&I



Source: Authors based on CORDIS data.

In addition to Health Programmes, other EU funding instruments such as the Framework Programmes on research and innovation (i.e., the 7th Framework Programme, Horizon 2020, and Horizon Europe), the EU's Structural and Investment Funds, and the European Defence Fund, include strands on health. Among these additional funding instruments, the Research Programmes represent the most important driver for biomedical and pharmaceutical collaborative R&D, for both enterprises and academia. The financial envelope for the health priority has steadily increased over the years (see figure below) and so the areas addressed.

2.2.7 The European health R&D panorama

The European panorama includes a wide array of institutes and initiatives involved in biomedical and pharmaceutical R&D. The initiatives with European scope range from Joint Undertaking and no-profit organisations to European Research Infrastructures either in ERIC or intergovernmental organisation. The key traits of the main players and initiatives are discussed below.

2.2.7.1 European research infrastructures

The oldest and well-renowned example of pan-European research infrastructure in biomedical research is the European Molecular Biology Laboratory (EMBL). EMBL is an intergovernmental organisation (EIROforum Member) established in 1974 by ten funding countries. According to EMBL itself:

> *It was founded because the scientific community was able to show to member states that such an organisation was needed in Europe and that it had to be established with long term perspective and with the agreement to pool resources to carry out a scientific programme that is revised every five years. EMBL was not established as a project-based organisation with short term objectives but with the understanding that it would continue to change and adapt its strategy according to its members' needs*. Source: EMBL (2011).

Today, it is supported by 27 among EU Member States and Associated Countries, two associate third countries (Australia and Argentina), and two prospect Members (Latvia, Estonia). EMBL pursues five interlined missions: 1) to perform fundamental research in molecular biology; 2) to offer services to the scientific community (the most widely used services are the biological databases built and hosted at EMBL's European Bioinformatics Institute in the UK); 3) to train the next generation of scientists; 4) to work closely with industrial partners to develop new instruments and technologies (to this end, in 1999, EMBL's technology transfer arm, EMBLEM, was founded); and 5) coordinate and integrate European life science research. EMBL's activities are

planned in five-year programmes structured along these five mission areas and accompanied by a funding plan agreed by the Member States.

Currently, research at EMBL is conducted by approximately 85 independent groups covering the spectrum of molecular biology. The laboratory operates from six sites. The main laboratory in Heidelberg, and outstations in Hinxton (the European Bioinformatics Institute - EBI, in England), Grenoble (France), Hamburg (Germany), Rome (Italy) and Barcelona (Spain). According to the 2019 EMBL Annual Report (EMBL, 2019), the staff included 1,791 full-time equivalent and the total budget was about EUR 270 million, most of which (around 41%) came from Member State contributions. Over the years, many scientific breakthroughs have been made at EMBL, including two of which have been recognized with Nobel Prizes in Medicine (1995) and Chemistry (2017).

Beyond EMBL, there are three medical research infrastructures with an ERIC status: the European Research Infrastructure for Translational Medicine (EATRIS), the European Clinical Research Infrastructure Network (ECRIN) and the European research infrastructure for biobanking (BBMRI), working together under the umbrella of the Alliance of Medical Research Infrastructures. In 2018, these three organisations expressed joint interest in working more closely together to provide better services to the biomedical community and to support a more cost-effective research process.

Early in 2019, the Alliance of Medical Research Infrastructures solidified through the signing of a long-term collaboration agreement. Annex III reports the main features of these three medical research infrastructures and other research infrastructures in the life-science which have a close tie with health research. It is interesting to note that EMBL coordinated the setup of two of the listed infrastructures: ELIXIR and EURO-BIOIMAGING. It also participates in four other infrastructures: INFRAFRONTIER, BBMRI, INSTRUCT, and EU-OPENSCREEN.

2.2.7.2 Other pan-European R&D initiatives

Turning to other pan-European R&D initiatives, the Innovative Medicines Initiative (IMI) is worth noting. It is a Joint Undertaking, a public-private partnership (PPP) between the EC and the European Federation of Pharmaceutical Industries and Associations (EFPIA), with the objective of supporting collaborative pre-competitive pharmaceutical research. Established in 2007, the IMI was renovated in 2014. For the IMI1 programme (2008-2013), the total budget was EUR 2 billion, of which EUR 1 billion came from the 'Health theme' of the EU's Seventh Framework Programme for Research (FP7) and another EUR 1 billion came from in-kind contributions by EFPIA companies. For the IMI2 programme (2014-2020), the total budget was increased to EUR 3.276 billion. Of that, half the budget comes from the Health, Demographic Change and Wellbeing Societal Challenge of Horizon 2020, and EUR 1.425 billion is committed to the programme by EFPIA companies. The remaining part (up to EUR 213 million) can be committed by other life science industries or organisations that contribute to IMI2 as members or Associated Partners in individual projects.

The rationale for IMI was to overcome the fragmentation and partners' short-term commitment of regular calls for proposals under the various Framework Programmes on research and innovation, which in fact can promote multi-national, multi-disciplinary and cross-sectoral collaboration on health matters but only at the project level rather than based on a commonly agreed research agenda. The IMI driving force is twofold (see Council Regulation No 557/2014). One hand, it has public health purpose as it aims to address Europe's health challenges such as antimicrobial resistance, rare diseases and vaccines. Indeed, the Council Regulation 557/2014 specifies that IMI2 should focus on priority medicines identified by WHO and increase the success rates of clinical trials. One the other hand, it is shaped by the competitiveness logic as it is also meant to ensure that Europe's pharmaceutical industry remains competitive. IMI has its own strategic research agenda and funds projects selected following calls for proposals. In particular, it funds collaborative research projects proposed by consortia, which may include universities,

research centres, patient organisations, medicine regulators, pharmaceutical and other industries except for large companies in kind. The research results, including the rights attached to them, are appropriated by the projects' participants. IP issues are agreed upon before the launch of the project.

In 2021-2027, the IMI will be replaced by a more ambitious initiative, the Innovative Health Initiative (IHI), under the Horizon Europe Pillar 2 Cluster "Health". IHI is not meant to be a direct continuation of IMI2, rather it will have a broadened scope with new technology areas covered (medtech, biotech, vaccines, digital) in addition to pharma. Five industry associations (EFPIA, COCIR, MedTech Europe, EuropaBio and Vaccines Europe) representing pharmaceutical, biotech and medical technologies industries operating in Europe have come together to work on the IHI Strategic Research Agenda, which is still under development. According to the draft proposal (see EC, 2020), IHI will cover a variety of health technology domains and therapeutic areas, with activities including but not limited to: discovery; development and testing; post launch studies supporting (e.g., development of methodologies for assessment of safety; health outcomes or for health-economic evaluation); pre-standardisation activities; regulatory science; pilots/proof of feasibility. The budget is still undefined. What is clear is the funding model which will be characterised by a mandatory 50/50 ratio of in-kind vs EU funding at project level.

Finally, in the EU panorama for health research there is the EIT Health which is a non-profit organisation under German law established in 2015. The headquarter is in Munich, Germany, but is has a pan-EU representation via six regional Innovation Hubs (in Germany, France, Spain, the UK-Ireland, Belgium-Netherlands, Scandinavia) which operate as independent organisations connected to EIT Health. For the current period (2016-2022) the EIT Health has an indicative budget of EUR 2.2 billion (see EIT Health, 2018). Out of this, approximately EUR 455 million comes from Horizon 2020 programme. The remaining budget comes from partners' own revenues and resources (approximately EUR 1.8 billion) as well as private and/or public funding at national, regional and EU level (approximately EUR 10.4 million). Between 2016 and 2022, EIT Health strategy is focusing its activities in the areas of healthy living and active ageing, as well as improvement and sustainability of the healthcare systems in Europe, thus addressing the challenges posed by increase of chronic diseases and an ageing population. In the first four years of operation (2016-2019), the EIT Health has supported the launch of 87 products or services. However, according to the reviewed strategy published in May 2020, the initiative is not sufficiently sustainable. Therefore, in the future it will narrow its activities by focusing on delivering high-value solutions to transform healthcare, on building and scaling European healthcare companies, as well as on educating the entrepreneurs, change-agents and professionals that enable this.

A key trait of partnership either in the form of Joint Undertakings or of no-profit organisation is that while they all have strategic agendas guiding their operations, they are bottom-up initiatives. In other words, they fund projects proposed by different research communities without a strict convergence towards a common objective.

Beyond infrastructures and consortia working at European level, there is a high number of publicly-funded research infrastructures at the national level.

2.2.7.3 The limits of the current European policy approach

As seen above, there is no lack of R&D entities and initiatives within the EU. However, European institutions, compared to the US federal government agencies, tend to disperse resources in several overlapping initiatives and organisations that pursue their own goals without a coordinating mechanism. As a result, funded projects do not have the critical mass necessary to achieve the EU programmatic objectives.

EU programs and initiatives have pushed health R&D forward, but according to the Scientific Panel for Health (2018), they are insufficient. According to this report, there still is a lack of critical mass,

funding continuity, coordination and vision within the EU and between EU and the Member States for biomedical and health research. This is, in contrast, to what happens in the US, where government-sponsored research institutions (see Box 3) have significant budgets (both for funding third-party research activity and in-house research) and their own research roadmaps.

Box 3. US Panorama

In the United States, there are some exceptional examples of government-sponsored research institutions in the biomedical domain, namely the National Institutes of Health (NIH) and the Biomedical advanced research and development authority (BARDA).

The National Institute of Health (NIH) is the largest public funder of biomedical research in the world. NIH funded research has led to breakthroughs and new treatments, helping people live longer, healthier lives, and building the research foundation that drives discovery. More than 80% of NIH's funding is awarded for extramural research, largely through almost 50,000 competitive grants to more than 300,000 researchers at more than 2,500 universities, medical schools, and other research institutions in every state. About 10% of the NIH's budget supports projects conducted by nearly 6,000 scientists in its own laboratories, most of which are on the NIH campus in Bethesda, Maryland. Funding for NIH comes primarily from annual Labor and Education Appropriations Acts, with an additional smaller amount for the Superfund Research Program from the Interior/Environment Appropriations. Those two bills provide NIH discretionary budget authority. In 2020, NIH has a budget of USD 41.7 billion and has received emergency supplemental appropriations in three coronavirus supplemental appropriations acts, totalling over USD 3.59 billion. The administration's FY2021 budget request, as amended by a March 2020 letter, proposes an FY2021 program level of USD 39.133 billion—a 6.1% decrease from the FY2020 program level.

The Biomedical Advanced Research and Development Authority (BARDA), which reports to the Office of the Assistant Secretary for Preparedness and Response part of the US Department of Health & Human Services, was established to aid in securing US from chemical, biological, radiological, and nuclear threats, as well as from pandemic influenza (PI) and emerging infectious diseases. BARDA supports the transition of medical countermeasures such as vaccines, drugs, and diagnostics from research through advanced development towards consideration for approval by the FDA and inclusion into the Strategic National Stockpile. BARDA's support includes funding, technical assistance and core services, ranging from a clinical research organisation network to Centers for Innovation in Advanced Development and Manufacturing, and a fill-finish manufacturing network. BARDA supports a diverse portfolio of medical countermeasures and these products have received a total of 57 FDA approvals, licensures, or clearances. The Fiscal Year 2021 request is USD 1.4 billion, which is USD 150 million less than the FY 2020 enacted budget. BARDA works with public and private partners to transition candidates for medical countermeasures from early development into the advanced and late-stages of development and approval. So far, BARDA has successfully advanced 54 innovative products to the Food and Drug Administration for approval, including 10 during 2019 alone.

Source : authors based on www.nih.gova and www.phe.gov/about/barda/Pages/default.aspx

The EU approach to fund health research has two main drawbacks:

- **First, it is a matter of scale and lack of fund concentration.** As seen in section 2.2.6, in the period 2021-2017, through the EU4Health programme and Horizon Europe, the EC is expected to mobilise roughly EUR 13 billion to health R&D, or 1.86 billion per year, which is a modest fraction of the single NIH budget for 2021 (around ESD 39 billion) or even much below the

above-mentioned NIH Intramural Research program with around USD 4 billion per years. According to Bouillon et al (2015) public investment in biomedical and health research in the US is up to 3 times more per person per year than in the EU. The issue of critical mass is further exacerbated by the use of tender mechanisms which distribute resources in the order of a few million euros spread over several years per each project. The funding dispersion is coupled with the 'broadness' of European R&I missions, which can easily accommodate a wide range of projects not clearly linked to a common ambitious objective (Mazzucato, 2018).

- **Second, it is a matter of and short-termism and continuity**. Tenders in European Programmes funding health and biomedical research and innovation typically focus on short-term collaborative projects of 3-5 years proposed by temporarily consortia of universities and research institutes and only marginally enterprises – yet innovation cycle in pharmaceutical and biomedical projects is long, approximately 10 years (the Scientific Panel for Health, 2018). Thus, the EU funding system tends to attract universities and other institutes, which are chronically in need of funding for rolling out their own strategies and projects, rather than large-scale collaborative projects which require long-lasting and stable financing. Indeed, as noted by the Scientific Panel for Health (2018), the lack of continuation of funding undermines the sustainability of collaborative research projects.

More research funding within a fragmented and short-term system is not the best strategy to address the market failures mentioned in this report and to put Europe at the forefront of biomedical and pharmaceutical research.

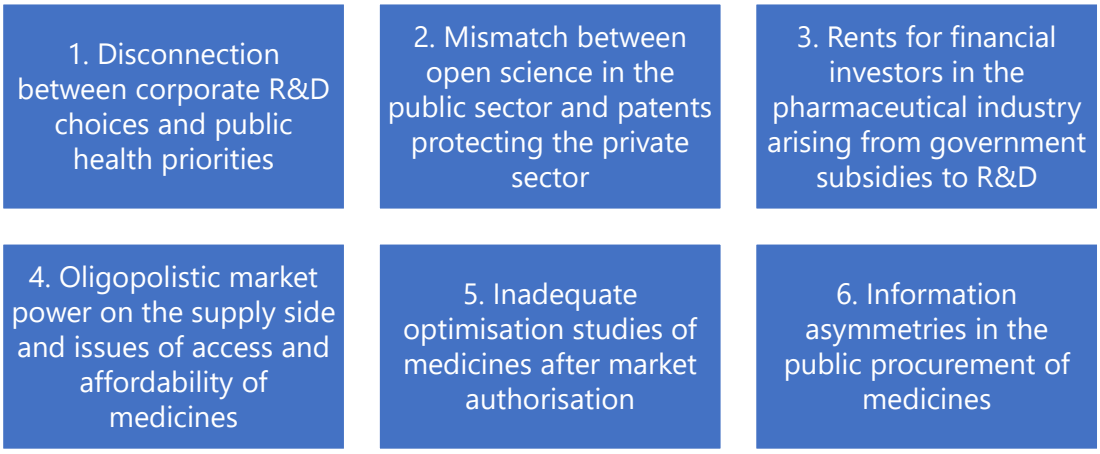
3 Discussion: the concept of a European R&D infrastructure for medicines

The previous sections of this report have identified some failures in the pharmaceutical supply and demand mechanisms, based on the literature review. In this section, we extend the analysis of such evidence in the perspective of European health policy, particularly in relation to medicines. The discussion below starts with an overview of the main concerns about both market and policy failures. We turn then to a new approach based on the concept of a large-scale and long-term European research, development, and innovation infrastructure for medicines; subsequently, we discuss intellectual property rights models for such a new entity and -more briefly- selected implementation issues (legal base, organisation, funding). The section is concluded with some social cost-benefit analysis considerations.

