



European pharmaceutical research and development

Could public
infrastructure
overcome market
failures?

STUDY

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European pharmaceutical research and development

Could public infrastructure overcome market failures?

With a focus on research and development in the area of innovative medicines, this study 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 such European medicines infrastructure should focus on threats and areas of research and development that are underinvested under the current business model. More specifically, the study uses an extensive literature review and a targeted survey of international experts from science, industry, public health and government institutions, 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.

On the basis of their research, the authors present a range of policy options. The most ambitious of these considers a Europe-wide public infrastructure equipped 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 the course of 30 years, in partnership with third-party research centres at national or European level and with companies. It would be the most important global player in biomedical innovation in the world.

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Executive summary

Introduction

Europe's pharmaceutical sector and related biomedical activities are major contributors to the European Union (EU) economy in terms of added value, highly skilled jobs, research and development (R&D) investment, and innovation. However, the Covid-19 pandemic has spotlighted some critical issues in the way the pharmaceutical industry sets its R&D priorities. The current design and management of public funding policies for pharmaceutical research and market regulation do also contribute to such criticalities in terms of prioritisation of investments, and their effectiveness and efficiency.

On 1 June 2020, the European Commission published a [roadmap](#) for a pharmaceutical strategy for Europe, and the related [communication](#) was adopted by the Commission on 25 November 2020 (COM(2020) 761 final). The strategy has the overall goal of ensuring Europe's supply of safe and affordable medicines and supporting the European pharmaceutical industry's innovation efforts. It is a key component of building a stronger European Health Union, as advocated by the European Commission President, Ursula von der Leyen, in her September 2020 State of the Union address.

In such a context of rethinking a European approach to pharmaceutical policy, the STOA Panel of the European Parliament has launched the present study to investigate the current model of pharmaceutical research and innovation system. The study explores 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). In contrast to the European Health Emergency Preparedness and Response Authority (HERA), the organisation proposed here, the European medicines infrastructure, would be an R&D and delivery institution for medicines, vaccines, and related biomedical innovations with a mission going beyond emergency, as it would aim at structural change in the public interest of the current model of pharmaceutical R&D. HERA and the proposed European medicines infrastructure may be seen as complementary, with shared public health values and different missions and tools.

Methods of the study

The methodology employed to draft the document at hand combines a selective literature/documentary review and a survey of expert stakeholders, belonging to four groups: (1) researchers, clinicians and research managers; (2) representatives of the pharmaceutical industry; (3) public health experts; and (4) experts within European institutions and national and international organisations. The interviewees were selected through a combination of purposive and snowball sampling. Out of an initial list of over one hundred experts, in total, 56 participants from 48 different organisations were included in the study. The interviews took place between January and May 2021 and were transcribed *ad verbatim* upon their conclusion. The data collected were analysed in June and July 2020. The respondents were guaranteed anonymity.

Results

The study identifies six failures affecting the functioning and regulation of the pharmaceutical market, for which the current public policies and regulatory remedies are less than adequate, namely:

- **Disconnection between corporate R&D choices and public health priorities:** While the industry has had and still has a brilliant track record of innovations, there is evidence that the productivity of its R&D has been shrinking, in terms of new medicines and their cost,

particularly in certain areas. From a public health perspective, this raises concerns around the disconnection between corporate R&D priorities and the most urgent needs for human well-being. Governments have frequently considered subsidies to corporate R&D as a way to curb this disconnection. The policy is currently implemented generously by several governments through a number of grant schemes, with the US subsidies to industry for Covid-19 vaccines a notable example. However, beyond the current emergency, which has seen an unprecedented amount of government money transferred to the industry, there is evidence that this policy is not efficient and effective in the long term.

- **Mismatch between open science in the public sector and patents protecting the investors:** The current business model of the pharmaceutical industry heavily relies on the 'legal monopoly' provided by filing a patent or family of patents. 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 from such public information. However, this disclosure mechanism has limited scope because trade secrets remain de facto undisclosed, not to mention economic information on actual R&D and production costs. The protection granted by patents is even more disproportionate in consideration of the increasing diffusion of open science practices in fundamental research, largely funded by public money, providing free access to a wealth of scientific results to private companies. In the legislation or actual practice, there is no evidence of systematic policy frameworks to deal with the protection of the public interest when a combination of open science upstream, government subsidies to R&D, patents and market authorisation leads to unfavourable outcomes (such as unaffordable prices, scarcity of medicines in certain fields, uncompetitive corporate strategies).
- **Rents for financial investors in the pharmaceutical industry arising from government subsidies to R&D:** For each new authorised medicine, the R&D cost is generally directly and indirectly supported by a combination of public sector grants to biomedical research either upstream or directly to firms. Unfortunately, there is no systematic public scrutiny of the social cost and benefits of such a mechanism of subsidies, while it clearly implies rents ultimately captured in the abnormal shareholder value of pharmaceutical companies, as showed by international evidence. Against this mechanism, corporate income taxation of extra-profits or monopoly rents is not an effective remedial policy as profit motivation is the main incentive to invest in research and innovation for firms. Moreover, an 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. However, lacking reliable cost information for the regulators, this seems a scarcely effective instrument to contain the increasing price of new medicines.
- **Oligopolistic market power on the supply side, and issues of access and affordability of medicines:** The pharmaceutical sector structure has a highly skewed distribution: an oligopolistic core with a fringe of companies acting in different submarkets or therapeutic areas. It effectively works as a set of legal or de facto monopolies on most medicines, with the unavoidable implications of market power: 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 optimised to extract rents for the top multinational corporations. This market structure contributes to high drug prices which, in turn, create affordability problems for patients and sustainability of healthcare systems. In order to break this spiral, several national authorities have adopted austerity measures and applied short-term cost-containment measures such as ad hoc price cuts, external reference pricing, and payback to pharmaceuticals. However, these measures often resulted in a risk of medicine shortages, which has become increasingly pressing in European countries.

- **Inadequate optimisation studies of medicines after market authorisation:** While companies have all the incentives to invest money in preparing clinical trials and other studies to support their applications for marketing authorisations, they have no incentive to perform comparative clinical trials and 'real life' studies after a drug has been authorised, especially if they include post-authorisation comparisons across medicines, including those of competitors. Regulators may try to convince companies to perform long-term studies, or they can commission such studies from third parties. The first approach may not be successful for lack of incentives. The second approach has been implemented, so far, only in a non-systematic and often voluntary manner by non-commercial entities.
- **Information asymmetries in the public procurement of medicines:** While a considerable quota of the market for medicines, particularly in Europe, is ultimately with a government payer (hospitals, public health authorities, etc.), pharmaceutical companies have no interest in sharing information on the cost structure of R&D, or the 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. Certain reforms may increase the competitiveness of the procurement of medicines by hospitals and other health authorities, but this study is dealing with the more upstream and structural problems of pharmaceutical R&D and delivery.

Such market and policy failures suggest exploring a policy approach based on a more direct public intervention (as it was successfully experienced for space policy and other science-based sectors): the creation of a pan-European R&D infrastructure and delivery organisation for medicines in certain critical areas. It should be based on frontier biomedical science, with an overarching public-health mission and a long-term vision and funding. More specifically, such European Medicines Infrastructure should:

- have the sole mission of fulfilling European citizens' interest in being offered under all circumstances safe, effective, innovative and affordable medicines in R&D areas affected by market failures and other issues of concern;
- have a comprehensive, forward-looking, long-term strategy and dedicated leadership and governance supported by the consensus of scientific communities and health authorities;
- own the results of the R&D projects it undertakes, either fully or in specific cases with public-private partnerships, and manage its intellectual property rights 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.

The main missions for the European Medicines Infrastructure may include:

- building a portfolio of innovative pharmaceutical R&D projects in selected pharmaceutical areas and related biomedical fields over a period of thirty years (2050) in the spirit of looking at the needs of the next generation of European citizens. In the most ambitious option, such projects should address therapeutic areas: (i) not sufficiently addressed by the private sector; or (ii) where the private sector charges exorbitant prices; or (iii) where there are shortages or supply is not secure.
- carrying out clinical studies relating to drugs already authorised such as: (i) comparative safety and effectiveness trials of existing drugs; (ii) long-term safety studies; and (iii) studies for drug repurposing.
- monitoring the supply of raw materials or components for drugs, often imported from outside the EU. Based on the results of the monitoring, it should also take action, when needed, to address bottlenecks in the supply, and promote projects aimed at improving the security of supply for Europe, in collaboration with other EU institutions.

Policy options

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

Policy option 0. This 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 setting-up 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. It will address vulnerabilities and strategic dependencies within the Union related to the development, production, procurement, stockpiling and distribution of medical countermeasures. It would also provide a strengthened health security coordination within the Union, bringing together the Member States, the industry and the relevant stakeholders in a common effort. However, this option remains profoundly grounded in the current public funding system for pharmaceutical research. According to the Commission proposal (COM(2021) 576 final), HERA will be tasked, among other activities, to promote advanced R&D of medical countermeasures – including diagnostics, therapeutics and vaccines – and related technologies. However, as far as the European Commission proposal is concerned, HERA apparently will not have the responsibility, resources and capacities to directly implement pharmaceutical R&D projects in the public interest. It would need to rely to the current players for R&D. As such, HERA will not have the critical mass to structurally shift pharmaceutical companies' R&D choices towards public-health priorities apart from a limited intervention area related to possible emergencies.

Policy option 1. Beyond such baseline, the first option, the most constrained one, involves the creation of a European Medicines 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 both top-level scientific and managerial skills), its own budget, and 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 public infrastructure. A core, but relatively limited, in-house R&D capacity (staff and laboratories) would be necessary for certain tasks.

Policy option 2. The second option is similar to the previous one but with a wider mission. Under this option, the infrastructure scope would include other fields where both the public and private sectors are under-investing, such as, again, vaccines and medicines for infectious diseases, but also for example medicines related to neurodegenerative conditions, rare diseases, some types of cancer and genetic conditions. It will work around missions designed by 'horizontal' R&D concepts, technologies and platforms. As in the previous option, the new organisation will have its own governance (with both scientific and managerial skills), budget, contractual arrangements with external suppliers and partners, and a core but relatively limited in-house laboratory and staff capacity. It will mainly work with a range of procurement contracts with third parties around the horizontal missions.

Policy option 3. The third option concerns the creation of a large-scale, mission-oriented, European Medicines Infrastructure with an exclusive focus on infectious diseases, but – differently from the previous two options – such a new organisation, while also working through contracts with third parties, would have its own hired scientific staff and world-class dedicated laboratories to manage most of its research in-house. It would cover most of the cycle from basic research to delivery of new medicines, with appropriate contractual arrangements with third parties, as in the above options, but would have greater R&D autonomy and delivery mechanisms.

Policy option 4. The fourth option is the most ambitious one in terms of scope and delivery mechanisms. It is similar to the previous one, as it concerns the creation of a large-scale, mission-

oriented European R&D infrastructure. It would have, however (similarly to Option 2), a wider R&D agenda, i.e. not constrained to infectious diseases, as compared to the previous option. This option would manage its own scientific staff and laboratories, and create the most important public R&D infrastructure in the world, at a scale comparable with the intramural research programme of the US federal government sponsored National Institutes for Health, and 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 pharmaceutical industry in terms of possible partnership on specific projects.

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List of abbreviations

AECID	Spanish Agency for International Development Cooperation
AFD	French Development Agency
AIM	International Association of Mutual Benefit Societies
AISBL	Association Internationale Sans But Lucratif
AMR	Antimicrobial resistance
API	Active pharmaceutical ingredient
BARDA	Biomedical advanced research and development authority
BBMRI	Biobanking and BioMolecular resources Research Infrastructure
BERD	Business enterprise expenditure for pharmaceutical R&D
BMBF	German Federal Ministry of Education and Research
CAPEX	Capital Expenditures
CBA	Cost-Benefit Analysis
CDC	US Centres for Disease Control and Prevention
CDMO	Contract Development and Manufacturing Organisations
CEPI	Coalition for Epidemic Preparedness Innovations
CERIC	Central European Research Infrastructure Consortium
CERN	European Organisation for Nuclear Research
CMO	Contract Manufacturing Organisations
COCIR	European Trade Association representing the medical imaging, radiotherapy, health ICT and electromedical industries
COM	European Commission's Communication
COVID	COronaVirus Disease 19
CRO	Contract Research Organisations
DDD	Defined Daily Doses
DG SANTE	European Commission's Directorate-General for Health and Food Safety
DGIS	Dutch Directorate-General for International Cooperation
DNDi	Drugs for Neglected Diseases Initiative
EATRIS	European Research Infrastructure for Translational Medicine
EBITDA	Earnings Before Interests Taxes Depreciation and Amortization
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECRIN	European Clinical Research Infrastructure Network
EEA	European Economic Area

EFPIA	European Federation of Pharmaceutical Industries and Associations
EIC	European Innovation Council
EIT	European Institute of Innovation and Technology
ELIXIR	European Life-science Infrastructure for Biological Information
EMA	European Medicines Agency
EMBL	European Molecular Biology Laboratory
EMBLEM	EMBL Enterprise Management Technology Transfer GmbH
EP	European Parliament
ERIC	European Research Infrastructure Consortium
ERINHA	European Research Infrastructure on Highly Pathogenic Agents
ERP	External Reference Pricing
ESA	European Space Agency
ESFRI	European Strategy Forum on Research Infrastructures
ESO	European Southern Observatory
ESRF	European Synchrotron Radiation Facility
EU	European Union
EU4Health	EU health programme
EuCHR	European Council for Health Research
EUCO	European Council
EUnetHTA	European Network for Health Technology Assessment
EUR	Euro
EURIPID	European Integrated Price Information Database Collaboration
FP	Framework Programme for Research
GBARD	Government outlays for health-related R&D
GDP	Gross Domestic Product
GmbH	Gesellschaft mit beschränkter Haftung
GPMB	Global Preparedness Monitoring Board
H2020	Horizon 2020
HaDEA	Health and Digital Executive Agency
HERA	European Health Emergency Preparedness and Response Authority
HIV/AIDS	Human immunodeficiency virus infection and acquired immunodeficiency syndrome
HTA	Health technology assessment
IARC	International Agency for Research on Cancer
IHI	Innovative Health Initiative