3.1 Overview of market and policy failures

As for the market and policy failures, according to a large consensus both in the international scholarly literature and in the responses of the over 50 experts interviewed, there are several concerns about the functioning and regulation of the pharmaceutical industry. To sum up some of the previous discussions in this report, the main issues are illustrated in Figure 7.

Figure 7: Market and policy failures in a nutshell



Source: Authors.

For each of these issues, we briefly mention why it is relevant, why current regulatory remedies are often less than adequate, and why a new policy approach should be considered based on public infrastructure. The new concept that this study suggests is creating a unique pan-European R&D infrastructure and delivery organisation for medicines in certain critical areas, based on frontier biomedical science, with an overarching public health mission and a long-term vision and funding.

More specifically, such infrastructure should:

- Have the sole mission of fulfilling European citizens' interest in being offered under all circumstances safe, effective, innovative, affordable medicines in areas affected by market failures and other issues of concern;

- Have a comprehensive, forward-looking, long-term strategy and dedicated leadership supported by the consensus of scientific communities and health authorities;
- Own the results of the R&D projects it supports, either fully or in specific cases with public-private partnerships, and manage its IPR and any other ownership rights on innovations exclusively in the public interest;
- Be largely open to collaborations, in partnership with third-party research centres at national or European level and with pharmaceutical companies, even outside the EU when needed, based on clear, transparent, contractual arrangements

For the sake of conciseness, the concept will be referred to in the rest of this report as the European research and development infrastructure for medicines, or for short, the European Medicines Infrastructure.

To clarify the policy issues at stake we have linked below the discussion of each market failure to both a traditional policy instrument, and to the rationales for a new approach based on the European research infrastructure concept.

3.1.1 Disconnection of corporate R&D and public health priorities

It has been mentioned in this report that the productivity of its R&D has been shrinking, for a complex set of reasons at the crossroad of economic, legal and scientific issues. The most important concern in a public health perspective is the disconnection between corporate R&D priorities and the most urgent needs for human wellbeings, such as new vaccines, new antibiotics and antivirals, and in general, diagnostic and treatment of emerging infectious diseases, affordable and effective medicines in certain areas of oncology, treatment of neurodegenerative diseases and other challenges related to ageing, orphan drugs for pathologies increasingly identified by molecular biology. The list is only indicative, see the further discussion below.

Governments have frequently considered subsidies to corporate R&D to curb such disconnection. The policy is currently implemented generously by governments through several grant schemes. The COVID-19 pandemic has revealed how quickly responsive the industry is to large government subsidies focused on a specific threat. Unfortunately, there is no evidence that this policy is efficient and effective in the long term beyond the current emergency. While governments and international agencies have since long identified the most important priorities for pharmaceutical research and made available large amounts of taxpayers' money, there is no evidence that the R&D portfolio composition of pharma companies is structurally influenced by such generous direct or indirect subsidies. The current pandemic shows a quick response, but the amount of public money involved (particularly by the US government, but also by China and some European countries) was unparalleled, the global market perspectives so wide, the fast-track marketing authorizations so unprecedented that this emergency approach cannot be considered as the main pathway for governments to influence corporate R&D in the next decades.

Hence, the opportunity to explore a different approach supported by several interviewed experts and by the literature review on research infrastructure: the creation of an R&D and innovation infrastructure where the alignment of the missions (further discussed below) and the long-term priorities of the public health system in the European Union should be established by design in the first place.

3.1.2 The mismatch between open science and patenting systems

The current business model of the pharmaceutical industry heavily relies on the 'legal monopoly' provided by filing a patent or family of patents at patent offices. This process, in turn, usually motivates further steps leading to marketing authorization by a public institution such as the EMA of the US FDA and other agencies. In this perspective, while heavily regulated by public authorities

and – as mentioned – heavily funded by public money, the pharma industry is based on IP arrangements that, according to several public health experts and some scholarly analyses we have reviewed, offer incentives to investors, and serve well private interest but do not adequately reflect the cumulative nature of knowledge. In fact, while universities and not-for-profit research institute increasingly adopt an open science model, allowing companies to access upstream knowledge for free, the legal arrangements in place do not protect the public interest adequately when a patent or a market authorization is granted to a company. The same applies when patents filed by a public sector entity are licensed by private companies for free or at a low cost.

The traditional aim of patent legislation is to counterbalance the private incentives of legal monopoly with an obligation to publicly disclose information on inventions in the patent files. This disclosure, in principle, would create a positive externality as the social value of a patent would be greater than its private value because third parties would benefit in two ways from such public information: firstly, because they could build further inventions based on the existing knowledge embodied in the patent, secondly because when the patent expires, the relevant knowledge is already in the public domain. Unfortunately, this disclosure mechanism has limited scope because trade secrets remain undisclosed, not to mention information on actual R&D and production costs.

The debate on the COVID-19 vaccines has revealed that even if patents were suspended, as per the resolution of the European Parliament (June 10, 2021), their owners would not implement the 'deep technology transfer' to third parties. Anyway, the industry has strongly rejected any attempt at even temporary suspension of patents on COVID-19 despite certain legal provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights at the World Trade Organisation. In the US, provisions in the Bayh-Dole Act (1980) for patents supported by government funds (so-called 'march in rights') for direct government intervention when pricing or other market conditions are 'unreasonable' have been evoked but never applied. Moreover, in the legislation or actual practice of the MS, there is no evidence of systematic policy frameworks to deal with the issue of how to protect the public interest when a combination of open science upstream, government subsidies to R&D, patents and market authorisation lead to such issues as unaffordable prices, scarcity of medicines in certain fields, uncompetitive corporate strategies. It seems unlikely that some legislation reforms could effectively deal with such structural features of the industry.

Hence, we shall discuss below in detail different strategies that a new European Medicines Infrastructure could adopt to protect in the public interest the IP of inventions in a way fundamentally different from the current model that is prevailing in the pharmaceutical industry. This report does not go as far as to propose wide reforms in this area but suggests that the new entity should experiment with a new IPR model.

3.1.3 Rents from government subsidies

We have mentioned that the industry currently absorbs gargantuan flows of taxpayers' money. For each new medicine (on average), the real R&D cost is directly and indirectly supported by a combination of public sector grants to biomedical research either upstream or directly to firms. The flow of taxpayers' money to the industry may cover, particularly for US-based companies through NIH and other grants, up to 50% of R&D costs (Light and Warburton, 2011). The evidence of public subsidies to the industry for Europe (including the UK and Switzerland) is unsystematic, but looking at the transfers from governments to public universities and research institutes and their connections with the industry, the indirect flow of taxpayers' money to support innovative medicines is far from negligible.

There is no systematic public scrutiny of the social cost and benefits of such a mechanism of subsidies. At the same time, it seems obvious that it implies rents ultimately captured in the shareholder value of pharma companies. The history of the COVID-19 vaccines, supported by

decades of previous research in not-for-profit institutes and universities, and then by emergency government subsidies (about USD 20 billion for Operation Warp Speed only, see Baker and Koons, 2020) followed by a sudden jump in the values of shares of certain companies, perfectly illustrates the asymmetry of returns for taxpayers and investors.

Against government subsidies to the industry, corporate income taxation of extra-profits or monopoly rents is not an effective remedial policy. To offer subsidies to R&D and then tax profits arising from patented and authorised drugs seems a rather contradictory policy, as profit motivations are the core incentive for firms. Moreover, a more aggressive tax policy on mainly multinational companies is unlikely to be effective. Several governments try to curb excess profits in the pharmaceutical industry by implementing certain price controls, which may or may not work, but seems a scarcely effective instrument to contain the price of new medicines, mainly because of lack of reliable cost information available to the regulators (see below).

A part of the inefficiency of the current system of direct and indirect government subsidies to the industry would be removed if there were a public infrastructure for R&D and delivery of new medicines in certain areas. As mentioned, the core inefficiency of any mechanism of subsidies is that to allow the beneficiary to change its behaviour, namely, to invest in certain R&D areas, taxpayers are de facto creating rents in addition to normal returns on invested capital. This would not be an issue when the recipient of public funds is a transparent not-for-profit entity. Laffont and Tirole (1993) show the built-in inefficiency of such a mechanism in the wider context of public regulation and procurement under asymmetric information. Moreover, another source of inefficiency in the system is the fragmentation of research grants, which would be partially corrected by creating a large-scale international infrastructure.

3.1.4 Market power and competition policy

As previously documented, the pharmaceutical industry has an intrinsically oligopolistic structure. It effectively works as a set of legal or de facto monopolies on most medicines, with the unavoidable implications of market power: corporate R&D budgets are ultimately shaped by balancing risks and returns to financial investors; prices, particularly for new medicines, are associated with wide margins over opaque costs; frequent mergers and acquisitions lead to further market concentration; production choice and the value chain are optimized to extract rents for the top multinational corporations.

The European Council (June 17 2016) required the Commission to study the issues in depth:

> *"The Council asked the Commission to prepare a 'report on recent expressed concerns that patients' access to affordable and innovative essential medicines may be endangered by a combination of (i) very high and unsustainable price levels; (ii) market withdrawals, or other business strategies by pharmaceutical companies; and (iii) the limited bargaining power of national governments against those pharmaceutical companies. The European Parliament expressed similar concerns in its resolution on EU options."*

In fact, since 2009, 29 decisions have been adopted by national competition authorities and by the EC, with fines totalling over EUR 1 billion. Several other cases have been investigated, over 100 in a decade, without any decision (EC, 2019).

Anti-trust decisions by a public authority are not unknown in the pharmaceutical industry (Hull and Clancy, 2021). These decisions, however, in the EU were less than three per year across 28 Member States and of rather limited scope compared with other industries.

The reason for such a relatively minor role of competition policy in the pharmaceutical industry probably lies in the potential conflict between different public policies. On the one hand, competition authorities would like to see a more open market. On the other hand, monopoly power results from innovation policies such as granting exclusive IPR through patents and market

authorisations. Moreover, the literature widely acknowledges economies of scope in the industry because only a fraction of the R&D projects achieves a positive outcome. Hence a project portfolio managed by a large corporation approach is probably more efficient than a fragmented supply-side structure.

Legal monopoly, economies of scope, and probably economies of scale in certain operations, including production and distribution, naturally lead to oligopolistic market power. Hence, it seems difficult for the regulators to order the break-down of companies or block M&A if the ultimate returns to patients of such policy would be unclear. Correcting excessive profits by corporate taxes is also difficult because some policy makers see such profits as the reward for legitimate monopolistic power. In any case, the taxation of income or wealth of multinational companies is notoriously elusive.

The well-established economic literature on regulated oligopolistic markets (De Fraja and Delbono 1990; Matsumura and Kanda 2005; Willner et al. 2018) states that the maximization of social welfare may benefit from the coexistence of private and not-for-profit players. The reason is that the profit-maximising behaviour of the former will be influenced by the latter. Moreover, oligopolistic collusion is more difficult when economic agents with different objectives, including a social welfare maximize agent, play a role in the arena.

3.1.5 Inadequate optimisation studies of treatments after marketing authorisation

While companies have all the incentives to invest money in preparing clinical trials and other studies to support their applications for marketing authorizations, they obviously have no incentive (Lacombe *et al*., 2019) to run comparative clinical trials and 'real life' studies to ascertain if a drug is more effective than an alternative one, if the social cost-benefit profile is optimal, if repurposing of another drug would be beneficial, to assess the long-term effects on patients with adequate statistical data.

Regulators may try to convince companies to perform such long-term studies, or they can try to commission such studies to third parties. The first policy may or may not be successful, because as mentioned, companies have limited interest in systematic post-authorisation comparisons across medicines, including those of competitors. At the moment, such studies have been performed non-systematic and voluntary in the post-approval stage by some non-commercial entities (EP, 2020a). In contrast, the new European research infrastructure would provide such studies independently and transparently, filling a relevant gap in applied research.

3.1.6 Information asymmetries in the public procurement of medicines

While a considerable market quota for medicines, particularly in Europe, is ultimate with a government payer (hospitals, public health authorities, etc.), pharmaceutical companies have no interest in sharing information on the cost structure of R&D, production, and distribution cost of medicines. Hence, most public authorities have limited data to ascertain whether their public procurement arrangements, including the long-term resilience of production capacity in a country, are efficient. Eventually, they rely on the limited information given by the company themselves and very few independent studies. In some countries, according to the literature, there are also issues of transparency and risks of corruption (Transparency International, 2016).

According to several experts, public procurement, in a broad sense, is an area where improvement is still possible, by adopting different procurement models (Mur *et al*., 2017). This issue is largely in the hands of lawmakers, governments, and regulators in each country, albeit with very wide differences within the EU.

A core advantage of establishing a European pharmaceutical infrastructure is that it would showcase information on the actual costs of R&D for biomedical and particularly pharmaceutical innovations. This is an area of considerable opacity, as the companies have no interest in disclosing the details on the cost of the different steps of their research efforts, including the costs of contracts with external organisations managing the clinical trials, manufacturing, distribution.

Finally, the portfolio of innovative pharmaceutical products owned by the new entity and duly approved by EMA and other agencies would be available for the public health system of the participating countries in the first place, and possibly of third parties, under not-for-profit strategies. Transparency of costs at the R&D stage would be followed by transparent licensing or other supply arrangements, with potential advantages in learning for public actors.

Having summarized the pharmaceutical industry's core market and policy failures, the deficiencies of traditional policies, and the advantages of a new approach leading to a large-scale European infrastructure for research, development, and innovation, we turn to a more detailed discussion of such a new concept.

3.2 The European Medicines Infrastructure concept: the core missions

The rest of this section discusses the mission and key features (as well as selected implementation issues) of the European Medicines Infrastructure: an organisation internalising a public health overarching mission, conducting research and innovation, and delivering pharmaceutical and related biomedical innovations through dedicated facilities, resources, and services available to the scientific community, enjoying budgetary autonomy.

It is useful to recall the definition of research infrastructure at the core of the proposal illustrated in this study. According to the EC (2017):

> *«Research infrastructures are facilities, resources, and services that are used by the research communities to conduct research and foster innovation in their fields. Where relevant, they may be used beyond research, e.g. for education or public services. They include: major scientific equipment (or sets of instruments); knowledge-based resources such as collections, archives, or scientific data; e-infrastructures, such as data and computing systems and communication networks … Such infrastructures may be 'single-sited', 'virtual' or 'distributed'… By offering high quality research services to users from different countries, by attracting young people to science and by networking facilities, research infrastructures help to structure the scientific community and play a key role in the construction of an efficient research and innovation environment».*

Why would a public infrastructure approach be appropriate in this context? Infrastructures for research, development, and innovation are at the frontier of knowledge production in different areas and have distinctive features compared with traditional academic institutes and corporate R&D.

According to Florio (2019), in the last decades, the organisation of scientific research has gradually evolved to the RI model due to two main determinants:

- the acknowledgement of the scientific community of the effectiveness and efficiency to create common open platforms, shared by a plurality of teams beyond national borders, and
- the advancement in information and communication technologies.

Florio (2019) also stylised the following main ingredients of the RI paradigm: bottom-up identification of priorities by the scientific community, endorsed rather than proposed by governments themselves; international coalitions of funders; flexible accessibility to common resources by multiple users; shared management; creation of human capital incubators; technological hubs with knowledge externalities; big data generators; adoption of open science models; public involvement through outreach.

In this perspective, the European Strategy Forum of Research Infrastructures (ESFRI) Roadmap 2018 mentions that some existing infrastructures such as BBMRI ERIC, EATRIS ERIC, ECRIN ERIC, ELIXIR, ERINHA (see Annex III) and others may potentially connect among themselves aiming at providing a pipeline for drug development. For example, the ESFRI Roadmap affirmed that the challenge of antimicrobial resistance and pandemics calls for an integrated effort by several scientific communities and tools. Therefore, according to ESFRI, it will be crucial to combine high-end technology platforms with specialised expertise, bringing together hospitals, research centres and the private sector in an integrated network that will offer a point of single access for the development of next-generation medicines. Examples of collaborative effort towards a mission-oriented approach are underlined by the recent joint statement from BBMRI, EATRIC, ECRIC and ELIXIR to contribute to the Horizon Europe Mission on Cancer (BBMRI ERIC, 2020) or the Alliance of Medical Research Infrastructures for a COVID-19 Fast Response Service. More in general the need for a new pan-European body for health research was already suggested by the Alliance for Biomedical Research in Europe, a federation of professional associations, that however covers a much more extensive ground (see box), while the European Medicines Infrastructure would specifically focus on research and development of medicines.

Box 4. European Integrated Price Information Database Collaboration

They called for the creation of a European Council for Health Research (EuCHR), an independent multi-disciplinary and multi-stakeholder body of excellent biomedical scientists would have a mandate to set long-term, sustainable, research programmes based on the likelihood of achieving translations of findings into innovative outcomes that will improve the health of citizens. So far, to the knowledge of authors, the proposed has not materialised.
Source: authors based on https://www.escardio.org/static-file/Escardio/EU-Affairs/health-research-concept-paper.pdf

We discuss the European Medicines Infrastructure concept having in mind this broad framework that defines frontier research infrastructures. Four core missions can be identified. They are discussed in what follows.

3.2.1 Mission 1: to build a portfolio of innovative pharmaceutical R&D projects

The European Medicines Infrastructure should be designed as a mission-oriented infrastructure. As regards its primary mission, the European Medicines Infrastructure should aim to ensure that in areas where there are market failures investment in R&D shapes Europe's pharmaceutical capability and continues to deliver benefits to the citizens of Europe and the world. To this end, the European Medicines Infrastructure should build a portfolio of purpose-led missions and projects in selected pharmaceutical areas and related biomedical fields (including fundamental and preclinical research) over twenty or thirty years (2050) in the spirit of looking at the needs of the next generation of European citizens.

Such portfolio should be built by selecting missions and projects of critical importance for human health of the 21st century based on an agenda of priorities established by the consensus of the scientific community and by the public health systems of the participating countries. The portfolio

should review and draw on the guidelines and studies of various European institutions, the WHO, and other international bodies that periodically identify the therapeutic areas most in need. The actual priorities for the European Medicines Infrastructure can only emerge from a careful periodic process of bottom-up consultation in style typical of research infrastructures, reconsidering the recommendations made by individual experts, government bodies and public organisations from the point of view of a public investor. The EC, DG RTD, has several times implemented such consultation mechanisms in relation to its own flagship programs.

The selection of public health priorities requires a long-term vision. At the same time, as things can change rapidly at the frontiers of pharmaceutical and biomedical research, the agenda of priorities should be a rolling plan that must be updated according to a cycle of evaluations. There are a number of contributions that can orient where to look to concretely designing a project portfolio. Concerning unmet needs, for instance, in 2015, the EMA carried out a study (see Papaluca et al., 2015) to identify the white spots in pharmaceutical pipelines, i.e. medical conditions for which effective treatment is neither available nor under clinical development, based on data available to EMA. By combining the data from different international databases, the study concluded that the main areas for white spots were oncology, infectious diseases and certain psychiatric conditions. As far as concerns oncology and infectious diseases, the study points out that, despite being apparently in the hub of pharmaceutical industry R&D investments, these remain areas of high demand for treatments, prevention and smart diagnostics, especially in the fields of rarer and pediatric cancers, and antibiotic-resistant infections and viral diseases.

Concerning psychiatric conditions, the study recognises that following repeated investments and drug development failures, these conditions stand out as a growing need to be addressed through basic research funding. Also, the study points out that there is a clear signal that while a large number of broadly defined pregnancy-related, congenital, perinatal and neonatal pathological conditions are common, they remain 'orphans' of appropriate treatment. It is worth noting that the disease burden on society was not taken into account by the study, but can be guessed as very high.

The association between the number of published randomised controlled trials and the global burden of disease, as estimated by the Global Burden of Disease Study, is the object of another study published in 2015 (Emdin et al., 2015). The study found a weak association across disease areas between the burden of disease and quantity of randomised trials, indicating that certain diseases are under-investigated relative to their attributable morbidity and mortality.

In principle, the European Medicines Infrastructure should prioritise therapeutic areas:

- not enough addressed by the private sector or
- where the private sector charges exorbitant prices, or
- where there are shortages or supply is not secure.

In this perspective, the evidence collected by the literature review and by interviews with experts concurs that long-term strategic projects on antimicrobials and antiviral drugs should be at the heart of the priority mission of the European Medicines Infrastructure, along with specific research areas in vaccines, orphan drugs, neurogenerative treatments, certain types of cancer. Collection or related digital health data is another potential priority frequently mentioned by the interviewed experts, even if there is no consensus about how to include data collection, storage, and access in the concept for the European Medicines Infrastructure.

Box 5 Antimicrobial resistance

According to OECD (2019), around 20% of infections are currently due to antibiotic-resistant pathogens in the EU and the percentage is twice in countries such as Romania and Greece. The Review on Antimicrobial Resistance, a study for the British government, predicts that bacterial infections will cause about 10 million deaths a year worldwide by 2050. By comparison, there are 8.2 million deaths from cancer, 1.5 million from diabetes. For several years, the EU has been supporting projects on the subject[1]. In 2017, the EC adopted a new European action plan against antibiotic resistance.

A previous EC Decision (No 1082/2013 / EU on serious cross-border threats to health) already included the AMR among the list of serious cross-border threats to health. Among the various initiatives currently underway there is a collaborative research platform (JPIAMR) which coordinates national and European funding to support research and transnational activities on the topic of antibiotic resistance. Since 2011, JPIAMR has supported 99 projects and 1221 researchers, with funding of around EUR 80 million.

The new Pharmaceutical Strategy include various flagship initiatives on AMR, including the provision of innovative pull incentives, the review of the pharmaceutical legislation to introduce measures to restrict and optimise the use of antimicrobial medicines, and the promotion of investment and coordination of R&D, manufacturing, deployment and use for novel antibiotics as part of the new HERA.

Note: [1] https://ec.europa.eu/health/antimicrobial-resistance/research-projects-studies_en

This report will not discuss further details on the R&D agenda. The European Medicines Infrastructure should design such a strategic roadmap in transparent consultation with all the relevant stakeholders, including the scientific communities, public health authorities, patient associations, and the pharma industry.

As a final remark, it is worth noting that the missions should be both demand-driven (based on identifying the needs of the public health systems) and technology-driven and fully exploiting health digital databases. Therefore, the mix of available technologies contributes to shaping the research opportunities.

3.2.2 Mission 2: treatment optimisation studies

The need to optimise treatments after their marketing authorization is a problem that is becoming more and more pressing (EP, 2020a). As mentioned in the previous section, apparently the industry is not much interested in taking responsibility for such studies. In some cases, their results would imply a critical re-assessment of profitable drugs in the companies list.

Some optimization studies may review long-term safety and effectiveness compared with competing treatments, including with generics, and considerations of cost-effectiveness (for example in terms of Euros per quality adjusted life years gained, or similar cost-effectiveness metrics).

Academic research is also quite often scarcely interested in such studies, firstly because they are not funded by the industry, which is an important co-funder of academic research, particularly for costly large-scale clinical trials or multi-centric observational studies and, secondly, because the perception that results of studies on existing medicines (including replication studies) would not be seen as leading to publication in top journals (for an extensive study on treatment optimization see EP, 2020a).

To sum-up on this mission, the European Medicines Infrastructure should carry out clinical studies relating to drugs already authorized such as:

- Comparative safety and effectiveness trials of existing drugs. As mentioned, for obvious reasons, in most cases, the pharmaceutical companies do not fund comparative clinical studies of this type, which could be very important from a public health perspective. EMA and most drug agencies do not seem to fully have the mandate to order companies or third parties to perform comparative effectiveness clinical trials after authorisation; therefore, this area remains highly fragmented (see Vella Bonanno et al., 2019; EC, 2018) and underinvestigated.
- Long term safety studies. The same considerations apply to systematic safety studies, which would be different from pharmacovigilance (which is alerted when some adverse effects are revealed by patients, physicians, o pharmacists).
- Studies for drug repurposing could be another area of action. These studies are needed to investigate if drugs whose patents have already expired and approved by the medicine agencies and health authorities for certain specific uses could be used to treat other diseases.

3.2.3 Mission 3: improving generics' safety and affordability for Europe

Another mission for the European Medicines Infrastructure could concern the development of (possibly entrusted to selected CDMOs) generics with unjustifiably high prices or poorly verifiable quality as they are produced outside the EU. This mission is not a priority for the new infrastructure to tackle, but the literature suggests that the topic needs further consideration. Indeed, there may be a role for a centralised public procurement agency, as suggested by Mennini et al. (2017) and as partially implemented by countries participating in the Beneluxa initiative. The latter aims for sustainable access to, and appropriate use of, medicines in the participating countries: Belgium, the Netherlands, Luxembourg, Austria, and Ireland. The participants cooperate on health technology assessments, horizon scanning, exchange of strategic information and price/reimbursement negotiations.

3.2.4 Summing up

To sum up our discussion so far, the European Medicines Infrastructure - in its most ambitious configuration - should be an RDI infrastructure and a 'delivery organisation' (in opposition to a mere funding or coordination organisation) which should work synergically with the newly established HERA and with other European agencies and institutes. The European Medicines Infrastructure's main responsibilities would be:

- elaborating and implementing a long-term European portfolio of purpose-led missions (such as for example on future coronaviruses drugs and vaccines and other infectious diseases);
- elaborating and implementing R&D projects under each mission;
- coordinating and implementing R&D projects in collaboration with third-party research centres at the national or European level and with selected pharmaceutical companies;
- ensuring that new drugs, vaccines and other biomedical innovations are eventually rolled out and made available to national health systems, after authorisation by EMA;
- ensuring effectiveness, safety and efficiency of selected medicines through optimizations studies;
- ensuring safety and affordability of existing medicines in the long term (coordinating its efforts with HERA, ECDC and other EU and international bodies, including WHO in terms of preparedness).

A crucial aspect for such a European R&D infrastructure is the adoption of an appropriate strategy on IP in the public interest. Because of its importance this specific issue is discussed in the next section.

3.3 The European Medicines Infrastructure as a promoter of new approaches to IP of pharmaceutical innovations

A key aspect of the European Medicines Infrastructure concept is that new knowledge on pharmaceutical innovations is generated to benefit all European citizens and possibly as global public goods. Hence at the core of the concept, there is the appropriate management of IP of the innovations arising from the work of the European Medicines Infrastructure.

Several options are available in order to boost accessibility to affordable and lifesaving treatments. These go from the traditional form of protection of innovation through IPRs, to the free accessibility to innovation. However, several intermediate options are available, through what can be defined a flexible and responsible IP management (Access to Medicine Foundation, 2021) that allows for a public-oriented use of IP.

An important aspect to consider concerns the research and development focus and the involvement of the infrastructure in the lifecycle of pharmaceutical products. In most cases, in the pharmaceutical industry, external companies take care of registration, manufacturing and commercialization only if IPRs protect the technology they are transferred. Moreover, if external companies carry out the manufacturing and commercialization steps, patents might be an alternative to clauses in the contracts that clarify that the European Medicines Infrastructure carried out the innovation and that the external company might not apply for a patent.

For the above-mentioned reasons, a flexible approach characterised by different frameworks for the management of IP is recommended. The blend of approaches to IPR that should be adopted by the European Medicines Infrastructure depends upon several features of its design, and should be flexible enough to deal with different types of projects, given the scope of the above-mentioned three missions. In what follows the characteristics of different possible frameworks are illustrated.

3.3.1 Revenues-oriented approach

In specific cases, the new infrastructure might decide to license or sell its IPR to third parties at market prices. This choice might involve a fraction of its own IP, and different forms of IP management may be considered according to the beneficiary: a revenues-oriented IP management may be adopted in combination to the flexible forms of management of IPR described in the next paragraph.

In order to market its technology, the new infrastructure may rely on typical bilateral agreements, or might delegate clearinghouses to sell its IP more effectively that it could do itself. The advantage of a profit-oriented management of IPRs is the possibility to finance R&D through IP rent revenues. Moreover, patents strength the ability to ensure control of the development process and to negotiate with partners. In particular, patent protection may be essential in the ability to transfer innovations to the private sectors for further development and commercialisation (Stevens et al., 2016).

Patents might also be necessary to ensure accessibility of the end product (Drugs for Neglected Diseases initiative, 2018). For these reasons, patenting is not only adopted by for-profit pharmaceutical firms, but sometimes it is also adopted by access-oriented organisations, which consider pharmaceutical innovation as a public good, or by national agencies. For example, when this is needed in order to best achieve its mission of accessibility, the Drugs for Neglected Diseases initiative (DNDi) resorts to patents to protect its innovations, and legal actions are undertaken in order to grant enforcement. IPRs are the standard approach for the US NIH, since they allow NIH to move their technology to the private sector for further development and commercialization.

Patenting of the research results is also adopted by some public-private partnership (defined "partnership-focused" by Stevens et al. (2016).

3.3.2 Socially-responsible IP management

Even protecting its innovations through IPR, the European Medicines Infrastructure may still stimulate further innovation by sharing its knowledge assets, such as data, technology, compounds, or molecule libraries, with qualified third-party researchers working on specific topics. This may be done through bilateral negotiations or using specific IP sharing platforms. Of these platforms, WIPO Re:Search (see box) has established the highest number of collaborations, while none of the initiatives have resulted in a product yet (WIPO Re:Search, 2017).

Box 6. WIPO

The goal of the WIPO Re:Search tool, resulting from a global public-private partnership between WIPO and BIO Ventures for Global Health, is to support early-stage R&D and to enable partnerships between members. Through the WIPO expertise in IP and its long-standing relation with inventors, this tool allows its members, belonging both to the private and public sector, to create new R&D markets for underutilized assets (Krattiger et al., 2018). Provider members share their IP assets royalty-free with qualified other members working on new solutions for neglected tropical diseases, malaria, and tuberculosis (which represent non-profitable markets); user members may exploit these assets to address public health needs (in terms of R&D or production) related to these diseases in least developed countries. User members may thus benefit from reduced development and transaction costs and save time. Many academic institutions, for-profit organisations and NGOs contribute to the tool providing IP assets, but each member might be both a provider and a user.

Source : authors

Another way to share IP assets, as well as to pool the risks of R&D projects, is through participation in R&D partnerships with governments, private and philanthropic partners. Within the area of pharmaceutical R&D, there are essentially two types of partnership: product-development ones, whose goal is to develop new pharmaceutical solutions, and precompetitive partnership, focusing on research models, databases' creation, and the identification of disease targets (de Vrueh & Crommelin, 2017).

The number of partnerships has been dramatically increasing (Lim, 2014) (de Vrueh & Crommelin, 2017), and in 2018 close to a third of R&D projects were developed in partnership. Slightly more than a quarter of these involved explicitly access-oriented organisations having a public health mission of drugs' accessibility, such as the Medicines for Malaria Venture; the DNDi; the Innovative Medicines Initiative, an EU public-private partnership; the COVID-19 Therapeutics Accelerator, launched by the Bill and Melinda Gates Foundation, Wellcome and Mastercard; the Global Antibiotic Research & Development Partnership (Access to Medicine Foundation, 2018).