IMI	Innovative Medicines Initiative
IO	International Organisation
IP	Intellectual property
IPR	Intellectual property rights
IRP	Intramural Research Program
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
JTI	Joint Technology Initiatives
JU	Joint Undertaking
M&A	Merger and acquisition
MERS	Middle East respiratory syndrome
MetOp	Meteorological Operational satellite
MRP	Mutual recognition procedure
MS	Member State
NACE	Nomenclature statistique des activités économiques dans la Communauté européenne
NGOs	Non-governmental organisations
NIH	National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
OPEX	Operating Expense
PDP	Product Development Partnerships
PI	Pandemic Influenza
PPP	Public-private partnership
PRV	Priority Review Vouchers
R&D	Research and Development
R&I	Research and Innovation
RAMIRI	Realising and Managing International Research Infrastructures
RI	Research Infrastructure
SARS	Severe acute respiratory syndrome
SDC	Swiss Agency for Development and Cooperation
STOA	Panel for the Future of Science and Technology
TEU	Treaties of the European Union
TFEU	Treaty on the functioning of the European Union
US FDA	The United States Food and Drug Administration
USD	Dollars
VAT	Value added tax
X	

VOSL	Value of a statistical life
WHO	World Health Organisation
WIPO	World Intellectual Property Organisation

Country codes:

AT: Austria	LT: Lithuania
BE: Belgium	LU: Luxembourg
BG: Bulgaria	LV: Latvia
CH: Switzerland	ML: Mali
CY: Cyprus	NL: Netherlands
CZ: Czech Republic	NO: Norway
DE: Germany	PL: Poland
EE: Estonia	PT: Portugal
ES: Spain	SE: Sweden
FI: Finland	SI: Slovenia
FR: France	SK: Slovakia
GR: Greece	TR: Turkey
HU: Hungary	UK: United Kingdom
IE: Ireland	US: United States
IT: Italy	

Glossary

Active pharmaceutical ingredient (API): any substance, or mixture of substances, intended to be used in the manufacture of a drug (medical) product and that, when used in the production of a drug, becomes an active ingredient of the product in terms of therapeutic effect.

Big Pharma: a term usually used to refer to the world's largest publicly traded pharmaceutical companies typically in terms of value market share.

Clearing houses: these are platforms or intermediaries, whose services range from databases of information to technology exchange platforms and royalty-collecting organisations.

Corporate venture capital activity: this is a subset of venture capital investment and occurs when corporations invest in an affiliated unit to make equity investments in promising start-up companies, usually related to the company's own industry.

Data exclusivity: this is the period of time during which an applicant to a medicines agency cannot rely on the data in support of another marketing authorisation for the purposes of submitting an own application and of obtaining marketing authorisation or placing the product on the market.

European Institute of Innovation and Technology (EIT): a body created by the European Union (EU) in 2008, under the EU's Framework Programme for Research and Innovation, to strengthen Europe's ability to innovate. The EIT supports the development of long-term European partnerships (called Knowledge and Innovation Communities) among companies, research labs and higher education in different fields affected by specific global challenge. EIT Health is one of Knowledge and Innovation Communities supported by EIT.

European Research Infrastructure Consortia (ERIC): a specific legal form that facilitates the establishment and operation of Research Infrastructures with European interest. ERICs rely on diverse funding instruments to operate, including, among others, grants from the EU Research Framework Programmes, national funding schemes, member country fees.

External reference pricing: a mechanism used as a benchmark to set the list price of a medicine through comparison of prices of equivalent or similar medicines in other countries.

Good manufacturing practice: this describes the minimum standard that a medicines manufacturer must meet in their production processes.

Heads of Medicines Agencies: a network of the heads of the 'national competent authorities', the agencies responsible for the regulation of human and veterinary medicines in the individual countries of the European Economic Area.

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

Key starting materials: these are raw material refers to chemical compounds that are used as a base to make an active pharmaceutical ingredient (API).

Intermediates: a chemical compound that is in the process of becoming an API (see the definition above) from a raw material called an intermediate. Some APIs pass through over 10 kinds of intermediates in a process when changing from being a raw material into an API.

List price: the price a drug manufacturer initially sets. List prices are the only price information publicly available to researchers and citizens. However, actual prices paid by health insurers, governments

and healthcare providers can be significantly lower thanks to off-invoice discounts and rebates. According to various studies, including Morgan et al. (2017), confidential agreements on drug price are becoming more frequent and as a consequence the list prices are increasingly disconnected from actual prices.

Managed entry agreements: these are arrangements between firms and healthcare payers that allow for coverage of new medicines while managing uncertainty around their financial impact or performance.

Market exclusivity: this is the period of time during which a generic, hybrid or biosimilar cannot be placed on the market, even if the medicinal product has already received a marketing authorisation. Article 14(11) of Regulation (EC) No 726/2004. According to the same article, the market exclusivity can be extended to 11 years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which are held to bring a significant clinical benefit in comparison with existing therapies.

Mutual-recognition procedure: when a company has a medicine authorised in one EU Member States, it can apply for this authorisation to be recognised in other EU countries. This process allows Member States to rely on each other's scientific assessments.

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

Payback: the European Commission (2012) defines payback policies as a process that 'requires manufacturers to pay back a share of their revenue if a pre-specified budget ceiling for public pharmaceutical expenditure is exceeded'.

Priority review vouchers (PRVs): these entitle a company to a fast-track review for the registration of some of their drugs by the US regulatory authority if the company has obtained marketing approval from the Food and Drug Administration for a new treatment for a neglected disease or a paediatric orphan disease. Such fast-track review enables to advance the marketing date by four to six months, thereby generating substantial differential revenue. PRVs can also be traded on the PRV market.

Shortage episodes: according to Article 81 of Directive 2001/83/EU, medicine shortage occurs when the supply of medicines identified as essential by the health system is insufficient to meet patient needs for a period of more than two weeks.

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

1 Introduction

1.1 Background

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 public health of European citizens, for the overall productivity of the EU economy, and for the global role of the EU to address current and future health challenges.

However, the Covid-19 pandemic has spotlighted some critical issues in the way governments have been designing and managing 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 pandemic has highlighted the value of collaborative R&D to develop new approaches for 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 has the overall goal of ensuring Europe's supply of safe and affordable medicines and supporting 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.

1.2 Objective

In such a context of rethinking a European approach to pharmaceutical policy, the STOA Panel of the European Parliament (EP) has launched the present 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 this study.

More specifically, the study discusses the strengths and weaknesses of the current pharmaceutical R&D and business model and explore options for a European R&D infrastructure to address some market failures and other issues of concern from the perspective of public health. 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 but also a delivery organisation with a transboundary public health mission. A terminological issue: the study mentions pharmaceutical R&D for the sake of conciseness, but several issues dealt with here are also applicable to biological products, testing technologies and diagnostic innovations, and to other fields of biomedical research.

The infrastructure under investigation could take different legal forms, such as an EU agency or a permanent and mission-oriented organisation with its own budget, according to a model inspired by the experience of the European Molecular Biology Laboratory (EMBL), the European Space Agency (ESA), or the European Organisation for Nuclear Research (CERN), possibly with the EU as the core stakeholder, but with flexible arrangements in terms of membership of states, ownership

of tangible and intangible assets, governance, hiring of personnel, and procurement policy. The study discusses different options from such a broad perspective.

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 own 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 US\$41.7 billion and 1.6 billion. The NIH is mainly a funding organisation, but its Intramural Research Program (IRP), with around US\$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 with an interest in biomedical research include DARPA, (Defence Advanced Research Projects Agency), the DoE (Department of Energy), some of the National Laboratories, and other entities with federal funding. Overall, the US government is by far the top global player in the public support to biomedical R&D.

***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, as done so far. Such limits cannot be even solved by creating additional authorities or agencies with limited budgets, possibly with some coordination powers, but without their own 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.

1.3 Structure

This report is structured as follows:

- Section 2 presents the methodology and resources used to write the literature review section of the report. It then presents the results of the desk-based research, i.e. it provides stylised facts on pharmaceutical industry, an overview of the European pharmaceutical sector and of its market failures, an overview of the European policy framework and the European health R&D panorama.
- Section 3 presents the methods and results of the survey to expert stakeholders.
- Section 4 discusses the concept for the new European infrastructure including an initial discussion of its mission, legal basis, financing, and IP management.
- Section 5 presents the policy options.
- Additional details, including the survey questionnaire, are given in the Annexes.

2 Literature review

2.1 Methodology and resources used

The methodology employed to draft the document at hand combines a selective literature/documentary review and a survey of expert stakeholders. The method for the literature review is presented below, while the method for the survey is presented in section 4, before the presentation of the findings.

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 body of literature in scholarly databases such as REPEC and PUBMED decide whether it is necessary to adjust the terms or include additional ones.
- Additional references were collected through advice from around twenty experts, either persons willing to share their knowledge with the principal investigator once informed about the study topic or interviewed as part of the study.
- 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 make sure we include both 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

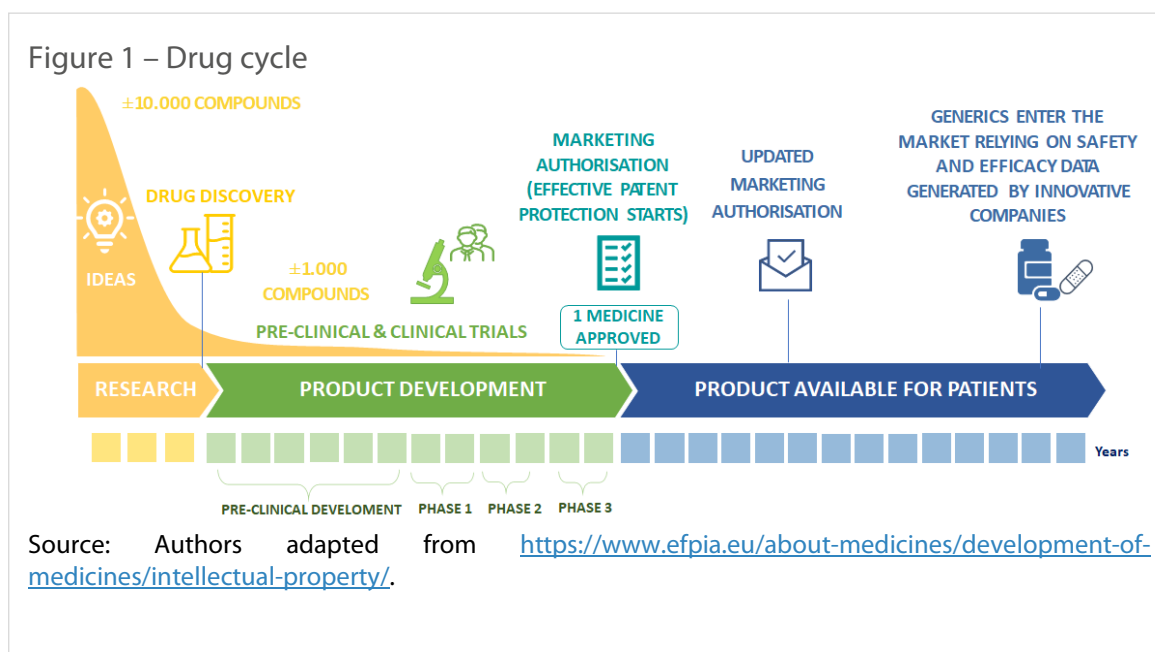
2.2.1 Background on pharmaceutical industry

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, 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.



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, 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 has many implications:

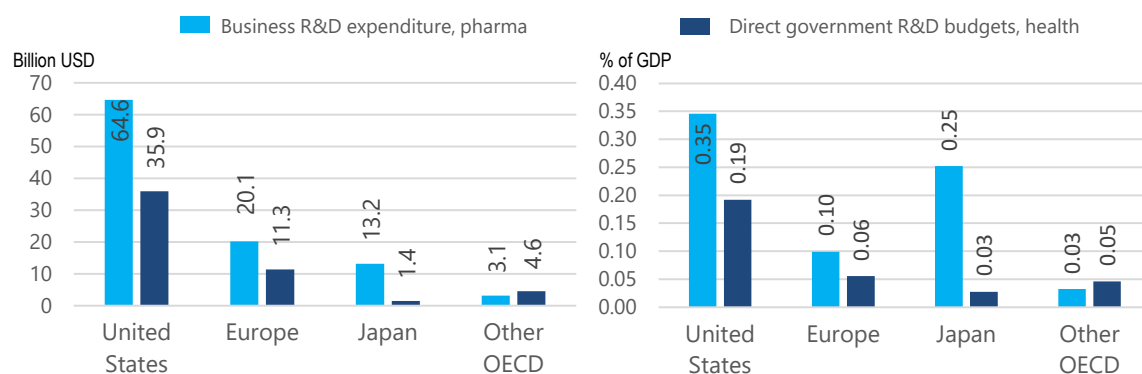
- First, with such a long investment (and economic return) gestation lag, it is optimal for investors to exploit the economies of scope, which requires building up heterogeneous portfolios of patents and R&D projects, which in turn requires a considerable amount of capital. Indeed the long journey leading to marketing authorisation is usually not sustainable by 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 the 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 US\$93 billion, of which US\$26.1 billion was spent by the United States NIH, followed by the EC (US\$3.7 billion), and the United Kingdom Medical Research Council (US\$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 US\$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 US\$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 US\$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 US\$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 US\$800 million and US\$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 US\$985 million and an average value of US\$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 out 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 rather 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 US\$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 insurances (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, for 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, Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Italy, Luxembourg, Netherlands, Portugal, Slovak Republic, Slovenia, Spain, 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; consumption for 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 by specific market features.