In collaboration with public and private partners, access-oriented organizations develop new, urgently needed treatments and ensure their affordability and availability. Even if the organisation does not always have the capacity or infrastructure to undertake early-stage development projects in-house, usually every phase of the R&D process is managed by the organisation, which acts as a facilitator coordinating partners activities and allocating resources. The goal is the development of pharmaceutical products of use as a public good.

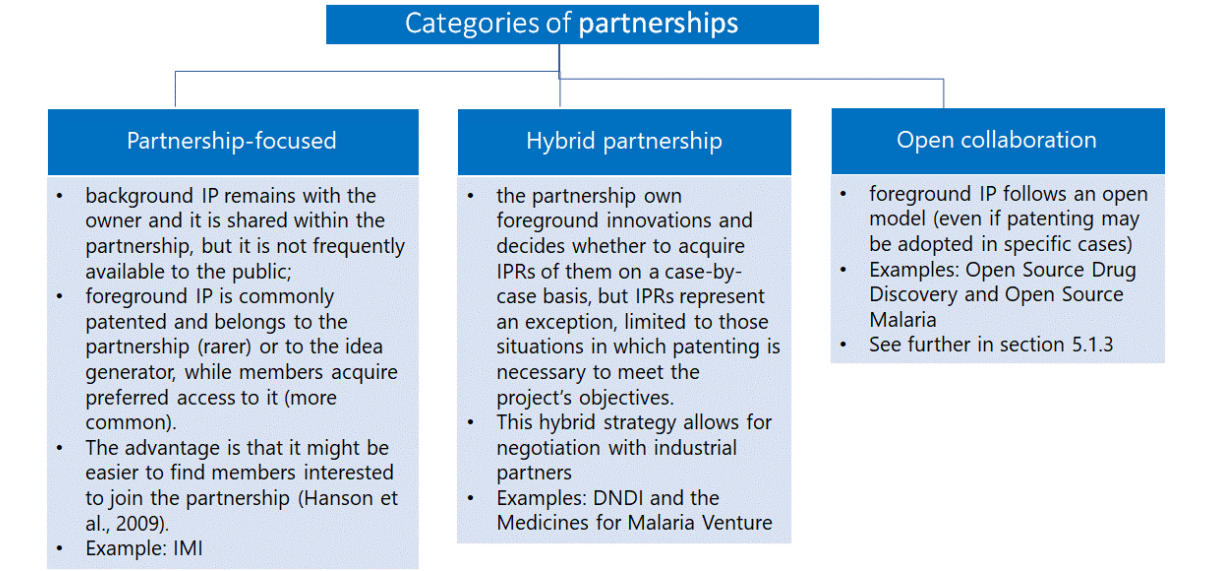
When partners share their IP assets ("background" (Innovative Medicines Initiative, 2007)), and in particular patents, with an access-oriented organisation, they are required to manage them in a way that does not impede equitable and affordable access to the products of the research project

("foreground" (Innovative Medicines Initiative, 2007)) or that obstacles follow-on research by the initiative, its partners, or other researchers. The partner remains the owner of its IP asset, and the organisation negotiates from the patent owner a license (exclusive for example in the case of the Medicines for Malaria Venture, non-exclusive in the case of the DNDi, or the Innovative Medicines Initiative), which may include the payment of reasonable royalty fees. This holds for all IP assets in the case of the Innovative Medicines Initiative, while it holds only for compounds more advanced in development for the DNDi. The license is transferable to other partners in the case of the Medicines for Malaria Venture or the DNDi, while under the IMI other participants are granted access to the assets shared by the participants only in the context of the project (on a royalty-free basis), or of the usage of the output of the research project (under reasonable terms or royalty-free) (Innovative Medicines Initiative, 2007).

The success of a partnership depends on clear agreements, set at the onset of the project, about the IP related to the project's outcome (Stevens et al. 2016). In the case of the Innovative Medicines Initiative, the output of the research project belongs to the participants who generated it, who shall grant access rights to third parties on a non-exclusive basis under fair and reasonable terms (Innovative Medicines Initiative, 2007). Similarly, although each partnership developed with the support of WIPO is governed by its own specific agreement, the output of the partnership belongs to its members. These are nevertheless expected to provide royalty-free licenses for any product developed through WIPO Re: Search that is used and sold in least-developed countries, and to grant accessibility in all developing countries, as well as to make new inventions available to other members of WIPO Re:Search (WIPO Re:Search, 2017). In the DNDi instead the output of the research may belong to the initiative itself. In this case, partners should commit to not protecting it, while the initiative decides whether to acquire IPRs on a case-by-case basis; however, patenting is the exception rather than the rule, and the organisation do not finance its research and operations through IP rent revenues (Drugs for Neglected Diseases initiative, 2018).

According to background and foreground IP management, Stevens et al. (2016) classify public-private partnerships in three categories (see Figure 8).

Figure 8: Types of partnership



Source: Authors.

Finally, open infrastructures represent another way to share IP assets and facilities, and to foster collaborations. For example, GlaxoSmithKline established the Tres Cantos Open Lab, in Spain,

allowing visiting scientists from universities, not-for-profit organisations, and other research institutes to work on their own projects relevant for developing countries while using the company's infrastructure and expertise. For some projects, the company also contributed its patents. The project's research outcome shall be available in least-developed countries royalty-free (Access to Medicines Foundation, 2012).

If the manufacturing is externally performed, to keep the information control granted by patents, and to facilitate access to patented medicines at affordable prices, the European Medicines Infrastructure may resort to patent waivers or to non-exclusive voluntary licensing:

- In the case of patent waivers, or non-assert declarations, the patent holder pledges not to enforce the patent under certain conditions or in given countries. This has been the case for few medicines, which were tested as a COVID-19 treatment, during the pandemic.
- With a non-exclusive voluntary license, the patent holder voluntary grants multiple manufacturers permission to develop and manufacture generic versions of the drug, granting the production of cheaper drugs under access-friendly terms (see exaples in box 7). The licensing agreement with generic manufacturers may include one or more countries where the generic product may be sold. As pointed out by Friedman et al. (2003), pharmaceutical companies are more likely to grant voluntary licenses at low or null prices for less profitable markets.

Box 7. Examples of non-exclusive voluntary licenses

As in 2016, seven pharmaceutical companies used non-exclusive voluntary licenses to enable generic versions of their products: all these licenses had been granted for communicable disease products (HIV or hepatitis C) (Access to Medicine Foundation, 2018); recently, further non-exclusive voluntary licenses have been granted for tuberculosis and COVID-19. In 2020 there were twenty-two compounds, belonging to seven pharmaceutical companies, covered by non-assert declarations or non-exclusive licenses; all these agreements involved low- and middle- income countries, with definitely greater numbers for low-income ones (Access to Medicine Foundation, 2021).

Source : authors

Non-exclusive voluntary licenses may be granted directly to manufacturers, through bilateral licenses, or managed through NGOs or international organisations, such as the WHO, which organise a patent pool. This is a portfolio of patents held by various actors but that relate to the use of a same technology (OECD, 2011). Patent pools are a relatively new concept in public health, where they have been recently applied to address some of the access challenges in low- and middle-income countries (Burrone, 2018; Galasso and Schankerman, 2020). Differently from patent pools characterising other industries, those in public health are non-profit; their primary goal is humanitarian (to ensure drugs' accessibility) - in addition to the reduction of the royalty stacking problem and of transaction costs (Merges & Mattioli, 2017); they do not include multiparty agreements between the patent owners (Van Zimmeren et al., 2011).

The Medicines Patent Pool, a United Nations-backed public health organisation established in 2010, is the first effective public health patent pool. While currently the mandate of the Medicines Patent Pool involves the treatment of HIV, tuberculosis, and hepatitis C (these last two diseases were included in the mandate in 2015), and is primarily on small-molecule medicines, rather than biotherapeutics, in 2016 the WHO, the Lancet Commission on Essential Medicines Policies and other stakeholders called for an expansion of the mandate (Wirtz, et al., 2017).

Through pools, licensors save negotiation costs, while licensees gain through potential economies of scale in search costs and save negotiation costs. Moreover, licenses negotiated with the pool

contain the most access-enabling terms (Access to Medicine Foundation, 2021). The licensing of patent bundles operated by patent pools is also particularly useful for the development and commercialisation of (new) product in those situations where the different patents belong to different organisations (Van Zimmeren et al., 2011; Van Overwalle, 2009).

While there might be several challenges for life-science patent pools, as opposed to patent pools in other industries (OECD, 2011), several papers analysing the Medicines Patent Pool have highlighted positive results. The net present value of direct savings generated by licenses for patented antiretroviral medicines negotiated by the Medicines Patent Pool by 2028 has been estimated to amount to USD 2.3 billion, with an estimated cost-benefit ratio of 1:43 (Juneja et al., 2017). Moreover, the pool also facilitated the development of new drugs formulations, different from what happened when patent pools were introduced in other industries, where innovation decreased (Lampe & Moser, 2016). Also, drugs accessibility has improved, through increased competition by generic producers, partly because of the reduction in asymmetric information about the geographical scope of the patents (Martinelli et al., 2020). Using data on licensing and sales for essential drugs for HIV, tuberculosis, and hepatitis-C for the period 2005-2018, Galasso and Schankerman, (2020) show that there is an immediate and large rise in licensing for products whose patent is included in the Medicines Patent Pool in countries included in the agreement; however, the effect on actual entry and sales is much smaller. Indeed, while licensees react with more launches, larger quantities, and lower prices (see also Wang, 2020), the licensors are less likely to enter the market, possibly protracting the time needed for the product to be launched in the market. Indeed, if the originator has not registered the product in the country, this hurdle falls back to the generic manufacturers. Moreover, it is also important to notice that smaller markets can also deter the entrance of generic manufacturers (Access to Medicine Foundation, 2021).

3.3.3 Open and free access to innovations

In the context of the pharmaceutical sector, it is important to distinguish between open innovation and freely available innovations:

- In an open innovation initiative, only the research problem is public domain, while potential solutions are not (Balasegaram, et al., 2017).
- In the case of freely accessible innovations, researchers may access prior discoveries and research tool, and have an independent access to them.

In some cases, in order to reach a freely accessible innovation, the use of IPRs may be needed, not as a way to exclude others but as a mechanism to keep knowledge free for use. For example, in the field of information technology, the Linux community had acquired patents in the relevant technical field and has patented its inventions when this was needed to avoid others from seeking patent protection.

In the pharmaceutical sector, innovations obtained by the not-for-profit parallel drug development are freely available. In this case, the governments identify and communicate specific challenges related to R&D, usually in those areas in which the industry is not keen to invest, and public institutes are asked, through coalitions and collaborations, to solve the needs. Resulting innovations are generally not protected (Directorate general for internal policies, 2016).

Also, the outcome of some public-private partnerships follows an open model (these partnerships are defined as “open collaborations” by Stevens et al., 2016). In many “open collaborations”, access to and use of the research results are limited by some boundaries, such as the acceptance of some agreements. For example, users can improve, modify, or use the research results for both commercial and non-commercial purposes. Still, this subsequent knowledge has to be contributed back to the partnership and be openly accessible to the partners, as in the case of Open Source Drug Discovery (Sugumaran, 2012) and, if protected by a patent, the patent cannot block the

partnership's activities. At the opposite, in other cases, such as in Open Source Malaria, users can improve, modify, or use for both commercial and non-commercial purposes IP shared within the community and patent it without any duty concerning the project itself.

While the Open Source Drug Discovery is an example of open-source partnership, the Structural Genomics Consortium is an open access one (Stevens et al., 2016). The former uses IPRs to ensure free access to innovations, with patented innovations that are licensed non-exclusively (Sugumaran, 2012), while the latter relies on social norms and it is therefore characterised by lower costs, not having to support the costs of patenting protection (OECD, 2011). In particular, the Structural Genomics Consortium does not seek, nor permit its affiliate to seek patents over its research outputs. Similarly, also the Istituto di Ricerche Farmacologiche Mario Negri, an Italian non-profit organisation, does not seek patents to protect its innovations. Differently form the Structural Genomics Consortium, which focus mainly on early-stage R&D, the Istituto is involved on the different stages of the R&D process, including clinical trials.

Usually, an open model framework is adopted when the project outcome involves databases, models, research tools and platform technologies (IP assets that contribute to the drug development, but whose scope is unclear) but not a drug itself. Indeed, for these IP assets the patenting cost represent a clear obstacle (Stevens et al., 2016). An exception is represented by drugs for neglected diseases, characterised by a reduced market size (Sugumaran, 2012). The Agora Open Science Trust, for example, has as a goal to create affordable new drugs for unmet therapeutic needs through open science. Agora incorporates wholly owned subsidiary companies that coordinate drug discovery projects in specific therapeutic areas, focusing on late-stage assets. Project participants and subsidiary companies do not own the foreground inventions, thus avoiding profit-driven research agendas. The research outputs are not patented, but they benefit from market exclusivity granted to orphan drugs in many countries, including the US, Japan, Europe and Australia, and from regulatory data exclusivity. These exclusivities provide commercial partners the incentives for manufacturing and distributing the products. As recalled above, most of the innovations by the DNDi are not protected by IPRs, and the organisation does not finance its research and operations through IP rent revenues. Interestingly, an open model framework is adopted also by the Istituto di Ricerche Farmacologiche Mario Negri, whose areas of research include, but are not limited to, neglected diseases.

Balasegaram et al. (2017) provide an overview of the potential advantages of freely accessible innovations. Murray et al. (2016) estimate the positive effect that open innovations have in stimulating the entrance of new researchers, further R&D, the variety of follow-on R&D, and new results. They exploit a natural experiment constituted by NIH agreements to provide open access to methods to engineer mice with particular characteristics.

3.4 Selected implementation issues

We briefly discuss below some implementation issues: the legal basis for the new entity, organisational structure, funding mechanisms. Further details on such implementation issues are given in Annex IV, while detailed studies should follow after a consensus is reached on the main policy options.

3.4.1 Legal basis

In principle, different legal basis options could be adopted to set up a European pharmaceutical R&D infrastructure: national law, international law, or EU Community law. The choice of the legal basis has long-term implications for the operation and management of the infrastructure. Table 5 below summarises three types of legal basis with some examples of research infrastructures and other scientific organisations.

Table 4: – Legal forms

Jurisdiction	Model
National law	- Company model. Some examples: - French 'Societé civile' for the European Synchroton Radiation Facility (ESRF) - German, Gesellschaft mit beschränkter Haftung German, Gesellschaft mit beschränkter Haftung (GmbH)' for the European X-Ray Free Electron Laser Project - UK, Limited liability Company (Ltd)' for Diamond Light Source - Foundation under national law. Example: Pierre Auger Observatory - Association of independent national or regional infrastructures.
International law	- International/ /intergovernmental Organisation. Examples: CERN, EMBL, ESO, ESA.
EU Community law	- Joint Undertaking under the EC Treaty. Examples: Galileo, IMI - European Economic Interest Grouping. Example: European & Developing Countries Clinical Trials Partnership - European Research Infrastructure Consortium (ERIC). Examples: ECRIN ERIC, EATRIS ERIC, BBMRI ERIC, European Spallation Source ERIC, CERIC ERIC

Source: authors based on OECD (2010), EC (2008).

Table 6 shows some advantages and disadvantages of each legal model, according to the literature review and interviews for this study.

Regardless of its legal form, the European Medicines Infrastructure should have a legal personality and all the requirements to apply independently or through its own controlled organisation for patents and the marketing authorization to place drugs on the market and for any contracts with third parties such as pharma companies, CROs, CDMOs, or suppliers of technologies and products.