In Europe overall, the most important purchasers are national health services or insurance schemes. Indeed, governments, differently 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 the marketing authorization by 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

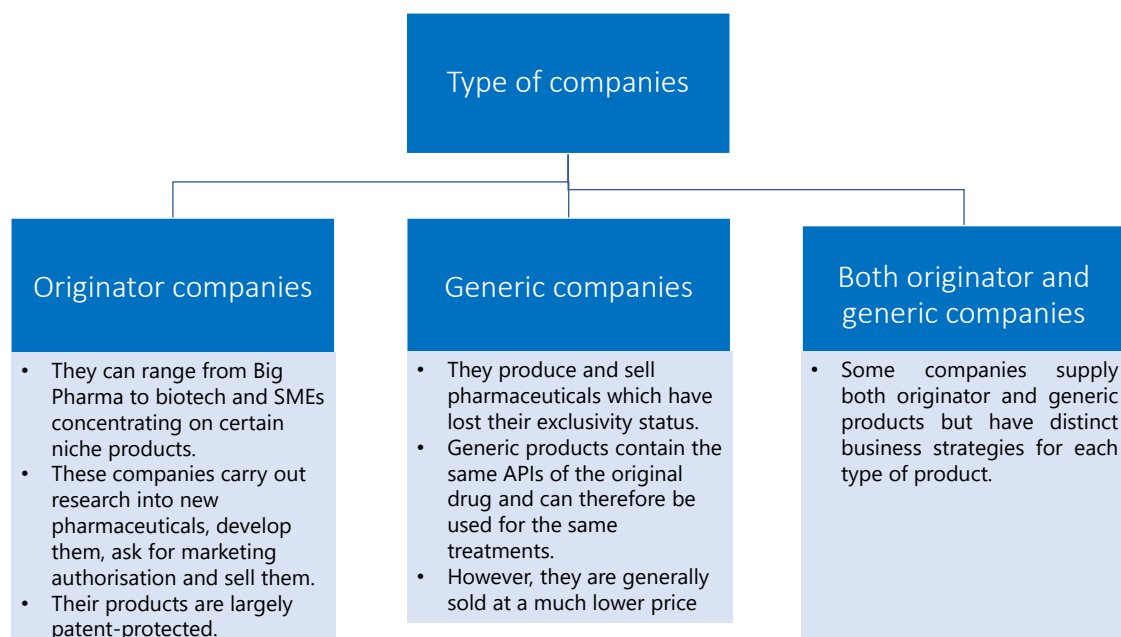
On the supply side, the pharmaceutical sector is characterised primarily by three types of companies (EC, 2009). See Figure 3 below.

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 pharmaceuticals manufacturing sector in 2016. Together they employed 568 thousand persons (in 2018, they were raised to 652) and generated €96.4 billion of value added (in 2018, it was raised to €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 sector in the EU. In 2017, the total turnover amounted to €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 €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 industry spent US\$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 €11.1 billion and exported €7.4 billion APIs, generating a trade deficit of €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 which top pharmaceutical 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 has increased up to 19% in 2020.

The review of the literature suggests that Big Pharma are increasingly disinvesting from 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 of 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 euro (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 Organisations (CMO) has grown considerably. According to estimates of 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 pharmaceutical 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 pharmaceutical 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 of 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 Drug-prices regulation in the EU

Governments of the EU Member States follow different price regulations and reimbursement policies (Stargardt and Vondoros, 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 the

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 Vondoros, 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 €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 the 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 Vondoros, 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.

Source : authors based on www.euripid.eu

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 the 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 technologies 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).

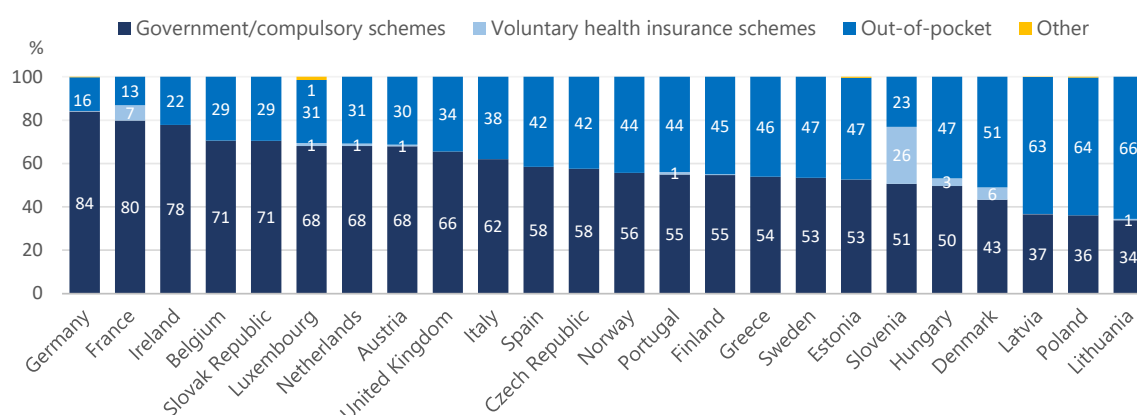
Box 2. Concerns on out-of-reach prices

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>

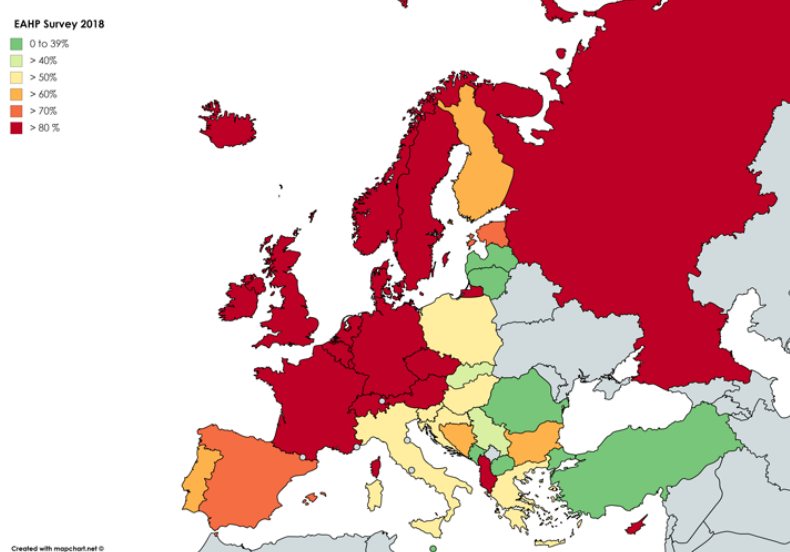
Yet analysing expenditure on retail pharmaceuticals only gives a partial picture of spending since it does not include the costs of pharmaceuticals used for hospital inpatient care. While retail pharmaceutical spending grew at a slower pace or even declined since 2008 due to austerity measures (Belloni 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

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

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.

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 membership to map the impact of medicine shortages from the community pharmacists' perspective. The results of the 2019 survey not only shows 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, pharmaceutical 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 pharmaceutical companies. According to PharmaProjects (2020), cancer candidates comprise 36.7% of all pharmaceutical 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). Differently 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 Gurría, 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 the 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 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 for 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 to 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, the 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 pharmaceutical market, which means that average production costs fall over a large range of output quantity. 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 the 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 that 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 pharmaceutical 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 requires 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 141/2000 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 lack of knowledge to understand and interpret publicly available information. 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 certain extent physicians, to do 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 became 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 legislation¹, 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.

¹ 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.

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 remain 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	Requirements and procedures for marketing authorisation and for monitoring authorised products
Regulation (EC) No 726/2004	
Directive 2001/20/EC	Common rules for the conduct of clinical trials in the EU
Regulation EU No 536/2014	
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.

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 summarised 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 €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 need 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 €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 US\$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, often governments are poorly collaborative, and they provided 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.	<ul style="list-style-type: none"> ➤ 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	<ul style="list-style-type: none"> ➤ 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.	<ul style="list-style-type: none"> ➤ 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	<ul style="list-style-type: none"> ➤ 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	<ul style="list-style-type: none"> ➤ 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 €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 €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 (€312 million in 2003-2007; €321.5 million in 2008-2013; €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 €5.1 billion, EU4Health will become the largest EU health programme ever in monetary terms.

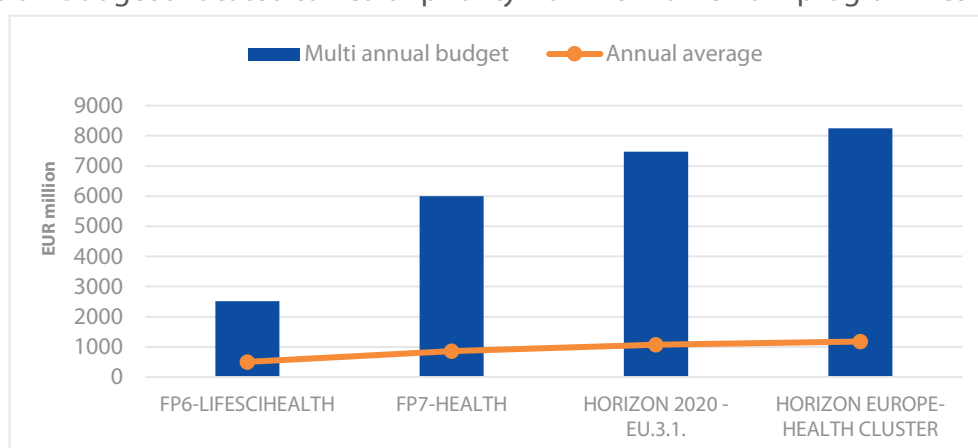
The EU4Health programme has three general objectives:

- 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.

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

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



Source: Authors based on CORDIS data.

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 non-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 €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, INSTRUMENT, and EU-OPENSOURCE.

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 €2 billion, of which €1 billion came from the 'Health theme' of the EU's Seventh Framework Programme for Research (FP7) and another €1 billion came from in-kind contributions by EFPIA companies. For the IMI2 programme (2014-2020), the total budget was increased to €3.276 billion. Of that, half the budget comes from the Health, Demographic Change and Wellbeing Societal Challenge of Horizon 2020, and €1.425 billion is committed to the programme by EFPIA companies. The remaining part (up to €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. On 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 it 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 €2.2 billion (see EIT Health, 2018). Out of this, approximately €455 million comes from Horizon 2020 programme. The remaining budget comes from partners' own revenues and resources (approximately €1.8 billion) as well as private and/or public funding at national, regional and EU level (approximately €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 US\$41.7 billion and has received emergency supplemental appropriations in three coronavirus supplemental appropriations acts, totalling over US\$3.59 billion. The administration's FY2021 budget request, as amended by a March 2020 letter, proposes an FY2021 program level of US\$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 US\$1.4 billion, which is US\$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.gov 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 €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 US\$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 euro 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 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 Findings from the survey of experts

3.1 Methods of the survey of expert stakeholders

The study topic was further explored through semi-structured interviews to selected international experts. The survey strategy is briefly presented in what follows.

It is essential to underline that data gathered by qualitative research are not reproducible, and the focus is not on reliability and generalisability. It focuses rather on explaining the thinking behind the primary data that might otherwise be omitted. However, the sample is large enough to conclude that if the very diverse group of stakeholders from different socio-cultural backgrounds agree on the statement or action to be taken, it could be more reliable than traditional qualitative research, usually based on smaller samples.

3.1.1 Recruitment of participants

3.1.1.1 First round - Pilot interviews

The survey process was initiated with some pilot interviews carried out by the principal investigator with the aim to collect preliminary opinions about the study topic from a selected shortlist of informed stakeholders and feedback on the questionnaire. These interviews were also useful to collect documentations and being advised on other people to be interviewed.

The potential participants to pilot interviews were selected in agreement with the STOA Panel through a purposive sampling method. In total, 13 persons on behalf of 10 different organisations take part in the pilot interviews. The interviewees were evenly distributed across the targeted stakeholder groups (see table 4 below).

3.1.1.2 Second round

After pilot interviews, a broader survey was launched. 124 candidates for interviews were identified according to several criteria, including international reputation and their position in key-organisations. Out of them, 51 accepted the interview and were interviewed. In the end, the responses of 43 interviewees (belonging to 38 different organisations) were considered complete enough to be analysed. It was not uncommon for the interviewee to be accompanied by a lawyer or a colleague who did not participate in the interview. In other cases, however, the opinions of the additional participant were recorded as well. They were instrumental if there were differences in the opinions as, according to Wilson et al. (2016), it allows for a deeper understanding of the subject's reasoning.

The interviewees were evenly distributed across the targeted stakeholder groups (see table 4).

Table 4 – Number of experts interviewed per stakeholder group

Stakeholder group	1 st ROUND (PILOT) Number of experts interviewed	2 nd ROUND Number of experts interviewed
Researchers, clinicians and research managers	3 (3)	14 (12)
Representatives of the pharmaceutical industry	2 (2)	8 (8)
Public health experts	3 (3)	11 (11)
European institutions and national and international organisations	5 (2)	10 (7)
TOTAL	13 (10)	43 (38)

Note : The number of organisations to whom the interviewees belong is indicated in bracket.

Source: authors

In total, 56 participants from 48 different organisations were included in the study.