Table 5: – Legal basis models

Option	Advantage	Disadvantage
#1 Company	- Easy to set up because they are part of the legal framework of the country where the research infrastructure is located - Clear management, governance and accountability; also avoid high costs of intergovernmental institutes. - Flexibility in terms of partnership (public, private, European, non-European) and staff policy - Adapted to industrial use	- Legal forms for companies are specific to each country (some countries do not even have such legal forms). - There is reluctance by partners from different countries to accept a foreign legislation - Does not clearly reflect the spirit of a truly European endeavour that should correspond to a European research infrastructure
#2 Intergovernmental treaty leading to an international organisation	- Sound and complete treaty (mission, function and structure) binding the partner on a long-term solid ground. - Clear management and governance. - Attractive salaries, privileges and immunities for staff. Advantages such as tax exemptions (VAT and salary taxes) - Possible cooperation with non-EU states.	- Heavy and lengthy negotiation procedures for reaching a formal agreement between Member States - Difficulty in modifying/amending such agreements - Private actors cannot be part of an international treaty
#3 ERIC	- Ready-to-use legal form that ensures immediate recognition and effect in all Member States - No need for potentially lengthy and complex parliamentary processes - Recognised by the country hosting its seat as an international organisation for the purposes of the directives on value-added tax, excise duties, and public procurement	- Private actors cannot be part of an ERIC neither as members nor as observers - Should pursue its principal tasks on a non-economic basis. Not well suited to manage industrial research
#4 Long-term public-private partnership in the form of JTIs	- Clear management and governance; - Sound and effective financial rules ensure the effective management of major programmes combining public and private sources of funding; - Adapted to industrial use.	- It needs initiative from the EC, long negotiations at Council level which require very strong Community involvement; - Difficulty for non-European countries to join; - Often considered as Community Bodies whenever the Community has to contribute.
#5 European decentralised agency	- Closely connected to EU institutions. - May have the powers to adopt binding decisions.	- The creation needs legislative measures at EU level - Not used to manage and deliver research activities directly

Source: authors

3.4.2 Organisational structure

In principle, different organisational options could be adopted for research infrastructures, as suggested by the extant literature (Hallosten, 2020; Sumathipala, 2014; Henrich and an Gradl, 2013; Pérez-Llantada, 2012). These go from a brand-new infrastructure to a virtual network of existing organisations. However, some intermediate options are available. For instance, there may be a central hub that coordinates a number of existing laboratories/institutes. The choice of the best organisational option should consider two main aspects. First of all, the legal basis of the organisation. The second aspect to consider concerns the research focus and the organization's involvement in the lifecycle of pharmaceutical products.

Table 7 shows the different structures with selected examples. In a context such as Europe which is rich in excellent research centres, presumably, the most appropriate organisational model could be a polycentric organism with a central hub (identified in one of the existing infrastructures) to which decentralized but integrated laboratories are connected. A reference model in this respect is the EMBL one. The EMBL operates from six sites across Europe. The main hub is in Heidelberg, Germany, and it is equipped with eight core facilities which cover the following areas: advanced light microscopy; chemical biology; electron microscopy; flow cytometry; genomics; metabolomics; and protein expression and purification proteomics. Then there are five decentralised units (the European Bioinformatics Institute in Hinxton, UK; two units on research and services for structural biology in Grenoble, France, and Hamburg, Germany; the epigenetics and neurobiology unit in Rome, Italy; and the tissue biology and disease modelling unit in Barcelona, Spain) hosted in existing infrastructures. One possibility is that the existing EMBL infrastructure and mission are enlarged to host or become the new European Medicines Infrastructure.

Table 6: – Organisational models

Model	Definition	Advantages	Disadvantages
New single-sited infrastructure	- Single-sited research infrastructure is an organisational structure already adopted in the ESFRI landmark, particularly in the areas of energy and physics sciences & engineering (ESFRI, 2018). - Basically, a new "single-sited research infrastructure" refers to a newly constituted single facility with a specific geographical location (ESFRI, 2019, 2018).	- Easier to be managed since it is located in a specific geographical location and it has exclusive facilities	- Requires the definition and the design of a completely new organisation, together with the required facilities and laboratories, but also to identify a specific geographical location across European countries. - The construction of such research infrastructure requires high costs in term of physical investment, human resources, and organisational structure to make the research infrastructure working effectively and efficiently
Hub of functionally integrated laboratories	- This model takes inspiration from the concept of "distributed research infrastructure" already existing in the European landmark, as well as in the international one (ESFRI, 2019, 2018; OECD, 2014). - A distributed RI is a multinational association of geographically separated entities that jointly perform research activities and provide supplementary services to users (OECD, 2014). - A distributed RI is made up by a central hub and other national facilities and labs acting as national nodes (Schneider et al., 2019; ESFRI, 2019, 2018). - The central hub may be constituted ex-novo, or an existing RI can be identified as the central hub.	- This structure is widely implemented in the health field (see, e.g. EATRIS, ECRIN, BBMRI). - National nodes are generally represented by already existing RI, laboratories or facilities that devote a part of their total functioning time to the activities of the network. This allows for cost containment. - Strengthening collaboration across national laboratories and facilities that provide different but complementary services may reduce fragmentation and create synergies across European countries involved, thus enhancing European research competitiveness (Larsson et al., 2018; Van Ommen et al., 2015). - Making existing labs, facilities, and infrastructures working together increases collaborative research, provision of services and lastly, it facilitates the sharing of knowledge, complementary skills, technology and data.	- By involving different existing national laboratories and infrastructures, it may be difficult to identify a shared mission that fully aligns with the strategic agenda of each organisation as well as with the strategic investment at the country level. - Given the distributed nature of this model, specific coordination mechanisms and access policy should be defined as shared according to all the member countries.
Virtual/digital network of	- This model takes inspiration from the idea of virtual – or digital –	- They generally connect already existing RI, laboratories or facilities that devote a part of	- The main difference with the hub model is that in this kind of option, the research institutes

Model	Definition	Advantages	Disadvantages
existing organisations	research infrastructure, according to which the service is provided electronically, through a specific digital environment. - Specifically, virtual research infrastructures are mainly devoted to providing interactive spaces that facilitate collaboration among several researchers and/or providing common repositories for sharing large quantities of data.	their total functioning time to the activities of the network. This allows for cost containment	remain independent of each other and only share data and research results through a common digital infrastructure. As such and considering the potential future mission of the European Medicines Infrastructure, this option does not seem appropriate

Source: authors

3.4.3 Budget

An organisation with the functions described in section 4.2 should have substantial and stable financial resources. All the interviewed people agreed on this point. The European Medicines Infrastructure should have an annual budget sufficient to launch a significant portfolio of R&D projects over 20-30 years. Taking as a benchmark the R&D cost per drug of about Euro 1 billion per project (see section 2.2.3), the order of magnitude for the European Medicines Infrastructure annual budget is the order of several billion. To set the lower bound, it is possible to take as a reference the annual budget of the Intramural Research Program of NIH of around USD 4 billion per year (equalling about EUR 3.5 billion). To set an upper bound, it is possible to take as a reference the ESA budget for 2021, which amounts to EUR 6.49 billion (see ESA website). In other words, the European Medicines Infrastructure should have at least an annual budget equal to about 0.025% of EU GDP (pre-COVID, the annual GDP of the EU, no longer including the United Kingdom, was approximately 14,000 billion euros nominal), or proportionally less if third countries such as Switzerland, UK, Norway and others also participate. This would be something as 8 Euro per capita per year. Nevertheless, EUR 3.5 billion is a downside estimate compared with Operation Warp Speed initiated by the US government to facilitate and accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics. The program was initially funded with USD 10 billion. Then, funding was increased to about USD 18 billion by October 2020 (Lancet Commission on COVID-19 Vaccines and Therapeutics Task Force Members, 2021; Baker and Koons, 2020). This was around 54 USD per capita in just one year.

Table 8 illustrates the potential types of streams of resources considered in the context of this study.

Table 7: – Funding sources

	Topic(s)ƒ
Contribution from members	- Annual transfers from the budget of Member States; - Multi-year transfer commitment from Member States to ensure stability; - Equity or initial endowment provided by founding parties;
Contribution from EU budget	- Transfers from the Multiannual Financial Framework (7 years) of the EU; - Grants, i.e. project-based funding stemming from European institutions funding research which, are awarded on the basis of a selection process
Contribution from EU cooperation agencies, philanthropic organisations and private funds	- Grants, i.e. project-based funding stemming from EU cooperation agencies or private funds or philanthropic organisations funding research which are awarded on the basis of a selection process - Donations from philanthropic organisations, charities, private funds
Revenues	- Revenues deriving from production licences of the new drugs to national health systems; - Fees or payments for services from pharmaceutical companies similar to those paid to regulatory agencies;
Financial instruments	- Loans from European Investment Bank or other financial institutions.

Source: authors

Each of these options, taken individually, has specific constraints, and the most appropriate solution is to rely on a mix of funding sources. Indeed, RIs typically combine different funding sources through a unique overall funding model (Ramiri Handbook, 2018).

The funding model somehow depends on the legal basis, and the organisational model adopted. For instance, the largest share of the budget for all European RI with the status of international organisation comes from contributions of their Member States. Differently, for most EU decentralised agencies, the budget comes primely from the Union's budget and at least one other source of financing, which may consist of (EP, 2018):

- Fees or payments for services. For instance, in the case of EMA, companies pay fees for the authorisation of new medicines.
- Voluntary contributions by Member States.
- A combination of fees and voluntary contributions by Member States. This is, for instance, the case of ECDC.
- Contributions from participating third countries.

3.4.4 Social costs and benefits considerations

Regardless of how the European Medicines Infrastructure will be funded, it is worth discussing its costs compared to its benefits. As a social benefit, the greatest return on the infrastructure would come from the lower economic impact of severe pathologies. To proxy this benefit, it is possible to refer to the avoided cost of future epidemics and pandemics since there is little doubt about the possible recurrence of pandemics (Fan et al., 2018). GPMB (2019) reports the estimated costs of some past events and predictions of hypothetical pandemics (see table 9):

Table 8: – Cost of past epidemics

Event	Loss	Source
2003 SARS epidemic	Over USD 40 billion	Lee J-W, McKibbin WJ. (2004).
2014-2016 West Africa Ebola	USD 53 billion	Fan et al. (2015). Huber et al. (2018).
2009 H1N1 influenza pandemic	USD 45-55 billion	Resolve to Save Lives, A Disease Threat Anywhere is a Disease Threat Everywhere, factsheet 3, 2019.
Global influenza pandemic akin to the Spanish flu	USD 3 trillion or 4.8% of global GDP	World Bank (2014)
Moderately virulent influenza pandemic	2.2% of global GDP	World Bank (2014)

Source: authors based on GPMB (2019) and cited sources.

Looking at the COVID-19 pandemic, the prediction of Word Bank (2014) is probably wrong downward. According to the World Bank itself, the global contraction of GDP in 2020 is 5.2%, and around 7% in advanced economies (World Bank, 2020). The Coalition for Epidemic Preparedness Innovations (CEPI) reports a similar prediction on its website where it states that COVID-19 could cost the global economy USD 4.1 trillion, or almost 5% of the global gross domestic product. The analysis of the Joint Research Centre, using data from the Commission's spring 2020 economic forecast and the RHOMOLO model, shows the GDP impact on EU regions is, on average -6.44%. The rate at which the economies will recover is uncertain, but it seems that two years will be at least necessary. Levy Yeyati and Filippini (2021) attempted to approximate the output loss over a 10-year window. By accumulating the differences between the realised real GDP in 2020 and the one projected right before the pandemic, and between pre- and post-COVID projections for 2021-2030, they calculated a loss equal to 53% of the 2019 global GDP (i.e., around USD 46 trillion over

a 10-year window). A comprehensive calculation of the economic cost of the pandemic cannot ignore the value of excess deaths caused by the pandemic (i.e., the human cost).[3] However, for the sake of simplicity, let's ignore the economic value of the avoided deaths and let's focus on avoided GDP loss. Let's conservatively set the expected economic loss[4] of a new moderate or severe pandemic equal to 0.3% of the annual EU GDP as suggested by Fan et al. (2018). Then, an annual investment of 4 billion euros, 0,03% of the EU's GDP, in the European Medicines Infrastructure for the R&D of vaccines, drugs, and any other countermeasures for preventing or managing a pandemic episode would be justified as a sort of social insurance for avoided risks amounting to 0.3% of the annual EU GDP. Beyond the avoided costs of pandemics, there are other diseases for which the industry is unlikely to invest in the future, thus preventing health improvements that are not considered in this rough cost-benefit calculation.

From a microeconomic standpoint, the European Medicines Infrastructure's socio-economic impact could also be calculated following the social cost-benefit analysis framework provided by Florio (2019). The core concept of cost-benefit analysis is that the socio-economic impact of infrastructure is represented by the difference over time in the benefits to different agents and the costs of producing such benefits, all of which are expressed in an appropriate accounting unit such as money (see Boardman et al., 2018). However, prices in the CBA context are not necessarily market prices because for many goods, such prices do not exist or do not provide information about the social welfare effects (see Florio, 2014; Boardman et al., 2018). Hence, CBA should not be confused with the financial analysis of a project. A key difference between financial evaluations (mostly used in the private sector) and CBA (used in the public sector) is the perspective. CBA tries to consider all costs and benefits to society as a whole. For this reason, CBA is often referred to as social cost-benefit analysis.

As the other RI, the costs of the European Medicines Infrastructure would encompass the initial investment for setting up the infrastructure, periodic reinvestment costs, and the annual operating costs. The two latter spread over the entire infrastructure's lifetime. On the side of benefits, the European Medicines Infrastructure would generate health benefits in terms of reduced mortality or morbidity for patients which can benefit from innovative drugs, cost savings for the health systems, a positive spillover in terms of knowledge creation, and technological and other types of learning and spillover for firms involved in procurement contracts with the European Medicines Infrastructure for the production of innovative drugs. Of course, the exact calculation of net benefit with respect to the do-nothing-scenario would be only possible once the infrastructure design, mission, functioning has been determined.

[3] Following a well-established literature (see e.g. OECD, 2012; Kniesner and Viscusi, 2019) the calculation of the value of excess in deaths caused by the pandemic is based on the concept of the value of a statistical life (VOSL), defined as the value that a society deems should be spent in order to avoid the death of an undefined individual.

[4] The expected loss combines both the risk of a moderate or severe pandemic and the losses from that event should the event occur. Fan (2018) reported that a modelling exercise for the insurance industry concluded that the annual risk of an influenza outbreak on the scale of the 1918 pandemic lies between 0.5% and 1.0%.

4 Policy options

In this concluding section of the study, a set of four evidence-based policy options are presented. In light of what was discussed in section 4.1, all the identified options involve setting up a new wide-European organisation modelled on the key features of the R&D infrastructure model. A lesson from the current COVID-19 pandemic is that challenges for health, crucially including the lack of innovative vaccines and medicines when needed, are largely cross-border issues. This does not exclude essential roles for the Member States on health policy. Still, the overwhelming consensus of the literature and the interviewed experts is that a research and development infrastructure for medicines should have at least an EU-wide scale of operations.

Before discussing policy options, it would be useful to briefly provide an overview of the differences between the proposed European Medicines Infrastructure and the newly decided HERA. As it emerges from Table 10, the European Medicines Infrastructure is envisaged to be complementary to HERA. While HERA could act, according to the EC Decision (C(2021) 6712 final) and the EC Communication COM(2021) 576 final, as an enabler of strategic R&D projects on vaccines and medicines for infectious diseases by pooling capacities and creating a long-term and large-scale EU platform for multi-centre clinical trials, it will not have the responsibility, resources, and capacities to directly implement a large portfolio of pharmaceutical (and related biomedical) R&D projects. Managing such a portfolio is precisely the main mission of the European Medicines Infrastructure.