3.1.2 Interview preparation

Upon showing interest to participate by replying to the invitation that was addressed to them, each interviewee was sent the interview guide, i.e., the questions that had to be asked during the interview. This allowed them to prepare their responses beforehand, which improved the overall flow of the interview session. The interview questionnaire was designed based on a preliminary review of the available literature and press, adjusted based on the comments received from our counterpart at STOA, and it was tested with pilot interviews. In addition, interviewees were informed that their replies would be recorded but remain anonymous in any reports and publications.

3.1.3 Timing and logistics of interviews

Most of the interviews were conducted via videoconference systems (Skype®, Zoom®, Teams® and Google Meet®) between January and May 2021. A small number of interviews were conducted in writing, always after a call to explain and discuss the objectives. To minimise bias as a result of interviewer variance, the principal investigator, Professor Massimo Florio was responsible for personally performing all the pilot interviews, with the assistance of at least one of the team members. The second round of interviews was carried out by Dr. David Anthony Procházka from the Prague University of Economics and Business.

The sessions were recorded using the software MP3 Skype Recorder or the Zoom Recorder function. However, in view of the protection of the participants' privacy, the interview recordings did not contain the interviewees' names. A back-up of the audio file was made and stored on a thumb drive after each interview to ensure no data would be lost. All files will be destroyed once the study will be concluded. All of this was mentioned during the interview so that the participants were aware of how their data would be handled.

3.1.4 Content of interviews

It was planned that all interviewees were asked the same questions in the same order to allow for comparisons and to minimise the risk of order effects bias. However, some questions had to be adapted to accommodate each individual stakeholder group. Moreover, depending on the answers that were provided by the participants, some additional questions may have been posed with the intent of further clarifying the interviewees' standpoints, while the interviewees in some cases declined to answer one or more question because they did not feel to be expert enough on the specific topic.

The interview guide is reported in Annex 1.

3.1.5 Ethical conduct

To sum up, the consultation followed the following conduct:

- 1 Potential interviewee were approached via an invitation email with enclosed the Letter of recommendation from STOA;
- 2 If the potential interviewee agreed to conduct the interview, the questionnaire was provided, and the date and hour of the meeting were set;
- 3 Stakeholders agreed with the recording for the transcription of the interview to be deleted after the analysis.
- 4 The interviewees were assured that:
 - a) Their name will not be mentioned anywhere within the study. It will be shared only with STOA and the principal investigator for the purposes of proper categorisation within the research.
 - b) The data will be immediately anonymised for the purpose of the analysis. After the analysis is performed, the anonymisation code will be deleted.
 - c) The data (recording, transcripts etc.) will be erased after analysis was performed.

3.1.6 Analysis of the data

In order to process the information collected from the interviews, a thematic analysis was used. Braun and Clark (2006) define thematic analysis as 'a method of identification, analyses and publication of patterns (topics) in the obtained data'. To this end, interview transcripts were analysed for capturing and examining common themes.

Bryman (2016) defines a code as a symbol or tag assigned to a section of text to classify or categorise it. Unique codes are assigned to relevant research questions, concepts, and topics across transcripts. The process of coding reduces large amounts of text into small meaningful parts which are simpler to read and understand. Being inductive analysis and not a linear process, the coding process requires going forward and backwards several times to find out what is relevant to a given category of stakeholders. Thanks to the use of codes, it was possible to organise information from different interviewees usefully and cross-examining it. When the data encoding was complete, the relevant topics were searched for across transcripts and combined again.

3.2 Results

The results of the survey are presented below across the main themes, which were explored during the interviews. The full questions can be found framed below each subheading. Collected answers have been presented in aggregate form to ensure anonymity. The results are referred to the overall consensus (see summary boxes) and to each stakeholder group, which as mentioned are:

- Researchers, clinicians and research managers;
- Representatives of the pharmaceutical industry;
- Public health experts;
- European institutions and national and international organisations.

When reporting the responses by groups, we report only the selected findings that qualify the overall view of the group, or dissenting views, without the need to repeat the overall consensus outlined in the summary box.

3.2.1 Pressing issues

Question 1. To what extent do you perceive as pressing issues the following?

- a) Misalignment between the R&D activity of the pharmaceutical industry and public health priorities;
- b) Inadequate returns to taxpayers against the public sector resources injected into pharmaceutical R&D activity;
- c) Access to and affordability of medicines.

Summary

- There was a strong majority consensus overall and within each of the four stakeholder groups that:
 - (a) misalignment between the R&D activity of the pharmaceutical industry and public health priorities, and
 - (c) access to and affordability of medicines
- are the two fundamental issues that need to be addressed by a new European pharmaceutical policy.
- In fact, the issue of misalignment of priorities was labelled as important or very important by all respondents regardless of the stakeholder's category, with only one dissenting view.
 - The issue of access and affordability of medicines, is perceived to be important or very important by most respondents, with limited dissenting views.
 - The issue of inadequate returns to taxpayers against the public sector resources injected into pharmaceutical R&D (issue (b) of the above-mentioned question), are viewed as important by all respondents. However, compared to the other two issues, it is perceived as less pressing in a policy perspective, with some different opinions across the stakeholders' group.

Researchers, clinicians and research managers

- Only one respondent answered that access to and affordability of medicines is irrelevant in the EU as access to most medicines is secured, meaning that everyone can obtain the medication they need within the EU. This is considered an outlier opinion, not supported by further evidence during the interviews.
- Two of the respondents stated that the taxpayers should not primarily consider the returns for injected resources but focus mainly (only) on the benefits it creates regardless of the costs.

Representatives of the pharmaceutical industry

- Most respondents revealed to be aware of the misalignment of priorities between the private and public actors in the pharmaceutical arena. This is a significant and, to a certain extent, unexpected finding as the literature review would have suggested a more defensive attitude.
- According to one respondent, the misalignment of priorities is more of a matter of fundamental science lagging behind rather the industry's lack of interest in certain areas. For instance, neurodegenerative diseases were mentioned as an example of a therapeutic area where there is a failure due to a lack of scientific knowledge. While this is an outlier opinion, to a certain extent, it is supported by structured reasoning about some fundamental gaps even in basic research.
- Some respondents mentioned the nature of the market and the nature of the goods to justify government funding of research and the level of return for the pharmaceutical industry.

- In regard to the affordability of medicines, one respondent stated that the pharmaceutical industry needs to charge different prices depending on the region of the world, i.e. higher prices in countries that can afford it, in order to tackle diseases worldwide. Another respondent pointed out that high price is also due to heavy regulations, especially within the EU market.

Public health experts

- According to several respondents, the COVID-19 pandemic has thoroughly exposed the problems due to misalignments of investment priorities. According to these experts, there was a lack of R&D investment on viral diseases by the industry, in spite of signals that there were pandemic risks at least after SARS-CoV-1.
- According to some respondents, the misalignment is embedded in the nature of how the system is currently shaped because the main objective of the pharmaceutical industry is to create value for its shareholders.
- While respondents overall agree that public priorities are not a guiding principle for the pharmaceutical industry, a number of them suggest that in some cases, there may be, to a certain extent, an alignment of interests in some fields. For instance, cancer R&D is a priority for European public health bodies, given the ageing population, and here there is an overlap between industry and public sector objectives, at least in terms of the scope of the R&D.
- Experts agree that there are therapeutical areas, for instance, rare diseases or paediatric medicines, which are neglected in terms of R&D because of a lack of expected profitability by the industry. There are hence no expectations that the industry will take a different course without funding or other incentives from governments.
- According to several respondents, the affordability issue is particularly relevant for products that benefit from orphan designation status. The latter was originally conceived to encourage R&D for rare diseases but now it is often used to create market exclusivity. The result is that orphan drugs are very expensive. At the other end of the scale, generic medicines are sometimes so cheap that there is no longer an incentive for the commercial sector to produce them (*'Too affordable to be sustainable from a private standpoint'*). This may create shortages and dependence on a single producer, typically based in China.

European institutions and national and international organisations

- Only one respondent stated that the misalignment of priorities is not an important issue. This was one individual's atypical opinion.
- According to some respondents, the public authorities can clearly see the health needs but they have often little bargaining power compared to the pharmaceutical industry to solve misalignments. To these respondents, there might be a need for more robust and dependable relationships for the pharmaceutical companies operating within the EU. Such relationships should offer stability for the pharmaceutical industry to invest in R&D aligned with the EU's public goals.

3.2.2 Creation of a new European public infrastructure for medicines

Question 3. Beyond an emergency mechanism, how would you comment on a possible concept of creating a European permanent public pharmaceutical R&D infrastructure (e.g., building on the models of CERN, EMBL, ESA, or the ERIC) in charge of R&D and the full pharma value chain in areas where the industry has a limited interest or where prices create affordability concerns?

Question 17. In your opinion, why has the EU not yet equipped itself with an independent infrastructure for research, development, and production of medicines?

- Little interest of the EU Member States;

- b) The mandate of the European institutions in the health sector is still too limited;
- c) Lack of real political interest at the EU Institutions so far;
- d) Resistance and opposition of Big Pharma;
- e) Much of production is delocalized, and a return to production in the EU seems unlikely;
- f) Other (specify).

Summary

- Generally, the overall concept is viewed as good, with many possibilities to bridge the gaps that the pharmaceutical industry cannot fill. Support is much stronger within all groups if the European permanent public infrastructure is focused mainly on antibiotics and orphan diseases and if the research does not go beyond the identified/agreed gaps. More profitable areas should be left to the private sector according to several respondents.
- There is also a broader consensus that little interest from the EU Member States and a lack of genuine political interest at EU institutions will be a formidable obstacle to overcome for the creation of such infrastructure. Most of the stakeholders also agree that the mandate of the European institutions in the health sector is currently too limited. Resistance and opposition from Big Pharma is viewed as less of a concern than the lack of support by EU institutions and Member States.
- Most respondents are aware of recent proposals from the EC about the reinforced role of EMA and ECDC as well as on the possible creation of HERA. That said, the majority of respondents see the benefit of having a new permanent, European public infrastructure for pharmaceutical research and development.

Researchers, clinicians and research managers

- Opinions are divided in this group. While few experts fully support the idea as it stands, the views of most 'Researchers, clinicians, research managers' range from pure scepticism about such infrastructure working if focused on drug development, to limited support. Such support is contingent upon the infrastructure focusing only on antibiotics and orphan diseases.
- There is mostly a consensus that the issue is that too much of the production is being delocalised, and that a return to production in the EU therefore seems unlikely. However, there are strong opposing views to that, stating that this point is not essential in order to set up an independent public biomedical infrastructure.

Representatives of the pharmaceutical industry

- Generally, the concept of a European infrastructure is seen as a good idea provided that (a) cooperation with the industry will be ensured; and (b) the new infrastructure will focus on areas that are not as profitable for the industry. Indeed, it would be beneficial for the industry to have a strong EU partner whom it can trust. This is an important finding of the survey that suggests that the industry may adopt a more favourable position if there is a partnership between public and private investment.
- Only one respondent within the group expressed dissent. According to him, if the new infrastructure will also focus on profitable pharmaceutical areas, this could create tension between the industry and the EU and move the operations away from the EU.

Public health experts

- Respondents support the concept mostly without any dissenting views.
- Some respondents pointed out that HERA and such a novel European permanent public pharmaceutical R&D infrastructure should coordinate their efforts somehow, given that both institutions are intended to build a robust value chain.

European institutions and national and international organisations.

- Respondents support the concept mostly without any dissenting views. This group believes such a novel European permanent infrastructure should focus on supporting the development of medicines and other health technologies to address public health priorities, especially in situations involving cross-border health threats. There should be strong stewardship by the public sector. It should aim to maximise public return on investment by ensuring that end products are widely available and affordable.
- The possible resistance and opposition from Big Pharma to creating such infrastructure is seen as a real issue within this group.

3.2.3 Priorities

Question 4. How would you list the priorities in a public health perspective for a European-sponsored pharmaceutical research agenda and infrastructure?

- a) Anti-microbial resistance
- b) Vaccines
- c) Antiviral drugs
- d) Neurodegenerative diseases
- e) Cancer
- f) Rare diseases and orphan drugs
- g) High quality and affordable generics
- h) Repositioning studies for existing drugs
- i) Research on disease control and prevention
- j) Collection and accessibility of digital health data
- k) Personalised medicines
- l) Others (please specify)

Summary

- Respondents agreed almost unanimously that the mission of the European infrastructure should focus on antimicrobial resistance and antiviral drugs (in particular, all respondents see an urgent and solid need for the proposed infrastructure to become involved in antimicrobial resistance drugs).
- Neurodegenerative diseases were the next most pressing concern, falling close behind the above mentioned priorities. There were primarily proponents across all the other topics, as well as opponents with mild or strong contrary opinions. For instance, many respondents believe that cancer R&D should be of paramount interest; however, several experts emphasise that drugs in this area are, and will be, profitable for the pharmaceutical industry; therefore, there is no need to set this as a priority for this infrastructure.
- The items that received the least amount of support were: high quality and affordable generics, and research on disease control and prevention. A higher number of respondents throughout all groups labelled these two items as less important than others or not important for the new infrastructure to tackle.
- Some respondents stressed that the mission should be defined by undertaking a detailed analysis of the European health research agenda, and a needs/opportunity analysis in each of the areas listed in the question. This would enable the mapping of gaps in each area.
- In regard to 'repositioning studies for existing drugs' and 'collection and accessibility of digital health data', many respondents have highlighted that these issues can readily cross and sit within different therapeutic areas. Therefore, these issues may require a different organisational structure if included in the mission.