Table 9: – Comparative overview

	European Medicines Infrastructure	HERA
Mission & tasks	- Elaborating and implementing a long-term European portfolio of R&D projects in collaboration with third-party research centres at the national or European level and if needed with selected pharmaceutical companies; - Ensuring that developed innovative drugs are eventually rolled out and made available to national health systems; - Ensuring effectiveness, safety and efficiency of selected medicines through optimizations studies; - Ensuring safety and affordability of selected generics when needed	One of the tasks of HERA will be to promote research on key and emerging pathogens and incentivise advanced research, innovation and development of relevant technologies and countermeasures – including vaccines. It will be done by: - Creating a common strategic EU research and innovation agenda for pandemic preparedness - Pooling fragmented pandemic preparedness research capacities across the EU - Creating a long-term and large-scale EU platform for multi-centre clinical trials and corresponding data platforms.
Budget	- EUR 4 billion per year for 30 years. - As a reference: the annual budget of the Intramural Research Program of NIH is around USD 4 billion per year	- EUR 6 billion for 6 years (one billion per year). - In addition, many EU programmes are expected to contribute directly and indirectly to health emergency preparedness with an estimated budget of EUR 24 million. - In the event of a public health emergency at Union level, in order to ensure the necessary flexibility and rapidity in implementation, the Council could also trigger financing through the Emergency Support Instrument.
Participant countries	- All potentially interested European countries, including for example Norway, the UK, and Switzerland. - The role of different countries depends on the legal model adopted.	- HERA is established within the European Commission as a shared resource for Member States and EU alike.

Source: authors based on the EC Decision C(2021) 6712 final and the EC Communication COM(2021) 576 final.

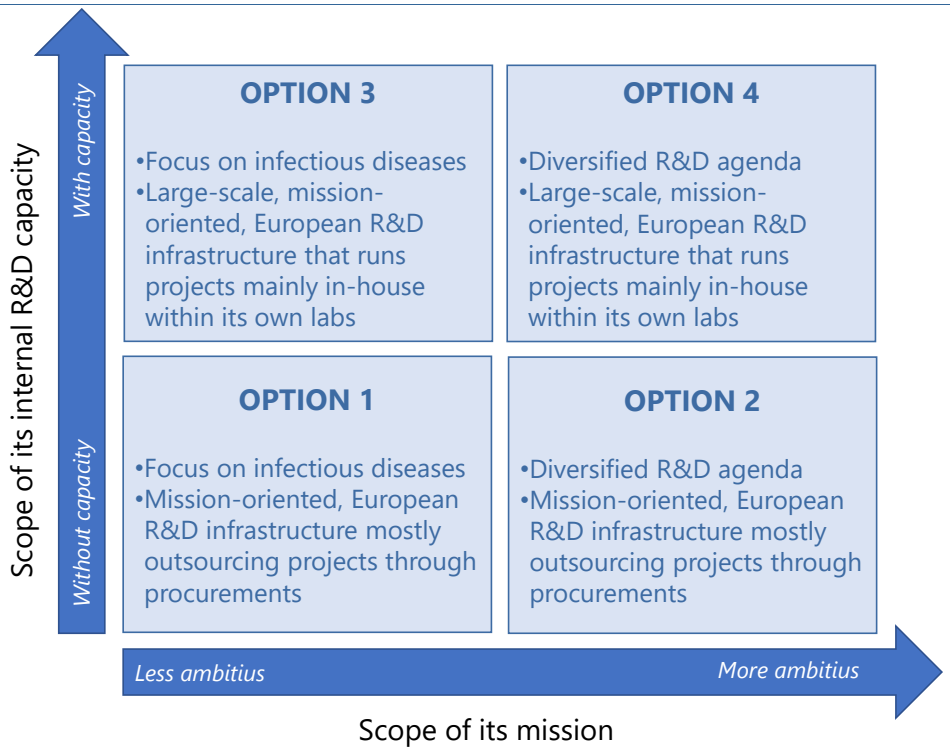
Two dimensions define the policy options in relation to the European Medicines Infrastructure: the scope of its mission on one side, the internal R&D capacity on the other side. The set of options arising from the combination of such dimension are presented below, and pros and cons of each option are discussed.

In a nutshell:

- The *mission* of the European Medicines Infrastructure should either be strictly focused on a R&D priority goal such as medicines and vaccines for infectious diseases, or alternatively
- the mission should be broader and include a portfolio of R&D fields in several areas inadequately covered by the industry.
- The *role* should mainly be that of a European R&D infrastructure for new medicines mostly outsourcing R&D projects to external laboratories under procurement mechanisms, or alternatively

- a large-scale, mission-oriented, European R&D infrastructure for medicines, that runs R&D projects mainly in-house within its own laboratories, in combination with external resources.
- Hence the matrix of combinations defines four policy options (see Figure 9 below).

Figure 9: Policy options



Source: authors.

In addition to a "baseline scenario", the above-illustrated options with their advantages and disadvantages are discussed in what follows.

Policy option 0. It is the baseline scenario. In this scenario, the market and policy failures identified in the present study might be addressed to a limited extent in the EU by the setup of HERA and the reinforced role of EMA and ECDC, as proposed by the European Commission. Such a scenario constitutes progress compared to the pre-COVID-19 situation as it will:

- address vulnerabilities and strategic dependencies within the Union related to the development, production, procurement, stockpiling and distribution of medical countermeasures and
- provide a strengthened health security coordination within the Union, and bring together the Member States, the industry and the relevant stakeholders in a common effort

However, this option remains grounded in the current public funding system for pharmaceutical research.

According to the EC Communication (COM(2021) 576 final), HERA's tasks in relation to R&D of medical countermeasures include:

- the creation of a common strategic EU research and innovation agenda for pandemic preparedness to help guide both EU and national funding and link with the planned Important Project of Common European Interest Health, which can include developing new generations of medical countermeasures or breakthrough manufacturing technologies;

- the creation of a long-term and large-scale EU platform for multi-centre clinical trials and corresponding data platforms.

However, HERA, as for the proposal of the COM(2021) 576 final, apparently will not be responsible for the implementation of a sustained pipeline of strategic pharmaceutical R&D projects, implementing them from basic research to marketing authorization and delivery. In fact, HERA will not have the critical mass in terms of budget, own research capacity, scientific personnel to structurally shift pharma companies' R&D choices towards public health priorities unless in a limited intervention area related to possible emergencies. In this scenario, the prioritization and allocation of EU funds for pharmaceutical R&D will continue to follow a "grant"-based approach, which risks dispersing funds towards a myriad of relatively small projects, risks the capture of EU funds from existing organizations and from the pharmaceutical companies, each with their own agendas, without a clear additionality.

Policy option 1. The first option, the most constrained one, involves creating a European infrastructure for pharmaceutical R&D in the public interest, based on its own agenda specifically in the highest priority field: R&D on vaccines and medicines for infectious/transmissible diseases and arrangements for their delivery. The new organisation will have its own governance (with top-level scientific and managerial skills), budget, and a core, but relatively limited in-house R&D laboratories. It would essentially work through R&D contracts with selected third parties. Such contracts are not to be seen as grants or subsidies to such third parties, but as public procurement arrangements, with the intellectual ownership rights of any discoveries and the delivery mechanisms of new medicines under the ultimate responsibility of the new European Medicines Infrastructure.

This option aims to ensure a coordinated EU approach to address the market and policy failures identified in the area of infectious diseases. The rationale is to promote a coordinated agenda of large projects in areas where the private sectors are under-investing but where problems could be tackled by acting in concert and mobilising a critical mass of funds. In other words, the new body will have the task to promote missions identified in section 4.2 limited to the area of infectious diseases through a delegated R&D model.

The new organisation should identify the agenda of R&D projects in the field of infectious diseases in agreement with relevant stakeholders such as EMA, ECDC, HERA, ERC, EIC, or EMBL and other biomedical research bodies in order to avoid overlaps. Implementing such an agenda and delivering new medicines will be the sole responsibility of the new organisation, which will act through procurement contracts with academia, existing R&D institutions, and pharmaceutical companies.

Unlike many existing European initiatives, this option will not involve creating an executive agency or a funding body that allocates funds through competitive calls to many small-size projects with a loose connection to its wide-research agenda. Rather, it involves creating a planning, management, and delivery organisation that defines its own long-term portfolio of R&D projects and enters into contracts with third parties to implement them.

Advantages:

- Lighter solution in terms of fixed investment and hiring of personnel compared with Options 3 and 4;
- Creates a long- term portofolio of projects and improves coordination of bodies in the field of infectious diseases.

Disadvantages:

- To a certain extent it may overlap with HERA;
- Has limited access to critical information arising from own R&D capacity;

- Relies mainly on implementation capacity of external actors.

Policy option 2. The second option is similar to the previous one but with a wider mission. The scope of the European Medicines Infrastructure under this option would include other fields where both public and private sectors are under-investing such as, again, vaccines and medicines for infectious diseases, but also for example medicines related to neurogenerative conditions, rare diseases, some types of cancer and genetic conditions. It will work around missions designed by 'horizontal' R&D concepts, technologies and platforms.

The business model created within this option is the same as to the previous one but more ambitious in terms of reach.

Advantages:

- Lighter solution in terms of fixed investment and hiring of personnel;
- Creates a long- term portofolio of projects and improves coordination of bodies in areas inadequately covered by the industry.

Disadvantages:

- The same as above.

Policy option 3. The third option concerns the creation of large-scale, mission-oriented, European Medicines infrastructure focusing on infectious diseases and covering most of the cycle from basic research to delivery of new medicines.

Taking advantage of the experience of US federal institutions such as BARDA and NIAID (the National Institute of Allergy and Infectious Diseases), the new organisation while may also work through procurement contracts with third parties (as for Options 1-2), would have own considerable laboratories and hired scientific staff to run R&D projects in-house.

While performing in-house research, the new organisation would be largely open to R&D collaborations on vaccines and therapies for diseases arising from viruses and other pathogens, including research on pathogens resistant to existing antibiotics, in partnership with third-party research centres at the national or European level and with selected pharmaceutical companies (those which are seriously willing to invest in this area), even outside the EU when needed. Such collaborations will be based on clear, transparent, contractual arrangements, including on IP of discoveries that should be secured to the European Medicines Infrastructure in the public interest and marketing authorization.

Advantages:

- Creates a long- term portofolio of projects and improves coordination of bodies in the field of infectious diseases;
- Based on the successful model of US federal institutions;
- Mainly relies on own laboratories and knowledge created in-house;
- Own the results of the R&D projects it carries out, either fully or in specific cases with public-private partnerships, and manage its IPR and any other ownership rights on innovations exclusively in the public interest.

Disadvantages:

- Requires a budget larger than option 1 and 2;
- Implies a long-term commitment to risky projects and needs adequate top management;
- Needs a stronger coalition-building process among policy-makers and scientific communities.

Policy Option 4. The fourth option, which is the most ambitious in terms of scope, is similar to the previous one as it concerns the creation of a large-scale, mission-oriented, European Medicine infrastructure but with a focus on a wider R&D agenda.

The business model created within this option is the same as the previous one (Option 3), it is however not constrained to infectious diseases, but should adopt a wider R&D agenda (similarly to Option 2). The latter should focus on areas where the industry is underinvesting based on priorities set by the scientific communities and health policy authorities.

The history of discovery in medicines, vaccines, and other biotech innovation (including for diagnostic and materials) suggests that science-based advances in different fields spring from new ideas and technologies with unexpected outcomes and scope. A notable example is mRNA vaccines for COVID-19, built on scientific and technological advances in molecular biology initially understood as supporting a broad range of new therapeutic approaches involving the production of certain proteins. In this perspective, therapies for cancer or neurodegenerative diseases are not completely different from therapies or vaccines for infectious diseases. This is just an example of why the scientific community would prefer a more flexible R&D mission for the proposed infrastructure, as envisaged in options 2 and 4.

This option would create the most important public R&D infrastructure in the world, at a scale comparable with the intramural research of the US federal government sponsored NIH, but going beyond it in terms of ownership and delivery mechanisms of innovative medicines and related technologies. It would firmly place Europe as the top global player in the field of R&D for medicines, with direct benefits for patients and public health systems, early career researchers, and also with potential benefits for the European pharma industry in terms of possible partnership on specific projects.

Advantages:

- Creates an own long- term portofolio of projects and improves coordination of bodies in areas inadequately covered by the industry;
- Based on the successful model of US federal institutions, but goes beyond it;
- Mainly relies on own laboratories
- Promotes open science and open data, but owns the results of the R&D projects it supports, either fully or in specific cases with public-private partnerships, and manage its IPR and any other ownership rights on innovations exclusively in the public interest.

Disadvantages:

- Requires a budget larger than the previous options;
- Implies a long-term commitment to projects in riskier areas than for the previous option;
- Needs a stronger coalition-building process among policy-makers and scientific communities.

As suggested in section 4.4.3, we could consider as references the annual budget of the NIH Intramural Research Program and the ESA just to give a very rough and tentative indication of the options' cost and outcome of large scale research infrastructures. The annual budget of the European Medicines Infrastructure under Options 1 and 2 could be set equal to that of the NIH Intramural Research Program, amounting to about EUR 3.5 billion. Instead, the annual budget for the most ambitious, i.e. Options 3 and 4, could be set equal to that of the ESA for 2021, amounting to nearly EUR 6.5 billion (including contributions to specific missions by some participants).

Given these yearly budgets, taking into account overheads and capital cost, and taking as a benchmark the R&D cost per drug of about Euro 1 billion per project (see section 2.2.3), the European Medicines Infrastructure may be expected to deliver from 2023 to 2050 a total of:

- 80/100 innovative medicines/technologies under option 1 or 2;
- 130/150 innovative medicines/technologies under option 3 or 4.

The budget could further increase if non-EU member states join the European Medicines Infrastructure, for example, with mission-specific additional budgets supported by different coalitions of governments as in the current functioning of the ESA.

5 Conclusions

The above policy options are offered for discussion to fill a gap in the current arrangements for pharmaceutical R&D in the public interest. While there may be variations to such options, they summarise the messages from a wide review of the literature. The implementation details are left to further studies (even if some issues have been discussed).

Four clear messages are arising from this study:

- The misalignment of priorities between the public health agenda and the pharmaceutical companies' R&D activity is a structural issue that cannot be effectively and efficiently corrected by governments offering in the next decades large public subsidies to the industry
- The EU has large capacities for biomedical research in general and pharmaceutical innovation in particular. Still, these capacities are fragmented and do not reach the critical mass needed to deal with future threats to health in fields underinvested by the industry.
- Without a new player with a European public mission in biomedical and pharmaceutical R&D and innovation, the EU will still lag behind others, particularly the US, which has reinforced its federal health agencies in terms of budget and scope and strongly supports the US-based pharma corporations.
- The EU can take advantage of the highly successful model of large-scale research infrastructure, which has proven to be an original solution to the fragmentation of R&D in several fields, from physics to space. A European Infrastructure for Medicines can become the top player in the world if supported by a long-term strategic commitment.

Although, as explained above, the setup of HERA and the reinforced role of EMA and ECDC constitutes progress compared to the pre-COVID-19 situation, such a scenario is not designed to address the market and the policy failures affecting the pharmaceutical R&D system.

In fact, while HERA could act as an enabler of strategic R&D projects on vaccines and medicines for infectious diseases by pooling capacities and creating a long-term and large-scale EU platform for multi-centre clinical trials, it will not have the critical mass to shift pharma companies and other players R&D choices towards public health priorities unless in a limited intervention area. The latter change is precisely the main mission of the European Medicines Infrastructure.

The four options considered in this study and particularly the most ambitious one (Option 4), aim at a structural change of the pharmaceutical R&D panorama in Europe in order to gradually fill the gap, particularly with the biomedical institutions sponsored by the US federal government, and to create in the EU the most advanced ecosystem for biomedical research worldwide.

Annexes

5.1 Annex I – Work strands of the new pharmaceutical strategy for Europe

Table 10: – Work strands of the new pharmaceutical strategy for Europe

Work strand	Specific objectives	Needs analysis	Flagship initative(s)
Delivering for patients: fulfilling unmet medical needs and ensuring accessibility and affordability of medicines	Prioritising unmet medical needs	R&D investment does not necessarily focus on the greatest unmet needs due to the absence of commercial interest or limitations of the science. Treatments for important diseases, for example, neurodegenerative diseases and paediatric cancers, are still lacking.[5] Lack of development of new antimicrobials, treatments or vaccines for emerging health threats[6]	Flagship initiatives on unmet needs - Propose to revise the legislation on medicines for children and rare diseases to improve the therapeutic landscape and address unmet needs through more tailored incentives – 2022. - Facilitate collaboration on unmet needs and evidence generation in joint meetings of existing committees/networks of regulators, health technology assessment (HTA) bodies and payers. Work with the EP and the Council towards the adoption of the Regulation on health technology assessment – 2021. Flagship initiatives related to antimicrobial resistance - Provide innovative pull incentives for novel antimicrobials – target date 2021. - Promote investment and coordinate R&D, manufacturing, deployment and use for novel antibiotics as part of the new HERA, prior to the start of the authority's operations preparatory action on AMR – 2021. - Consider in the review of the pharmaceutical legislation to introduce measures to restrict and optimise the use of antimicrobial medicines – 2022
	Ensuring patients' access to medicines	Patients' access to medicines is affected by the fact that companies are not obliged to market a	Flagship initiatives on access to medicines

5 Sources: Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products SWD(2020) 163.

6 Including those similar to the present pandemic, such as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or Middle East respiratory syndrome (MERS).

Work strand	Specific objectives	Needs analysis	Flagship initative(s)
		medicine in all EU countries; for various reasons[7] they may decide not to market their medicines in, or withdraw them from, one or more countries.	- Propose to revise the system of incentives and obligations in the pharmaceutical legislation taking into account the relationship with intellectual property rights, to support innovation, access and the affordability of medicines across the EU – 2022. - Review the pharmaceutical legislation to address market competition considerations and thus improve access to generic and biosimilar medicines, including interchangeability and the 'Bolar' exemption – 2022.
	Ensuring affordability of medicines for patients and health systems' financial and fiscal sustainability	There is a lack of transparency (in particular in R&D costs) and consensus on costing principles. Expenditure on medicines in hospital settings is incompletely reported at EU level and it is growing rapidly. Pharmaceutical budgets account for 20-30% of hospital expenditures and are growing faster than retail spending[8]	Flagship initiatives on affordability - Propose to revise the pharmaceutical legislation addressing aspects that impede the competitive functioning of the markets and to take account of market effects impacting on affordability – 2022. - Develop cooperation in a group of competent authorities, based on mutual learning and best-practice exchange on pricing, payment and procurement policies, to improve the affordability and cost-effectiveness of medicines and health system's sustainability – 2021-2024.
Supporting a competitive and innovative European pharmaceutical industry	Providing a fertile environment for Europe's industry	Established businesses are increasingly outsourcing functions and are focusing investment on a limited number of therapeutic areas, while disinvesting from others. There are differences in the application of patents and supplementary protection certificates in Member States. Industry and regulators require access to data through a robust EU-wide data infrastructure to support innovation. An interlinked system that gives access to comparable and interoperable	Flagship initiatives on competitiveness - Optimise the supplementary protection certificates system as foreseen in the Intellectual Property Action Plan – 2022. - Legislative proposal on a European Health Data Space, enabling better healthcare, health research, innovation and evidence-based decisions – 2021. - Establish by 2025 interoperable data access infrastructure for the European Health Data Space in order to facilitate secure cross-border

[7] such as national pricing and reimbursement policies, size of the population, the organisation of health systems and national administrative procedures resulting in smaller and less wealthy markets in particular facing these problems.

[8] European Commission, State of health in the EU: companion report 2019 (ISBN 978-92-76-10194-9

Work strand	Specific objectives	Needs analysis	Flagship initative(s)
		health data from across the EU would be a real multiplier in terms of research, regulation and evidence generation.	analysis of health data; tested in 2021 with a pilot project involving EMA and national authorities – 2021 – 2025. - Support public-private and public-public partnerships, financially and technically, for example, through the Innovative Health Initiative, with particular attention to SMEs, academia, not-for profit organisations, and through the health care systems transformation partnerships – 2021.
	Enabling innovation and digital transformation	'Bedside' manufacture of more individualised medicines could be a future trend. Innovative approaches to the development, approval and post-authorisation monitoring of vaccines and the repurposing of medicines are needed. Medicines, medical technologies and digital health are becoming increasingly integral to overarching therapeutic options	Flagship initiatives on innovation - Propose to revise the pharmaceutical legislation, to adapt to cutting-edge products, scientific developments and technological transformation and provide tailored incentives for innovation – 2022. - Enhance dialogue among regulatory and other relevant authorities in the area of medicines and medical devices to increase cooperation on evidence generation within their respective fields – 2021. - Support collaborative projects bringing together stakeholders to use high-performance computing and artificial intelligence in combination with EU health data for pharmaceutical innovation – 2021-2022. - Establish secure federated access to 10 million genomes across borders for research, innovation and clinical applications, including personalised medicine – 2025.
	A sound and flexible regulatory system	The management of variations of marketing authorisations and the assessment of quality files relating to active substances are two examples of areas in which simplification is required.	Flagship initiatives on regulatory efficiency - Propose to revise the pharmaceutical legislation to provide for simplification, the streamlining of approval procedures and flexibility for the timely adaptation of technical requirements to scientific and technological developments – 2022. - Propose to revise the variation framework for medicines through changes in legislation and guidelines to make the lifecycle management of medicines more efficient and adapted to digitalisation – 2021-2023.
Enhancing resilience: Diversified and secure supply chains; environmentally	Secure the supply of medicines across the EU and avoid shortages	Shortages are increasingly frequent for products that have been on the market for many years and are widely used. The reasons are complex; they include marketing strategies, parallel trade, scarce active pharmaceutical ingredients and raw materials, weak public	Flagship initiatives on open strategic autonomy - Propose to revise the pharmaceutical legislation to enhance the security of supply and address shortages through specific measures, including stronger obligations for supply and transparency, earlier notification of shortages and withdrawals, enhanced transparency of stocks and

Work strand	Specific objectives	Needs analysis	Flagship initative(s)
sustainable pharmaceuticals; crisis preparedness and response mechanisms		service obligations, supply quotas or issues linked to pricing and reimbursement. Even before the COVID-19 pandemic there were concerns about the resilience of pharmaceutical manufacturing chains, both the EUP and Member States have called on the Commission to address this issue.[9]	stronger EU coordination and mechanisms to monitor, manage and avoid shortages – 2022. - Follow up on the European Council request for open strategic autonomy and launch a structured dialogue with and between the actors in the pharmaceuticals manufacturing value chain and public authorities to identify vulnerabilities in the global supply chain of critical medicines, raw pharmaceutical materials, intermediates and active pharmaceutical substances in order to formulate policy options and propose actions to strengthen the continuity and security of supply in the EU – 2021. - Consider actions to ensure that the industry increases the transparency on the supply chains through voluntary process – 2021.
	High quality, safe and environmentally sustainable medicines	The recent experience with the presence of nitrosamines impurities in some medicines[10] has highlighted the importance of a sound system for detecting quality problems and of compliance management. There is still a lot of waste from unused medicines.	Flagship initiatives on quality and environmental sustainability - Propose to revise the manufacturing and supply provisions in the pharmaceutical legislation to improve transparency and reinforce oversight of the supply chain and clarify responsibilities to ensure overall environmental sustainability, safeguard the quality of medicines and ensure preparedness for new manufacturing technologies – 2022. - Propose to revise the pharmaceutical legislation to strengthen the environmental risk assessment requirements and conditions of use for medicines, and take stock of the results of research under the innovative medicines initiative – 2022.
	Enhancing Europe's health crisis response mechanisms	The nature and speed of the response to COVID-19 nevertheless illustrate the need for a more structural approach to preparedness, as well as weaknesses in the sector's ability rapidly to respond to and prepare for emergency health events	Flagship initiative on Europe's health crisis response mechanisms - Proposal for an EU Health Emergency Response Authority – 2021.

[9] European Parliament resolution of 17 September 2020 on the shortage of medicines — how to address an emerging problem (2020/2071(INI)) and European Council Conclusions of 2 October 2020 (EUCO 13/20).

[10] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities

Work strand	Specific objectives	Needs analysis	Flagship initative(s)
Ensuring a strong EU voice globally	/	The pharmaceuticals sector is economically strategic for the EU in terms of global trade.	Flagship initiative on international cooperation - Work at global level, with the EMA and the network of national regulators, in international fora and through bilateral cooperation to promote regulatory convergence to ensure access to safe, effective high-quality and affordable medicinal products globally – ongoing.

Source : authors based on COM(2020) 761 final

5.2 Annex II – Key info of ESFRI health RI

Table 11: – Key info of ESFRI health RI

RI	Type and Legal basis	Brief Description	Countries involved	Headquarters	Operation start	Estimated costs (M€)[1]
BBMRI Biobanking and BioMolecular resources Research Infrastructure[11]	Distributed; ERIC	It is the world's largest biorepository of human samples and associated clinical and research data, connecting more than 500 biobanks from 19 countries	19 countries – 17 Members and 3 Observers, and one International Organisation[12]	BBMRI ERIC Graz (AT)	2014	CAPEX: 195 OPEX: 3.5/y
EATRIS European Research Infrastructure for Translational Medicine [13]	Distributed; ERIC	Provides unique one-stop-shop access to the combined expertise and high-end technologies required to develop new products for translational medicine, from target validation to early clinical trials.	100 leading institutes in 13 countries – 12 Members and 1 Observer[14]	EATRIS ERIC Amsterdam (NL)	2013	CAPEX: 500 OPEX: 2.5/y
ECRIN European Clinical Research Infrastructure Network[15]	Distributed; ERIC	It supports the planning, set-up and operational management of multinational clinical research in Europe, providing access to patients and medical expertise throughout Europe. Currently, ECRIN is active in various projects funded by the EC addressing the COVID 19 pandemic, including the two large European adaptive platform trials projects (RECOVER and EU-RESPONSE), and soon il	8 Members and 1 Observer[16]	ECRIN ERIC Paris (FR)	2014	CAPEX: 5 OPEX: 5/y

[11] http://www.bbmri-eric.eu

[12] Members: AT, BE, BG, CZ, EE, FI, DE, GR, IT, LT, ML, NL, NO, PL, SE, UK. Observer: IARC/WHO, CY, TR, CH

[13] https://eatris.eu/

[14] Member countries: NL, CZ, EE, ES, FI, FR, IT, LU, NO, PT, SE, SI, BG. Observer: LV.

[15] http://www.ecrin.org

[16] Members: FR, DE, HU, IT, NO, ES, PT, CZ, IE) and Observer (CH, SK, PL) country.

RI	Type and Legal basis	Brief Description	Countries involved	Headquarters	Operation start	Estimated costs (M€)[1]
		will also contribute to VACCELERATE through the development of tools for harmonised data management and data sharing, as well as the development of master protocols.				
ELIXIR Distributed infrastructure for life-science information[17]	Distributed; ELIXIR Consortium Agreement	It coordinates and develops life science resources across Europe so that researchers can more easily find, analyse and share data, exchange expertise, implement best practices, and gain greater insights into how living organisms work.	20 countries and EMBL are members. In addition, there is one observer country	Wellcome Genome Campus, Hinxton (UK)	2014	CAPEX: 195 OPEX: 95/y
ERINHA European Research Infrastructure on Highly Pathogenic Agents	Distributed ; AISBL[18]	It encompasses basic research into pathogen isolation/characterisation, and the pathogenesis of human diseases caused by dangerous micro-organisms. It enables translational research to develop new counter measures, including diagnostic tools, therapeutics and prophylactics and applied research to improve knowledge, skills and the evidence-base around high containment working practices.	Member countries: FR, HU, PT, SE	ERINHA AISBL Brussels (BE) & ERINHA CCU Paris (FR)	2018	CAPEX: 5.8 OPEX: 0.7/y
EU-OPENSCREEN European Infrastructure of Open Screening Platforms for Chemical Biology[19]	Distributed; ERIC	It enables scientists to use compound screening methods to validate novel therapeutic targets and support basic mechanistic studies addressing fundamental questions in cellular physiology using the methods of chemical biology	Member countries: DE, CZ, DK, ES, FI, LV, NO, PL	EU-OPENSCREEN ERIC Berlin (DE)	2019	CAPEX: 82.3 OPEX: 1.2/y
EURO-BIOIMAGING European Research Infrastructure for Imaging Technologies in Biological	Distributed; ERIC	It provides a large-scale open physical user access to state-of-the-art imaging technologies for life scientists via 25 internationally renowned imaging facilities called Nodes.	11 countries and EMBL	Euro-BioImaging Hub Turku (FI)	2019	CAPEX: 90 OPEX: 1.6/y

[17] https://elixir-europe.org/

[18] AISBL means Association Internationale Sans But Lucratif, it was set up by a Belgian Royal Decree and it is funded through membership fees.

[19] https://www.eu-openscreen.eu/

RI	Type and Legal basis	Brief Description	Countries involved	Headquarters	Operation start	Estimated costs (M€)[1]
and Biomedical Sciences[20]						
INFRAFRONTIER European Research Infrastructure for the generation, phenotyping, archiving and distribution of mouse disease models[21]	Distributed; GmbH	By offering access to a unique collection of mouse models, research tools, associated data, and state-of-the-art technologies for mouse model development and phenotype analyses, the infrastructure allows studying the systemic effects of genetic alterations to unravel the role of gene function in human health and disease.	23 scientific partners from 15 European countries and Canada, and Israel	INFRAFRONTIER GmbH Munich (DE)	2013	CAPEX: 180 OPEX: 80/y
INSTRUCT ERIC Integrated Structural Biology Infrastructure[22]	Distributed; ERIC	It provides access to a broad palette of state-of-the-art technology and expertise as well as training and technique development in the area of integrated structural and cell biology, with the major goal of underpinning fundamental research and promoting innovation in the biological and medical sciences	15 member countries	Instruct ERIC Oxford (UK)	2017	CAPEX: 400 OPEX: 30/y

Note : [1] according to ESFRI Roadmap 2018
Source: authors based on RI websites and ESFRI Roadmap 2018

[20] https://www.eurobioimaging.eu/

[21] https://www.infrafrontier.eu/

[22] https://instruct-eric.eu/

5.3 Annex III - Implementation issues

Legal basis

Companies. It is widely recognised (OECD, 2010; EC, 2008; ESFRI, 2006) that companies are often used to set up RIs in Europe because they are well adapted to public-private needs. Indeed, companies can be set up with both public and private partners and are better integrated into the legal framework of the country where the research infrastructures are located (e.g. French Société Civile, UK Limited liability Company (Ltd), German Gesellschaft mit beschränkter Haftung (GmbH)).

Depending on the hosting county, companies may take different forms. Typically, they are limited liability companies where the shareholders have limited liability in proportion to their contribution to the capital (EC, 2008). Some national legislations (e.g. in Italy) envisage "not for profit" companies. The shareholders invest capital essentially to pursue the organisation's objectives and keep it running without earning any profits. Foundation is a typical legal form for a non-profit organisation governed by national law, often used for research organisations (e.g. in The Netherlands, the German-Dutch Wind Tunnel has been a very successful example according to EC, 2006). It emphasises the non-profit character of the research work and allows for a flexible governance structure (EC, 2008). Under Belgian Law, a specific legal form is envisaged for non-profit organisations called 'AISBL' (international non-profit organisation under Belgian Law). Such legal form is governed by Belgian national law but allows international partners and activities.