Researchers, clinicians and research managers

- Many respondents in this group mentioned not only antimicrobial resistance but the priority of infectious diseases, in general.
- One respondent pointed out that medicines and devices for rare diseases should be clearly mentioned as part of the mission of the new infrastructure. They should not remain hidden under the umbrella of areas where the industry has a limited interest or where prices create affordability concerns.

Representatives of the pharmaceutical industry

- Generally, respondents support the concept of a European infrastructure if its mission is focused on antimicrobial resistance research. Indeed, according to many respondents in this group, the industry has high costs to develop new anti-microbial resistance drugs but nearly no possibility of getting them on the market.

Public health experts

- Most of the possibilities listed in the question are viewed as important priorities for the new European infrastructure. Only repositioning studies for existing drugs have lower support within the group and are not viewed as important.
- The strong view is that the EU needs to spend more on healthcare technology to be prepared for coming threats such as antimicrobial resistance.

European institutions and national and international organisations

- There is a broad consensus that a higher priority should be given to treatments for cross-border health threats.
- High quality and affordable generics, repositioning studies for existing drugs and research on disease control and prevention are perceived as important but not as much as the rest of the list.

3.2.4 Steps in the pharmaceutical life cycle

Question 5. In your opinion, in which steps of the pharma cycle should such infrastructure be involved in? Why?

- a) Digital Health & AI applications
- b) Basic research (Drug discovery)
- c) Pre-clinical development
- d) Development (Clinical trials: phase 1, phase 2, phase 3)
- e) Comparative studies of drug efficacy and cost-effectiveness
- f) Registration
- g) Production
- h) Distribution
- i) Postmarketing surveillance

Summary

- Opinions are more divided on this question than the previous ones. Interestingly, the differences are more between groups than within groups, as we will report below.
- All groups share a very large consensus on the need for a focus on clinical trials, but the range of opinions is wide, with support for the full cycle or for an extensive scope of the infrastructure in descending order from 'Public health experts', 'Researchers, clinicians and research managers', 'European institutions and national and international organisations', and 'Representatives of the pharmaceutical industry'.

Researchers, clinicians and research managers

- Respondents in this group tend to favour a focus of the infrastructure upon the first five steps. The last steps are considered part of the field that public infrastructure should not control, or where it is unrealistic to be held, only sponsored. The infrastructure could, however, provide funding possibilities.

Representatives of the pharmaceutical industry

- Respondents in this group tend to favour a focus upon the infrastructure on the most expensive part of clinical trials (phase 3).
- Some respondents pointed out the infrastructure should also support distribution activities during health crises.

Public health experts

- Most respondents support the idea that covering the whole value chain is the only reasonable way to proceed.
- However, a couple of experts stated that the scope of the infrastructure should also depend on the projects/products portfolio. For some products (e.g. antibiotics, vaccines, and to some extent antivirals), the infrastructure could take responsibility for the whole cycle. In these cases, the private sector could play a role through contracts in various phases, including clinical trials, production, and distribution.
- What is considered key for all experts is that the new infrastructure can steer and control the entire process – and ensure that products are made available in the market.

European institutions and national and international organisations

- Many respondents think there is already a lot of basic research at public universities and research centres, so this novel European infrastructure should prioritise other steps of the R&D process; most notably, clinical trials.
- For this group, the new infrastructure's involvement in post-marketing surveillance (in the form of independent studies) would be relevant. Conversely, involvement in digital health and AI applications are not viewed as essential due to different national frameworks within the EU

3.2.5 Data governance and impact of digitalisation in pharmaceutical sector

Question 6. The EC, through its Data Strategy, is considering alternatives to the Big Tech platforms. Do you think that the European public Biomed research infrastructure under study should play a role in the European Health Data Space (an independent e-infrastructure/cloud for collection, storage, management, and accessibility of health data)?

Question 7. Digital technologies, especially Algorithms, Big Data, and Artificial Intelligence (AI), are transforming the biopharmaceutical sector at every stage of the production chain. In which activities do you consider digital technologies of strategic importance?

- Research and pre-clinical development for new products / therapies
- Clinical trials
- Automation of production processes
- Distribution and logistics
- Monitoring of therapeutics adherence and adverse reactions
- E-health services
- Other (specify)

Summary

- There is a strong consensus between the groups that the new European infrastructure should play a role in the European Health Data Space (EHDP).
- Concerning question 7, most respondents believe that digital technologies are of strategic importance for all the listed activities and especially in the research and pre-clinical development process for new products/therapies. Using digital technologies in the automation of production processes, distribution and logistics, and e-health services were perceived as less important than other areas.

Researchers, clinicians, research managers

- According to this group, if the new European infrastructure will not play a role in the EHDS, this would imply a threat to the autonomy of the EU (the data should not be operated/stored by the Big Tech platforms).
- There was a mention of pharmacological surveillance as another area to focus AI power on.

Representatives of the pharmaceutical industry

- Most of the representatives slightly or strongly support the idea that the new infrastructure plays a role in EHDS. Only one representative was firmly against it, reasoning that following this strategy would most probably hinder the data supply to the pharmaceutical industry.
- The prospect of crunching big data, having the novel European infrastructure involved in the EHDS, and providing open data, could provide endless possibilities. In several parts of clinical trials, this could mean a breakthrough; however, the data from researchers will need to be shared with the industry, and this usually occurs with delays when the industry is not a partner in the research.

Public health experts

- Even when there is a belief that some digital applications or storage space might be subcontracted, an independent, basic infrastructure for health data should be part of the new European infrastructure. Data sharing plays a central role in the innovation process; therefore, the data should be fully accessible for the researchers, institutions and Member States. In some cases the data exists but it is on different servers, not connected, in some cases there might be even duplication of efforts to gather already existing data as it is not known it is available.
- According to this group, AI and big data are undoubtedly transforming the healthcare sector. They will play a critical role in research and product development, not necessarily as a deciding element but as a provider of new avenues for researchers and enhancing decision-making. For example, the horizon for new AI-assisted molecular combinations or hypothetical targets, is endless. Given the potential of the technology, the experts within this group think huge investments in pharma-applied AI (particularly in the context of the new infrastructure) are worthwhile. However, the ultimate decision on which activities to focus AI technology on should rest in the hands of the researchers (via collective and interdisciplinary decision-making).

European institutions, national and international organisations

- It was mentioned three times that the infrastructure should be part of the EHDS and the data should be open. However, no further explanation of the reasons was provided.

3.2.6 Legal framework and organisational model

Question 8. Which should be the legal framework applicable to such infrastructure? In your opinion, which legal basis would be more appropriate to allow for private participation? A non-exhaustive list of possible options is:

- a) An intergovernmental treaty leading to an international organisation such as CERN (European Organisation for Nuclear Research) and EMBL (European Molecular Biology Laboratory);
- b) A consortium under the legal framework of ERIC (European Research Infrastructure Consortium);
- c) A European decentralized agency such as the ECDC (European Centre for Disease Prevention and Control);
- d) A long-term public-private partnership in the form of Joint Technology Initiatives (JTIs).
- e) Other (please specify).

Question 9. Which should be the organisational model applicable to such infrastructure? Should it be a new hub of functionally integrated laboratories (like the CERN), or would a cluster of existing organisations (like the Biobanking and BioMolecular resources Research Infrastructure (BBMRI-ERIC) and the European Clinical Research Infrastructure Network (ECRIN)) with a specialized mission be preferable?

Summary

- In regard to the preferred legal model there is a slight consensus within the individual groups and a rather large divergence of opinion between groups. All in all, the overall majority is in favour of an agency.
- In regard to the organisational model, there is more of a convergence of opinions. There is an overall consensus between most respondents that the hub of functionally integrated laboratories should be the way to proceed. All respondents agree that there are already good institutions with specialised missions all around Europe. It is, therefore, important not to 'reinvent the wheel' and avoid duplication. To this end, the new infrastructure should have the power and instruments to fulfil its mandatory programs by leveraging existing organisations and commissioning third-party facilities.
- There is also agreement that the organisational model will depend on the ambition of the scope, political will, and the timing involved in setting up the infrastructure.

Researchers, clinicians and research managers

- For many respondents in this group, ERIC is the preferred model. The rationale for such support by the majority is that such model is widely proven and flexible. Those who support the ERIC model think that an intergovernmental treaty would delay the start of functioning of the new agency because the ratification process by the European Parliament and all Member States is relatively slow.
- However, a couple of respondents expressed strong opposition to ERIC, seeing it as ineffective, because of a lack of coherence in its mission statement and inadequate management or coordination.
- A possible alternative option mentioned by those who support the ERIC is a decentralised agency.
- An additional possibility mentioned by one respondent is to extend the mandate of the EMA to include the functioning of such new infrastructure; one that follows the organisational model of the European Central Bank and its Banking Supervision that, in cooperation with the national supervisors, is responsible for overseeing the European banks within the Single Supervisory Mechanism. This option appears, according to this expert, to be the fastest way

of establishing such an infrastructure; however, it could create some conflicts of interest between the EMA and the proposed infrastructure in the future.

- In regard to the organisational model, some respondents mentioned that the structure of the new European infrastructure should be scalable.

Representatives of the pharmaceutical industry

- Most respondents expressed a preference for a long-term public-private partnership in the form of Joint Technology Initiatives, as it is the proven way of cooperation between public and private sectors. Overall, this is a minority view among the respondents of all groups.

Public health experts

- The intergovernmental treaty is the preferred option for most respondents. They believe that intergovernmental organisations provide a stable and permanent foundation, which would allow for a clear policy, long-term planning, and the synchronisation of the various processes. Moreover, the budget of such an organisation is intended to be devised fairly (share of the GDP) and can be used at its sole discretion. Under this arrangement, the Member States are free to decide on their level of involvement. One example given is that of ESA, which has mandatory programs carried out under the General Budget and the Space Science program budget and optional programs. Intergovernmental organisations are provided with equal footing within the international arena (international legal personality), facilitating cooperation with non-members. On the other hand, there may still be some concern about sovereignty among the Member States, but this aspect could be appropriately dealt with when designing membership rules.

European institutions and national and international organisations

- The intergovernmental treaty leading to an international organisation such as CERN is preferred for most respondents.
- A possible alternative option mentioned by a few respondents is a decentralised agency such as the ECDC.
- In regard to the organisational model, only one respondent expressed a preference for a cluster of existing organisations (including stakeholders such as policy-makers, patients/consumers, healthcare providers, payers etc.) rather than a hub-based model.

3.2.7 Intellectual property

Question 10. What should be the intellectual property (IP) policy of such infrastructure? A non-exhaustive list of possible options is:

- a) Patent applications filed with European Patent Office and/or national patent offices by the infrastructure
- b) No patent at all
- c) Leave the patent applications to pharma companies in a joint venture agreement
- d) Alternative IP models for public health-oriented patents (specify)

Summary

- There is no overall consensus between the stakeholder groups on the IP policy of the infrastructure. Opinions are divided between groups but also with each group of experts.
- The majority of respondents are not in favour of patents held by the public infrastructure, but there are strong dissenting views claiming that patents managed in the public interest should be filed by the European infrastructure.

Researchers, clinicians and research managers

- The group tends to prefer not having patents filed by the European infrastructure. The underpinning idea is that the infrastructure should be of public benefit since it is likely to be funded by taxpayers' money. Thus, many respondents in this group believe it is crucial to ensure that the knowledge developed within such an infrastructure is not locked away and is available for further research.
- At the same time, some representatives of the group would instead be in favour of the new infrastructure applying for patents to protect its authorisation powers and to safeguard against the exploitation of outcomes of costly research.

Representatives of the pharmaceutical industry

- Some representatives of the group pointed out that in the case of a joint venture, or other ways of funding the infrastructure by the industry, the industry should hold the patents created.

Public health experts

- This group tends to support the direct application for patents by the new infrastructure. However, they stressed two important aspects: (1) the infrastructure should have a public commitment (maybe in a mission statement) in terms of the use of the IP; and (2) the infrastructure should have a degree of discretion over the use of its patents (i.e. conditions on the use of the patent). In other words, there should be a management of the IP within the infrastructure so that it serves the public interest (i.e. a public oriented IP strategy).
- The approach adopted by the Drugs for Neglected Diseases Initiative (DNDi) was mentioned as an illustrative example by more than one expert.

European institutions and national and international organisations.

- Similar to respondents in the first group ('Researchers, clinicians and research managers'), interviewees in this group favour a policy of avoiding the filing of patents over discoveries.

3.2.8 Clinical trials

Question 11. Currently, a large share of drug development costs is related to clinical trials, do you think a public infrastructure offering a platform for cross-border multi-center clinical trials could be effective in reducing such costs?

Question 12. Which of the following solutions would be preferable to do clinical trials? Why?

- a) A system of conventions with the public health systems;
- b) The externalisation of such activity to specialised service centres (CRO - Contract Research Organisations);
- c) Delegate trials to pharma companies (in a joint venture agreement);
- d) Other (Specify).

Summary

- The overall majority of the respondents agree that a European public infrastructure offering a platform for cross-border multicentre clinical trials in selected areas (see section 3.2.4) would effectively reduce drug development costs.
- To a certain extent, this consensus replicates the general indication that this is a step in the project cycle to be covered (see above) by a European infrastructure. However, opinions are divided and the respondents made several qualifications of support.
- The importance of having robust contracts in place and close supervision by the public sector over how trials are conducted was stressed by many representatives of all groups except the 'pharmaceutical industry'.

Researchers, clinicians and research managers;

- All in all, this group is less supportive than others with respect to question 11.
- Most respondents in this group support the solution of delegating trials to pharmaceutical companies, probably because this is the current system that they are more aware of and accustomed to.