Among the not-for-profit organisations are the Product Development Partnerships, dedicated to promoting the development of R&D in neglected diseases through public/private partnerships projects while ensuring that the resulting goods will be made available at affordable prices to the most vulnerable populations. The first PDPs for R&D in neglected diseases were the International Aids Vaccine Initiative and Medicines for Malaria Venture. DNDi is an example of PDP created as a foundation under Swiss law in 2003 by five public research institutions from India, Brazil, Kenya, Malaysia and France, and Médecins sans Frontières with the participation of the WHO (Abecassis et al., 2019). Another example of a not-for-profit association is the CEPI, established as an international non-profit association under Norwegian law in 2016 by five founders[23] to respond to vaccine R&D needs for emerging infectious diseases.

Companies have the advantege to allow the participation of a wider array of partners, i.e. both private and public, coming from the host country and/or from any other state. On the other side, negotiations can take a long time as partners may dislike funding a legal entity that is controlled by the national law of another country and, even more, dislike the idea of long-term financial commitments subjected to taxation and generating returns in other Countries (OECD, 2010). Neither the interviewees mentioned the company nor the foundation models the most suitable legal form for the European Medicines Infrastructure.

Intergovernmental treaties. Organisations established through intergovernmental agreements/treaties have an international legal personality governed by international law. The first European research organisation based on an intergovernmental agreement was the European Organisation for Nuclear Research (CERN). It then become a model for other scientific organisations such as the European Molecular Biology Laboratory (EMBL). Intergovernmental agreements are concluded by intergovernmental agreements between states, state agencies, and other international organisations. Since these organisations operate under their own rules, reaching the agreement usually requires heavy and lengthy negotiations between the partners,

[23] Gates Foundation, the World Economic Forum, the Wellcome Trust, the India's Department of Biotechnology, and the Government of Norway.

especially about the funding of resources, the site and all other necessary elements to commission and operate the facility. Therefore, intergovernmental agreements are usually justified only for large international research infrastructures requiring sizeable investments (EC, 2006).

This legal form typically allows significant advantages such as tax exemptions and favourable staff policy. The specific status of personnel (international civil servants or United Nations types), with privileges and immunities, makes it possible to attract highly skilled collaborators (EC, 2008).

The successful experiences of CERN, ESA, EMBL and the European Southern Observatory make it possible to emphasise the well-established long-term advantages which can be drawn from an intergovernmental agreement. It is thus understandable why most interviewees viewed as desirable to set up the European Medicines Infrastructure in the form of an International Organisation (IO). However, it cannot be disregarded that most RIs in the form of IO date back to years before the EU's start. According to the RAMIRI Handbook, the situation leading to these cases has been unique, connected to the strong feeling for bringing people together and to the economic growth which followed the end of the 2nd World War. The perspective of governments in Europe is no longer so favourable to establishing RI in the form of IOs. Indeed, negotiating international treaties is not simple. It often requires the approval of each parliament, and governments do not always like the very independent position of IOs and the relatively rigid and incompressible budgets ensured by specific treaties (OECD, 2010).

European Research Infrastructures Consortium. In the 2000s, the ambition for developing new research infrastructures in Europe, particularly to implement the ESFRI Roadmaps, triggered discussions about an appropriate legal framework to establish and operate pan-European infrastructures. Such discussion is conveyed in the EC Council Regulation (No 723/2009), which sets up a common framework for establishing and operating infrastructures in a specific legal form called European Research Infrastructures Consortium (ERIC). The legal form can be subsequently used to establish individual legal persons, which should have the abbreviated word 'ERIC' as a part of their legal name. As a legal person, ERIC has two distinguishable features (EC, 2009; Moskovko et al., 2019). First, although different liability structures can be put forward in the statutes, the general rule is that ERIC members' liability is limited to their financial contributions (see Article 14(2)). Second, the Regulation grants ERIC the status of an intergovernmental organisation in two predetermined and delimited situations: (i) in general enjoying certain exemptions IOs get in terms of paying taxes (VAT and excise duties) (see Article 5(1)(d)); and (ii) from complying with public procurement rules, when buying goods and services (see Article 7(3)).

ERIC can be proposed by Member States and participated by Associated Countries and IOs. More specifically, it has to involve at least one Member State and two other countries, either Member States or associated countries. In addition, other (non-EU) countries and intergovernmental organisations can also join as members or observers. However, the statutory seat of the ERIC legal entity shall be in a Member State or associated country only (see Article 8(1)). Private actors cannot be part of an ERIC either as members or as observers.

The main advantage of ERIC is that it is a ready-to-use legal form that ensures immediate recognition and effect in all Member States[24]. Thus, avoiding lengthy negotiations between different states on the appropriate legal arrangement. Nevertheless, a feature of this legal instrument is that its use by the Member States is conditional upon authorisation by the Commission and its continuous monitoring that the RI in question operates in accordance with

[24] Immediate recognition does not apply to associated countries or third countries as the ERIC regulation is not directly applicable to them. Thus, they need to submit a binding declaration recognizing the legal personality and the privileges of an ERIC for possibly hosting (in the case of associated countries) or becoming a member' of an ERIC. European Commission (2014).

the ERIC regulation (Moskovko et al. 2019). Proponent countries have to submit an application for ERIC status to the Commission outlining the RI contribution to the European Research Area along with the proposed statute and a declaration by the host Member State that it will give the ERIC the status of an IO within its jurisdiction. The Commission's acceptance of an ERIC proposal is in the form of an implementing decision published in the EU's Official Journal, along with the main features of the statutes of the proposed ERIC.

Differently from the international bodies set up by treaty, human resources are subjected to the law of the hosting state (OECD, 2010). However, as already mentioned, an ERIC is recognised by the country hosting its seat as an international organisation for the purposes of the directives on value-added tax (VAT), excise duties, and public procurement. This solves a number of potential negotiation obstacles between interested states, as the non-host states would not need to worry about unequal positions in terms of obtaining benefits from investing in the infrastructure (Moskovko et al. 2019).

Another crucial feature of an ERIC is that it is not commercial and should therefore pursue its principal tasks on a non-economic basis (see Article 3(2)). However, it may carry out 'limited economic activities closely related to its task, provided that they are closely related to its principal task and do not jeopardise its achievement. Thus, there is the possibility for limited commercialisation of the research work of an ERIC, justified by boosting innovation and the transfer of technology. An example in this regard concerns the licensing of certain IP discovered and developed within the operations of an ERIC.

In the last decade, ERIC has become an increasingly adopted option for establishing both large and small European infrastructures (OECD, 2014, ESFRI 2018). A perceived advantage is that ministerial support is sufficient at the national level, without the necessity of engaging in potentially lengthy and complex parliamentary processes required for establishing an intergovernmental organisation (OECD, 2014). Despite this, ERIC has not become fully accepted at the levels of individual Member States. This is, for instance, evident when ERICs as legal persons engage in day-to-day encounters with such external actors as financial institutions or national registry offices (EC 2014a, 2018a). Moreover, it is unclear if an ERIC could manage the full-scale activities of the European Medicines Infrastructure downstream of R&D.

Joint technology in initiatives. Article 171 of the EC Treaty gives the possibility to set up a joint undertaking for the efficient execution of Community research, technological development and demonstration programmes. The decision to set up a joint undertaking is made by the Council based on a proposal from the EC. This possibility has been used recently to set up large-scale project such as the GALILEO satellite navigation system and for the Joint Technology Initiatives (JTIs): 'Clean Sky', 'European Nanoelectronics Initiative Advisory Council', 'IMI' and 'Artemis'. However, it should be noted that there is no research infrastructure implemented in the form of JU.

JTIs are long-term public-private partnerships (but limited in time) which support cooperative research across Europe in fields of key importance for industrial research, where there are identified common technological and economic objectives. JTIs are set up. The statutes or the rules of association of a JTI, as in general for a joint undertaking, are not fixed anywhere. Therefore, it is a legal instrument that theoretically leaves a lot of freedom to the founding members (EC, 2008). The establishment of JTIs requires a very strong institutional involvement as they require the EC's initiative and discussions at the Council level. The parties of a JTIs include the EC, not-for-profit

industry-led associations and, in some cases, Member/associated States.[25] Another possible disadvantage of JTIs is the difficulty for non-European Countries to join.

Agency. Beyond the above-discussed legal forms, typically adopted for Research Infrastructures, the present study considers establishing the European Medicines Infrastructure as a decentralised agency of the EU such as EMA and ECDC. According to (EP, 2018), these agencies can broadly be defined as:

> Bodies governed by European public law that are institutionally separate from the EU institutions, have their own legal personality and a certain degree of administrative and financial autonomy and have clearly specified tasks.

Agencies can be located in any Member State across the EU. The members of EU agencies are all Member States, but also other states may become members through agreements concluded between them and the EU.

At the moment, there is no general legal basis to create EU agencies[26] , and prevailing view in legal literature and case law of the European Court of Justice is that EU agencies may be created on the relevant Treaty article that provides the legal basis in a specific policy area (EP, 2018). For instance, EMA founds its legal basis in articles 114 and 168 (4)(c) of TFEU and ECDC in article 168.

Decentralised agencies can be distinguished according to various criteria, for instance, (i) their functions, (ii) their legal basis, (iii) the nature of their powers and the instruments that they can adopt, and (iv) how they can exercise their powers autonomously. As regards the legal basis, the creation of delegated agencies is always decided through legislative measures. However, agencies can be created by different types of acts: a Commission act (agencies created by the Commission are meant to assist the Commission in the implementation of EU programmes and are called executive agencies), a Council joint action, a Council act or a European Parliament and Council act. Regardless of the type of act, the decision requires agreement between several institutions: first, the Commission and the Council, and then the national government and the Parliament.

As regards the nature of powers and the instruments at their disposal, agencies can be divided into agencies with and without decision-making powers to adopt binding legal instruments. So far, only a few agencies (including EMA) have the powers to adopt binding decisions. Most agencies can only adopt a variety of informal documents (e.g., recommendations, opinions, standards, guidelines, strategic plans) and conclude informal agreements and memoranda of understanding with national or international organisations with a similar mandate (EP, 2018). Concerning the autonomy to exercise their powers, agencies may be divided into three categories: (i) agencies that need prior approval, (ii) agencies that need a prior consultation with the Commission, and (iii) agencies that can autonomously exercise their powers. As a result, there is no unique agency model.

Funding

The funding model depends on the legal basis and the adopted organisational model. For instance, the largest share of the budget for all European RI with the status of international organisation comes from contributions of their Member States. Differently, for most EU decentralised agencies,

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[25] The Commission and Member States that are part of the Joint Undertakings annually commit funds from their research budget. Industry commits matching in-kind contributions and funds –50% or more of the total costs of the projects to carry out the research.

[26] The Common Approach (2012) available here: https://europa.eu/european-union/sites/europaeu/files/docs/body/joint_statement_and_common_approach_2012_en.pdf does not provide guidance on this issue.

the budget comes primely from the Union's budget and at least one other source of financing, which may consist of (EP, 2018):

- *fees or payments for services*. For instance, in the case of EMA, companies pay fees for the authorisation of new medicines.
- *voluntary contributions by Member States* or a combination of fees and voluntary contributions by Member States. This is for instance the case of ECDC.
- contributions from participating third countries and other partners.

Annual contribution from each member is typically the main sources of funding for RIs. It can be based on different modes of calculation, for example (Ramiri Handbook, 2018; OECD, 2014): Fixed, identical contribution for all the partners; Contributions based on GDP or GDP per capita, or some other relevant indicator; Contributions based on an algorithm agreed between the partners.

The contribution of Member States could even be differentiated according to the activities each States is interested to support as it happens in the ESA (see Box 8).

The financial obligations of members are agreed in the founding agreement in the case of intergovernmental organisation and the statute in the case of ERIC. Being backed by a binding agreement, members commit to long-term and stable annual contributions, even if it may vary in the amount (normally, cash contributions are re-computed annually).

Contributions can be made in cash or in kind (such as personnel, equipment, utilities, software, hosting space etc.). The latter are typically easier to arrange, especially in case of distributed infrastructures (OECD, 2014).

The contribution from the EU can take two different forms. First, a new entity could enjoy transfers from the Multiannual Financial Framework of the EU as it happens with decentralised agencies or from the European research or health programmes, as is the case of the Joint Technology Initiatives. The drawback of these funding sources is that they are subject to negotiation every seven years, making the stream of resources uncertain in the long run, for example, if a 30 years horizon is adopted.

Second, the European Medicines Infrastructure could benefit from EU grants, i.e. project-based funding stemming from European institution funding research, which are awarded based on a selection process. While this is one of the main funding sources of existing ERICs, the drawback of grants (both European and national) is its project-based nature which is not adapted for the long-term sustainability of the research infrastructures (ESFRI, 2019).

Grants and donations provided by philanthropic organisations, charities, EU cooperation agencies (such as AFD in France, SDC in Switzerland, BMBF-KFW in Germany, DGIS in the Netherlands, and AECID in Spain) and private funds (such as the Bill & Melinda Gates Foundation, Médecins Sans Frontières, and the UK Wellcome Trust) suffer from the same uncertainties of project-based grants stemming from European institutions.

Another problem with donations is that they may endanger the research independence. Indeed, donors typically choose to earmark their funding by allocating it to the research of specific diseases (Abecassis et al., 2019). To limit this risk, research organisations may establish a limit to each donor's contribution. For instance, DNDi's fundraising policy states that no one donor can contribute over 25% of all donations.

Revenues are an income source that is fully under the control of the research infrastructure. Revenues typically result from the activities carried out, the services rendered by the RI, or the commercialisation of its results (Ramiri Handbook, 2018).

In the case of the European Medicines Infrastructure, revenues may derive from:

- Fees to access laboratories and to use research equipment charged to external researchers and businesses. For instance, to access the electron microscopy facility, EMBL charges academic visitor from its member and associated states an hourly usage fee of EUR 30 (EUR 135 per hour for industry visitor and other academic visitors);
- Access fees for individual students or collective agreements with some universities and institutes;
- Licensing of patents (see section 4.3);
- Licensing of the new drugs to national health systems;
- Royalties resulting from sales of drugs co-formulated with pharmaceutical companies;
- Granting access to data eligible for Priority Review Vouchers (PRV) by the US government. By letting its pharmaceutical partners using data generated within a legal partnership framework to register their own drugs and obtain a PRV, the European Medicines Infrastructure can claim to share the additional revenues enjoyed by the pharmaceutical companies. Of course, this option will be viable only if PBRi is involved in the research and marketing authorisation of new treatment, e.g. for a neglected or paediatric orphan disease.

Financial instruments, especially loans, may be an important mean for RIs to get pre-financing which are key to avoid cash flow unbalance. Since 2007, the EC has been cooperating with European Investment Bank (EIB) and the European Investment Fund to provide a platform for financing to innovative companies and research institutes/organisations. Under the Horizon 2020 programme, the InnovFin initiative provides financing to support R&I by companies and research infrastructure. Specifically, Europe's public or private research institutes/organisations can benefit from 'InnovFin Science' made available by the EIB in the form of debt or equity-type financing. The aim is to support R&I investments, including financing buildings and other infrastructure directly related to R&I activity. EIB also grants loans to pharmaceutical companies. For instance, in 2020, EIB provided BioNTech with up to EUR 100 million in debt financing for COVID-19 vaccine development and manufacturing (EIB Press, 2020).

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