Representatives of the pharmaceutical industry;

- For representatives of this group the main issue is that the new infrastructure should not take care of all phases of clinical trials in bulk. According to all of them, clinical trials should be delegated to pharmaceutical companies via joint venture agreements. Phase 3 would probably have the highest chance of being accepted by the industry as part of the mission of the new infrastructure. However, they think the infrastructure should not act through a platform but as a co-funder allowing the industry to test in the public interest.
- According to most respondents in these groups, the pharmaceutical industry has the capacities and a well-established network of contacts with the public health systems. Therefore, delegating clinical trials to them would be the most efficient solution. Creating a system of conventions with the public health systems was also mentioned as a possibility to be combined with the delegation of trials to pharmaceutical companies.

Public health experts

- The respondents of this group generally agree that a European public infrastructure would effectively reduce drug development costs.
- However, no preferences with respect to question 12 were expressed.

European institutions and national and international organisations.

- This group would choose to follow a system of conventions with the public health systems.
- Alternatively, the externalisation of clinical trials to Contract Research Organisations was mentioned by many.

3.2.9 Manufacturing and distribution

Question 13. In your opinion, which type of arrangements could be adopted for the production of drugs and why?

- a) Licenses to industrial partners;
- b) Owned or rented industrial plants;
- c) Agreements with CDMO (Contract Development and Manufacturing Organisations);
- d) Other (please specify).

Question 14. In your opinion, which type of arrangements could be adopted for the distribution of medicines and why?

- a) Logistics distribution network through the postal operators;
- b) Logistics distribution network through tenders open to specialised private firms;
- c) Other (please specify).

Summary

- Licenses to industrial partners are a preferred solution for most respondents in all stakeholder groups. Owned or rented industrial plants is a possible option to all stakeholders; however, there are many reservations about the implementation and costs of this option. Agreements with CDMO are seen as beneficial to attain more production flexibility. Ownership was more widely criticised for inefficiency and costs.
- Concerning distribution arrangements, there is a strong consensus that the most important factor is the reliability of the distributor, regardless of what kind of operator it is. At the moment, distribution is an aspect that has a robust national angle. Moreover, within the EU, distribution chains (and their reliability) differ from state to state. Therefore, the Member States should be part of the processes of mapping and offering solutions. Others generally mentioned the importance of relying on reliable distributors, regardless of their nature (e.g. specialised private firms or postal operators).

Researchers, clinicians and research managers

- According to most respondents, granting licenses to industrial partners is the preferred solution because it could also serve to foster European industrial partners and contribute to the re-industrialisation policy of the EU.
- Concerning distribution, there was a voice against postal operators where the distribution of prescription drugs is concerned, but no objections in principle by other respondents.

Representatives of the pharmaceutical industry

- In regard to production, the status quo is preferred as it is functional.
- Some respondents mentioned that distribution arrangements should be left to the producers (if they are multinational companies, they often have their distribution channels). Others generally mentioned the importance of relying on reliable distributors, regardless of their nature (e.g. specialised private firms or postal operators).

Public health experts

- There is a broad consensus within this group about the adoption by the public infrastructure of a mixed approach: granting of licenses to industrial partners and renting industrial plants for the production of drugs. Functionally integrated production facilities could be at the core (already existing or newly created manufacturing sites). Still, industrial partners could also be outside of the official network, as long as the latter complies with good manufacturing practice.
- In the case of production being licensed to industrial partners or CDMOs, many respondents of this groups stressed that the new infrastructure should retain control over quality, data protection, scheduling, cost, and accountability to avoid pitfalls (e.g., capacity shortages, demand outpacing supply over 16 months).

- In regard to distribution, the respondents generally think that, as long as the distributor complies with the EMA's assessed good distribution practice (GDP), it does not matter what type of operator is carrying out the task.
- According to the EMA's harmonising principles, the new European infrastructure should work out a delivery system for emergencies (similar to the National USPS Medical Countermeasure dispensing model proposed by Obama's administration). As the Covid-19 crisis hit, EMA and other partners struggled with ad hoc measurements (such as the creation in May 2020 of the EU Executive Steering Group on Shortages of Medicines Caused by Major Events). As a result of the absence of a proper emergency infrastructure able to deal with the severe logistic challenges arising from the constraints in the supply chain.

European institutions and national and international organisations

- To this stakeholder group, all three possibilities envisaged for the production of drugs have a good chance of succeeding.
- A key question for respondents of this group is who becomes the 'market authorisation holder'. If the idea is to develop products and then engage various companies (so there is a competition present) to market them, then issuing licenses to industrial partners might be the best option. On the other hand, if the plan is that the new infrastructure markets the products, then rented plants or agreements with CDMO would be preferable. It could also depend on the product; various models could be considered following an impact assessment on the multiple options.
- In regard to distribution, the group has no strong views on the options proposed. The only shared idea is that the Member States should be highly involved in the decision.

3.2.10 Financing

Question 16. In your opinion, which is the appropriate mix to finance the infrastructure?

- a) Equity or initial endowment provided by founding parties;
- b) Annual transfers from the budget of Member States (with multi-year commitments to ensure stability);
- c) Transfers from the Multiannual Financial Framework of the European Union as it happens for all EU decentralized agencies;
- d) Revenues deriving from production licenses of the new drugs to national health systems;
- e) Loans from European Investment Bank or other financial institutions;
- f) Contributions from pharma companies similar to those paid to regulatory agencies;
- g) Other (please specify).

Summary

- There is no consensus within stakeholder groups or between stakeholder groups on the most appropriate mix to finance the infrastructure. There is no clear favourite choice, each option according to the experts has pros and cons, but there are some shared views on certain options.
- Everyone seems to agree that the new infrastructure should be a permanent investment; therefore, it needs stable finances. Otherwise, it will not have a real chance to succeed. The key message is: a European infrastructure for medicines would be a costly intervention but it would be in the long-term interest of next generations of EU citizens as it will ensure the production of innovative and affordable products that ensure protection from health threats and savings for the public health systems. Therefore, it requires a long-term commitment from both the EU institutions and the MS.

- Annual transfers from the budget of Member States with a multi-year commitment was often mentioned as the best option; however, this option alone is considered unstable and would most probably cause the infrastructure to be out of funding soon due to delayed payments or policy changes at national level.
- Transfers from the Multiannual Financial Framework of the European Union as it happens for the EU decentralised agencies were also mentioned more often than other possibilities, however, with no clear preference within groups or between groups of stakeholders.
- Equity or initial endowment provided by founding parties, loans from the European Investment Bank or other financial institutions, and contributions from pharma companies (if they are part of the joint venture) have been also mentioned by some respondents as part of the hypothetical financing mix.

Researchers, clinicians and research managers

- There is no consensus within the group. Transfers from the Multiannual Financial Framework of the European Union, which happens for all EU decentralised agencies, were often mentioned as the first choice of the mix; however, this option alone is considered insufficient.

Representatives of the pharmaceutical industry

- There is no consensus within the groups. Contributions from pharmaceutical companies have been mentioned by some respondents as part of the hypothetical financing mix if they are part of some projects via joint ventures.
- The question was often regarded as a decision that policy-makers need to take.

Public health experts

- The sentiment within the group is that it would be wise to avoid linking financing of the infrastructure to only one type of funding.

European institutions and national and international organisations.

- Any mix seems to be possible to the group as a whole without having a clear favourite choice.

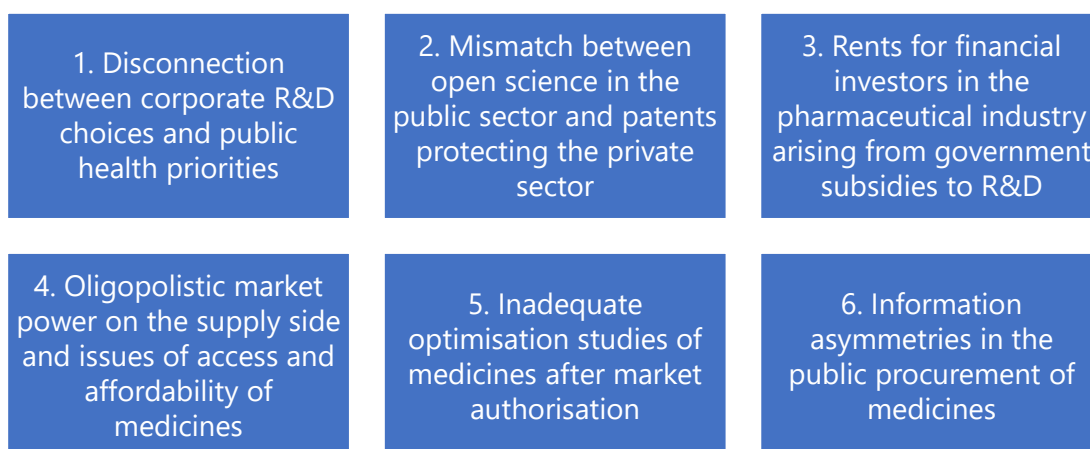
4 Discussion: The concept of a European R&D infrastructure for medicines

The previous sections of this report have identified some failures in the pharmaceutical supply and demand mechanisms, based on both the literature review and the findings from the survey to experts of four different stakeholders' groups. 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 concept of a large scale and long-term European research, development, innovation infrastructure for medicines; subsequently we discuss intellectual property rights models for such new entity, and -more briefly- selected implementations issues (legal base, organisation, funding). The section is concluded with some social cost-benefit analysis considerations.

4.1 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 we have interviewed for this study, 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.

4.1.1 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 well-beings, 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 pharmaceutical 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.

4.1.2 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 the 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 institutes 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 at 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 for 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.

4.1.3 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 the 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 pharmaceutical 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 US\$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.

4.1.4 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 €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 maximizer, play a role in the arena.

4.1.5 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.

4.1.6 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, 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.

4.2 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 acknowledgment 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, EATRIS, ECRIN 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.

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.

4.2.1 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.

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>

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 paediatric 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 to experts concur 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 subject¹. 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 €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

Source : authors based on OECD (2019a)

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 pharmaceutical 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.

4.2.2 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 euro per quality adjusted life years gained, or similar cost-effectiveness metrics).

Academic research is also quite often scarcely interested to 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, or 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.

4.2.3 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. According to the survey results, 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.

4.2.4 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 optimisations 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 an 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.

4.3 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 the 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.

4.3.1 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 than 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 strengthen 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)).

4.3.2 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 the participation to 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 Vruhe & Crommelin, 2017).

The number of partnerships has been dramatically increasing (Lim, 2014) (de Vruhe & 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.

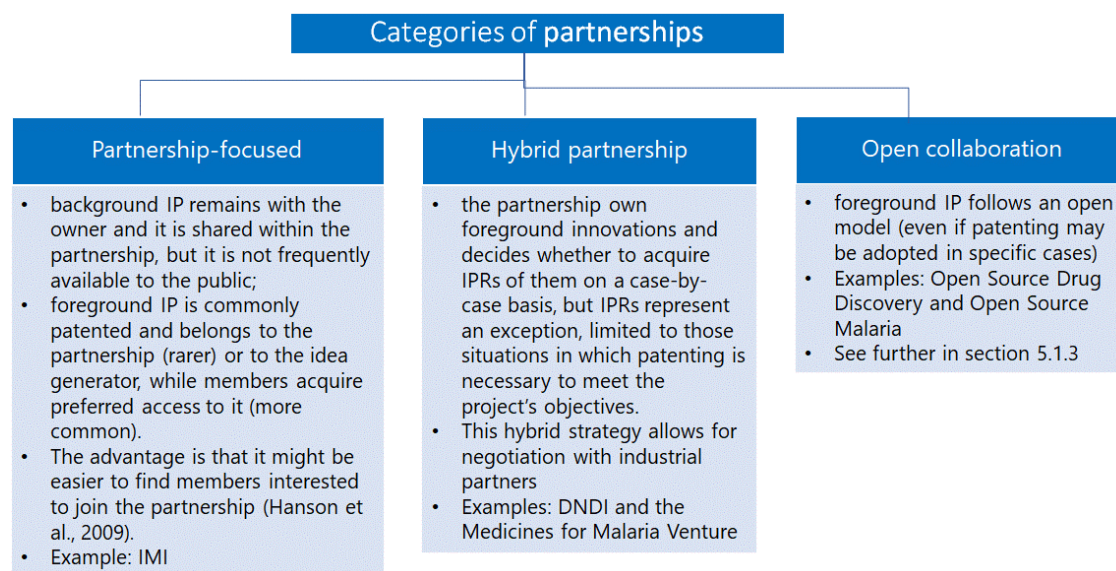
When partners share their IP assets ('background' (Innovative Medicines Initiative, 2007)), and in particular patents, with an access-oriented organisation, they are required to manage them in a way that does not impede equitable and affordable access to the products of the research project ('foreground' (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 voluntarily grants multiple manufacturers permission to develop and manufacture generic versions of the drug, granting the production of cheaper drugs under access-friendly terms (see examples 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.

Non-exclusive voluntary licenses may be granted directly to manufacturers, through bilateral

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

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 US\$2.3 billion, with an estimated cost-benefit ratio of 1:43 (Juneja et al., 2017). Moreover, the pool had 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).

4.3.3 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 from 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.

4.4 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.

4.4.1 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 5 – Legal forms

Giurisdiction	Model
National law	<ul style="list-style-type: none"> ➤ Company model. Some examples: ➤ French 'Société civile' for the European Synchrotron Radiation Facility (ESRF) ➤ 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	<ul style="list-style-type: none"> ➤ International / intergovernmental organisation. Examples: CERN, EMBL, ESO, ESA.
EU Community law	<ul style="list-style-type: none"> ➤ 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 pharmaceutical companies, CROs, CDMOs, or suppliers of technologies and products.

Table 6 – Legal basis models

Option	Advantage	Disadvantage
#1 Company	<ul style="list-style-type: none"> • 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; avoid also high costs of intergovernmental institutes. • Flexibility in terms of partnership (public, private, European, non-European) and staff policy • Adapted to industrial use 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 co-operation with non-EU states. 	<ul style="list-style-type: none"> • Heavy and lengthy negotiation procedures for reaching a formal agreement between Member States • Difficulty to modify / amend such agreements • Private actors cannot be part of an international treaty
#3 ERIC	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Closely connected to EU institutions. • May have the powers to adopt binding decisions. 	<ul style="list-style-type: none"> • The creation needs legislative measures at EU level • Not used to manage and deliver research activities directly

Source: authors

4.4.2 Organisational structure

In principle, different organisational options could be adopted for research infrastructures, as suggested by the extant literature (Hollosten, 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 the 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 7 – Organisational models

Model	Definition	Advantages	Disadvantages
New single-sited infrastructure	<ul style="list-style-type: none"> 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). 	<ul style="list-style-type: none"> Easier to be managed since it is located in a specific geographical location and it has exclusive facilities. 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> 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). 	<ul style="list-style-type: none"> 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.

		<ul style="list-style-type: none"> • 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. 	
Virtual/digital network of existing organisations	<ul style="list-style-type: none"> • This model takes inspiration from the idea of virtual – or digital – 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. 	<ul style="list-style-type: none"> • They generally connect 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 	<ul style="list-style-type: none"> • The main difference with the hub model is that in this kind of option, the research institutes 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

4.4.3 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 billions. 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 US\$4 billion per year (equalling about €3.5 billion). To set an upper bound, it is possible to take as a reference the ESA budget for 2021 that amounts to €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 euro 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, €3.5 billion is a downside estimate compared with the 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 US\$10 billion. Then, funding was increased to about US\$18 billion by October 2020 (Lancet Commission on COVID-19 Vaccines and Therapeutics Task Force Members, 2021; Baker and Koons, 2020). This was around US\$54 per capita in just one year.

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

Table 8 – Funding sources

	Topic(s) <i>f</i>
Contribution from members	<ul style="list-style-type: none"> ➤ 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	<ul style="list-style-type: none"> ➤ 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	<ul style="list-style-type: none"> ➤ 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	<ul style="list-style-type: none"> ➤ 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	<ul style="list-style-type: none"> ➤ 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 primarily 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.

4.4.4 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 of 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 9 – Cost of past epidemics

Event	Loss	Source
2003 SARS epidemic	Over US\$40 billion	Lee J-W, McKibbin WJ. (2004).
2014-2016 West Africa Ebola	US\$53 billion	Fan et al. (2015). Huber et al. (2018).
2009 H1N1 influenza pandemic	US\$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	US\$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 downward wrong. 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 in their website where it stated that COVID-19 could cost the global economy US\$4.1 trillion, or almost 5% of global GDP. 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 US\$46 trillion over a 10-year window). A comprehensive calculation of the economic cost of the pandemic cannot ignore the value of excess

in deaths caused by the pandemic (i.e., the human cost)². However, for the sake of simplicity, let us ignore the economic value of the avoided deaths and let us focus on avoided GDP loss. Let us conservatively set the expected economic loss³ 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 euro, 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 an 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.

² 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.

³ 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%.

5 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 Europe-wide 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 an R&D infrastructure for medicines should have at least an EU-wide scale of operations.

Before discussing of 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 10 – Comparative overview

	European Medicines Infrastructure	HERA
Mission & tasks	<ul style="list-style-type: none"> ➤ 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 the innovative drugs developed are eventually rolled out and made available to national health systems; ➤ Ensuring effectiveness, safety and efficiency of selected medicines through optimisations studies; ➤ Ensuring safety and affordability of selected generics when needed. 	<p>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:</p> <ul style="list-style-type: none"> ➤ 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	<ul style="list-style-type: none"> ➤ €4 billion per year for 30 years. ➤ As a reference: The annual budget of the Intramural Research Program of NIH is around US\$4 billion per year. 	<ul style="list-style-type: none"> ➤ €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 €24 billion; ➤ 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	<ul style="list-style-type: none"> ➤ All potentially interested European countries, including for example Norway, the UK and Switzerland; ➤ The role of different countries depends on the legal model adopted. 	<ul style="list-style-type: none"> ➤ HERA is established within the European Commission as a shared resource for Member States and EU alike.

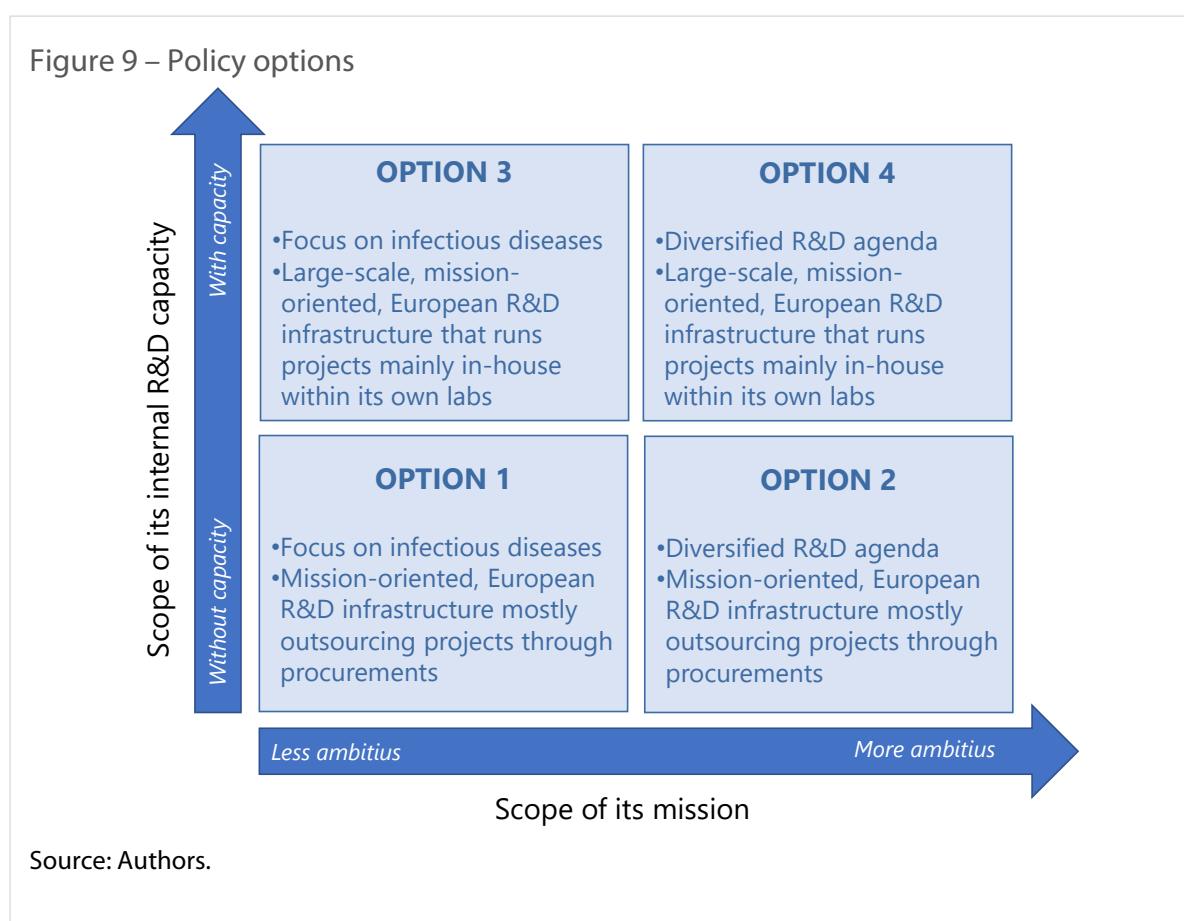
Source: authors based on the EC Decision C(2021) 6712 final and the EC Communication COM(2021) 576 final.

Two dimensions define the policy options in relation to the European Medicines Infrastructure: the scope of its mission on one side, and the internal R&D capacity on the other side. The set of options arising by the combination of such dimensions 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).



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 far as the proposal put forward in COM(2021) 576 final is concerned, 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 authorisation and delivery. In fact, HERA will not have the critical mass in terms of budget, own research capacity and scientific personnel to structurally shift pharmaceutical companies' R&D choices towards public health priorities, apart from a limited intervention area related to possible emergencies. In this scenario, the prioritisation and allocation of EU funds for pharmaceutical R&D will continue to follow a 'grant'-based approach, which risks to disperse funds towards a myriad of relatively small projects, and risks the capture of EU funds by existing organisations and 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, of 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 addressing 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 sector is 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 portfolio 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 the public and the private sector are under-investing such as, again, vaccines and medicines for infectious diseases, but also, for example, medicines related to neurodegenerative 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 portfolio 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 a 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 (National Institute of Allergy and Infectious Diseases), the new organisation, while it might also work through procurement contracts with third parties (as for Options 1 and 2), would have considerable own 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 authorisation.

Advantages:

- Creates a long- term portfolio 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;
- Owns the results of the R&D projects it carries out, either fully or in specific cases with public-private partnerships, and manages 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 Medicines Infrastructure but with a focus on a wider R&D agenda.

The business model created within this option is the same as to 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 diagnostics 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 of cancer or of neurodegenerative diseases are not completely different from therapies or vaccines of 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 pharmaceutical industry in terms of possible partnership on specific projects.

Advantages:

- Creates an own long-term portfolio 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 manages 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 large-scale research infrastructures such as the NIH Intramural Research Program and ESA, just to give a very rough and tentative indication of the different options' cost and outcomes. 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 €3.5 billion. Instead, the annual budget for the more ambitious Options 3 and 4 could be set equal to that of ESA for 2021, amounting to nearly €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 €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 a mission-specific additional budgets supported by different coalitions of governments as in the current functioning of ESA.

6 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 and a survey of experts. 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 pharmaceutical 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 Medicines Infrastructure 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 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 pharmaceutical companies' and other players' R&D choices towards public health priorities apart from 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.

7 Annexes

Annex I – Interview guide

1. TO WHAT EXTENT DO YOU PERCEIVE AS PRESSING ISSUES THE FOLLOWING?

	Very important	Fairly important	Important	Slightly important	Not at all important
a. Misalignment between the R&D activity of the pharma industry and public health priorities					
b. Inadequate returns to taxpayers against the public sector resources injected into pharmaceutical R&D activity					
c. Access to and affordability of medicines					

2. In response to the Coronavirus pandemic, the EC has proposed: A reinforced role for the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC).
 a. To set up HERA, an EU Health Emergency Preparedness and Response Authority.

Moreover, the European Parliament has commissioned the present study to investigate the possibility of creating a European permanent public biomed research infrastructure (e.g. building on the models of CERN - European Organisation for Nuclear Research, EMBL - European Molecular Biology Laboratory, ESA - European Space Agency, or the ERIC - The European Research Infrastructure Consortium framework⁴) in charge of R&D and the full pharma value chain in areas where the industry has a limited interest or where prices create affordability concerns. **HOW WOULD YOU COMMENT ON THESE PROPOSALS?**

Let's suppose that such infrastructure with an appropriate budget should be realised (For comparison: the US Biomedical Advanced Research and Development Authority (BARDA) yearly budget is US\$1.6 billion, the US National Institutes of Health (NIH) 2020 budget for intra-mural research is about US\$8.3 billion out of a total budget of US\$41.7 billion, the H2020 overall allocation for 'Health, demographic change & well-being' was about €7.5 billion for the period 2014-20). Could you please discuss the following topics:

3. **MISSION:** How would you list the priorities in a public health perspective for a European sponsored biomed research agenda and infrastructure?

	Very important	Fairly important	Important	Slightly important	Not at all important
a. Anti-microbial resistance					
b. Vaccines					
c. Antiviral drugs					
d. Neurodegenerative diseases					
e. Cancer					

⁴ The European Research Infrastructure Consortium is a specific legal form that facilitates the establishment and operation of Research Infrastructures with European interest. The ERIC allows the establishment and operation of new or existing Research Infrastructures on a non-economic basis.

	Very important	Fairly important	Important	Slightly important	Not at all important
f. Rare diseases and orphan drugs					
g. High quality and affordable generics					
h. Repositioning studies for existing drugs					
i. Research on disease control and prevention					
j. Collection and accessibility of digital health data					
k. Personalised medicines					
l. Others (please specify)					

4. **INVOLVEMENT IN THE LIFECYCLE OF PHARMACEUTICAL PRODUCTS:** In your opinion, in which steps of the pharma cycle should such infrastructure be involved? Could you please comment on the 2 answers with the highest score and with the lowest score?

	Strongly agree	Agree	Neither agree or disagree	2- Disagree	1- Strongly disagree
a. Digital Health & AI applications					
b. Basic research (Drug discovery)					
c. Pre-clinical development					
d. Development (Clinical trials: phase 1, phase 2, phase 3)					
e. Comparative studies of drug efficacy and cost-effectiveness					
f. Marketing Authorisation					
g. Production					
h. Distribution					
i. Post marketing surveillance					

5. **DATA GOVERNANCE: The EC through its Data Strategy⁵** is considering alternatives to cloud services offered by the Big Tech platforms. Do you think that the European public biomed research infrastructure under study should play a role in the European Health Data Space⁶ (an independent e-infrastructure/cloud for collection, storage, management, and accessibility of health data)?

⁵ https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age/european-data-strategy_en

⁶ The creation of a European Data Space is one of the priorities of the Commission 2019-2025, including the health sector. A common European Health Data Space will promote better exchange and access to different types of health data (electronic health records, genomics data, data from patient registries etc.), not only to support healthcare

6. **THE IMPACT OF DIGITALISATION IN PHARMA SECTOR:** Digital technologies, especially Algorithms, Big Data and Artificial Intelligence, are transforming the biopharmaceutical sector at every stage of the production chain. In which activities do you consider digital technologies of strategic importance?

	Very important	Fairly important	Important	Slightly important	Not at all important
a. Research and pre-clinical development for new products/therapies					
b. Clinic trials					
c. Automation of production processes					
d. Distribution and logistics					
e. Monitoring of therapeutics adherence and adverse reactions					
f. E-health services					
g. Other (specify)					

7. **LEGAL BASIS:** Which should be the legal framework applicable to such infrastructure? In your opinion, which legal basis would be more appropriate to allow for private participation? A non-exhaustive list of possible options is:

- a. An intergovernmental treaty leading to an international organisation such as CERN (European Organisation for Nuclear Research) and EMBL (European Molecular Biology Laboratory). Main features:
 - An international organisation is a legal entity with international legal personality under international law (i.e., it is a subject of international law)
 - A party of an international treaty can be a state, a state agency or an intergovernmental organisation. International organisations or any other subject of international law can conclude international agreements according to their founding treaty and in the case of the EU this is now codified by Article 47 TEU.
 - The making of a treaty is subjected to the Vienna Convention on the Law of Treaties (1969).
- b. A consortium under the legal framework of ERIC (European Research Infrastructure Consortium). Main features:
 - An ERIC is a legal entity with legal personality and full legal capacity recognised in all EU Member States. ERIC can be set up only for high-profile research infrastructures with a European dimension.
 - An ERIC shall pursue its principal tasks on a non-economic basis. However, it may carry out limited economic activities closely related to its task, provided that they are closely related to its principal task and that they do not jeopardise the achievement thereof.
 - ERIC members can only be states and intergovernmental organisations
 - An ERIC is recognised by the country hosting its seat as an international body or organisation for the directives on value added tax (VAT), excise duties, and public procurement;
- c. A European decentralised agency such as the ECDC (European Centre for Disease Prevention and Control). Main features;
 - A decentralised agency has its own legal personality and a certain degree of administrative and financial autonomy and have clearly specified tasks.
 - Presently, there is no general legal basis to create EU agencies. The current prevailing view is that EU agencies may be created on the relevant Treaty article that provides the legal basis in a specific policy

delivery (so-called primary use of data) but also for health research and health policy making purposes (so-called secondary use of data). See: https://ec.europa.eu/health/ehealth/dataspace_en

- area. The creation of agencies needs to have a legal basis that is suitable for those purposes, whilst also powers conferred upon these agencies by the EU legislator are limited.
- EU agencies are subjected to ex-ante and ex-post accountability mechanisms established by the Common Approach (2012).
 - Agencies are subjected to budgetary discharge by the European Parliament except if they are fully self-financed.
- d. A long-term public-private partnership in the form of Joint Technology Initiatives (JTIs). Main features:
- JTIs support co-operative research across Europe in fields of key importance for industrial research, where there are clearly identified common technological and economic objectives.
 - JTIs are established on the basis of Article 187 of TFEU which allows the Commission to set up Joint Undertakings for 'the efficient execution of Community research, technological development and demonstration programmes'. These Joint Undertakings can be implemented via a Council Regulation in agreement with Member States.
 - The parties of a JTIs include the EC, not-for-profit industry-led associations and, in some cases, Member/associated States.
 - 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 research projects' total cost.
- e. Other (please specify)
8. **ORGANISATION:** Which should be the organisational model applicable to such infrastructure? Should it be a new hub (campus) of functionally integrated laboratories (like the CERN) or would a cluster of existing organisations (like the Biobanking and BioMolecular resources Research Infrastructure (BBMRI-ERIC) and the European Clinical Research Infrastructure Network (ECRIN)) with a specialised mission be preferable?
9. **INTELLECTUAL PROPERTY (IP):** What should be the IP policy of such infrastructure? A non-exhaustive list of possible options is:
- a. Patent applications filed with European Patent Office and/or national patent offices by the infrastructure
 - b. No patent at all
 - c. Leave the patent applications to pharma companies in a joint venture agreement
 - d. Alternative IP models for public health-oriented patents. (Specify)
10. **CLINICAL TRIALS:** If you agreed in question 4 that such infrastructure should be involved in the clinical trials, which of the following solutions would be preferable? Why?
- a. A system of conventions with the public health systems;
 - b. The externalisation of such activity to specialised service centres (CRO - Contract Research Organisations);
 - c. Delegate trials to pharma companies (in a joint venture agreement);
 - d. Other (Specify).
11. **MANUFACTURING:** In your opinion, which type of arrangements (see list below) could be adopted for the production of drugs and why?
- a. Licences to industrial partners;
 - b. Owned or rented industrial plants;
 - c. Agreements with CDMO (Contract Development and Manufacturing Organisations);
 - d. Other (please specify).
12. **DISTRIBUTION:** In your opinion, which type of arrangements (see list below) could be adopted for the distribution of medicines and why?
- a. Logistics distribution network through the postal operators;
 - b. Logistics distribution network through tenders open to specialised private firms;

c. Other (please specify).

13. **FINANCING:** In your opinion, which is the appropriate mix to finance the infrastructure?

- a. Equity or initial endowment provided by founding parties;
- b. Annual transfers from the budget of Member States,
- c. Multi-year transfer commitment from Member States to ensure stability;
- d. Transfers from the Multiannual Financial Framework (7 years) of the EU as it happens for all EU decentralised agencies.⁷
- e. Revenues deriving from production licences of the new drugs to national health systems;
- f. Loans from European Investment Bank or other financial institutions;
- g. Contributions from Pharma companies similar to those paid to regulatory agencies;
- h. Other (please specify).

14. **POSSIBLE CRITICISMS:** In your opinion, why has the EU not yet equipped itself with an independent infrastructure for research, development and production of medicines?

	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
a. Little interest of the EU member states					
b. The mandate of the European institutions in the health sector is still too limited					
c. Lack of real political interest at the EU Institutions so far					
d. Resistance and opposition of Big Pharma					
e. Much of production is delocalized and a return to production in the EU seems unlikely					
f. Other (specify)					

15. **Do you have some personal recommendations** that the European Parliament and the EU institutions in general should consider to enhance biomedical research from a public health policy perspective?

⁷ In the vast majority of cases, agencies have at least one other source of financing in addition to the Union's budget.

Annex II – Work strands of the new pharmaceutical strategy for Europe

Table 11 – Work strands of the new pharmaceutical strategy for Europe

Work strand	Specific objectives	Needs analysis	Flagship initiative(s)
Delivering for patients: fulfilling unmet medical needs and ensuring accessibility and affordability of medicines	Prioritising unmet medical needs	<p>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.⁸</p> <p>Lack of development of new antimicrobials, treatments or vaccines for emerging health threats⁹</p>	<p>Flagship initiatives on unmet needs</p> <ul style="list-style-type: none"> ➤ 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. <p>Flagship initiatives related to antimicrobial resistance</p> <ul style="list-style-type: none"> ➤ 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	<p>Patients' access to medicines is affected by the fact that companies are not obliged to market a medicine in all EU countries; for various reasons¹⁰ they may decide not to market their</p>	<p>Flagship initiatives on access to medicines</p> <ul style="list-style-type: none"> ➤ 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.

⁸ 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.

⁹ 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).

¹⁰ 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.

		medicines in, or withdraw them from, one or more countries.	<ul style="list-style-type: none"> ➤ 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	<p>There is a lack of transparency (in particular in R&D costs) and consensus on costing principles.</p> <p>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 spending¹¹</p>	<p>Flagship initiatives on affordability</p> <ul style="list-style-type: none"> ➤ 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	<p>Established businesses are increasingly outsourcing functions and are focusing investment on a limited number of therapeutic areas, while disinvesting from others.</p> <p>There are differences in the application of patents and supplementary protection certificates in Member States.</p> <p>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 health data from across the EU would be a real multiplier in terms of research, regulation and evidence generation.</p>	<p>Flagship initiatives on competitiveness</p> <ul style="list-style-type: none"> ➤ 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 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	<p>'Bedside' manufacture of more individualised medicines could be a future trend.</p> <p>Innovative approaches to the development, approval and post-authorisation monitoring</p>	<p>Flagship initiatives on innovation</p> <ul style="list-style-type: none"> ➤ Propose to revise the pharmaceutical legislation, to adapt to cutting-edge products, scientific developments and technological transformation and provide tailored incentives for innovation – 2022.

¹¹ European Commission, State of health in the EU: companion report 2019 (ISBN 978-92-76-10194-9)

		<p>of vaccines and repurposing of medicines are needed.</p> <p>Medicines, medical technologies and digital health are becoming increasingly integral to overarching therapeutic options</p>	<ul style="list-style-type: none"> ➤ 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 take forward the use of high performance computing and artificial intelligence in combination with EU health data for pharmaceutical innovation – 2021-2022. ➤ Establish the 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	<p>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.</p>	<p>Flagship initiatives on regulatory efficiency</p> <ul style="list-style-type: none"> ➤ 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 sustainable pharmaceuticals; crisis preparedness and response mechanisms	Secure the supply of medicines across the EU and avoid shortages	<p>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 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.¹²</p>	<p>Flagship initiatives on open strategic autonomy</p> <ul style="list-style-type: none"> ➤ Propose to revise the pharmaceutical legislation to enhance 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 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.

¹² 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).

			<ul style="list-style-type: none"> ➤ 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	<p>The recent experience with the presence of nitrosamines impurities in some medicines¹³ has highlighted the importance of a sound system for detecting quality problems and of compliance management.</p> <p>There is still a lot of waste from unused medicines.</p>	<p>Flagship initiatives on quality and environmental sustainability</p> <ul style="list-style-type: none"> ➤ Propose to revise the manufacturing and supply provisions in the pharmaceutical legislation to improve the 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	<p>The nature and speed of the response to COVID-19 nevertheless illustrates 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</p>	<p>Flagship initiative on Europe's health crisis response mechanisms</p> <ul style="list-style-type: none"> ➤ Proposal for an EU Health Emergency Response Authority – 2021.
Ensuring a strong EU voice globally	/	<p>The pharmaceuticals sector is economically strategic for the EU in terms of global trade.</p>	<p>Flagship initiative on international cooperation</p> <ul style="list-style-type: none"> ➤ 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

¹³ <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities>

Annex III – Key info of ESFRI health RI

Table 12 – 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 ¹⁴	Distributed; ERIC	It is the world 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 ¹⁵	BBMRI ERIC Graz (AT)	2014	CAPEX: 195 OPEX: 3.5/y
EATRIS European Research Infrastructure for Translational Medicine ¹⁶	Distributed; ERIC	Provides a 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 ¹⁷	EATRIS ERIC Amsterdam (NL)	2013	CAPEX: 500 OPEX: 2.5/y
ECRIN European Clinical Research Infrastructure Network ¹⁸	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 it will also contribute to VACCELERATE through the development of tools for harmonised data	8 Members and 1 Observer ¹⁹	ECRIN ERIC Paris (FR)	2014	CAPEX: 5 OPEX: 5/y

¹⁴ <http://www.bbmri-eric.eu>

¹⁵ Members: AT, BE, BG, CZ, EE, FI, DE, GR, IT, LT, ML, NL, NO, PL, SE, UK. Observer: IARC/WHO, CY, TR, CH

¹⁶ <https://eatris.eu/>

¹⁷ Member countries: NL, CZ, EE, ES, FI, FR, IT, LU, NO, PT, SE, SI, BG. Observer: LV.

¹⁸ <http://www.ecriin.org>

¹⁹ Members: FR, DE, HU, IT, NO, ES, PT, CZ, IE) and Observer (CH, SK, PL) country.

		management and data sharing, as well as the development of master protocols.				
ELIXIR Distributed infrastructure for life-science information ²⁰	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, and 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 ²¹	It encompasses basic research into pathogen isolation/characterisation, 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-OPENSREEN European Infrastructure of Open Screening Platforms for Chemical Biology ²²	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-OPENSREEN ERIC Berlin (DE)	2019	CAPEX: 82.3 OPEX: 1.2/y
EURO-BIOIMAGING European Research Infrastructure for Imaging Technologies in Biological and Biomedical Sciences ²³	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-Biolmaging Hub Turku (FI)	2019	CAPEX: 90 OPEX: 1.6/y

²⁰ <https://elixir-europe.org/>

²¹ AISBL means Association Internationale Sans But Lucratif, it was set up by a Belgian Royal Decree and it is funded through membership fees.

²² <https://www.eu-openscreen.eu/>

²³ <https://www.eurobioimaging.eu/>

INFRAFRONTIER European Research Infrastructure for the generation, phenotyping, archiving and distribution of mouse disease models ²⁴	Distributed; GmbH	By offering access to a unique collection of mouse models and research tools and associated data, and to state-of-the-art technologies for mouse model development and phenotype analyses, the infrastructure allow 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 ²⁵	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

²⁴ <https://www.infrafrontier.eu/>

²⁵ <https://instruct-eric.eu/>

Annex IV - 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 country, 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 a capital essentially for pursuing the organisation's objectives and keeping it running but without earning any profits. Foundation is a typical legal form for 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 the Belgian Law, a specific legal form is envisaged for non-profit organisations called 'AISBL' (international non-profit organisation under the Belgian Law). Such legal form is governed by Belgian national law but allows international partners and activities.

Among the not-for-profit organisations are worth mentioning the Product Development Partnerships, which are 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 not-for-profit association is the CEPI established as an international non-profit association under Norwegian law in 2016 by five founders (the Gates Foundation, the World Economic Forum, the Wellcome Trust, the India's Department of Biotechnology, and the Government of Norway) to respond to vaccine R&D needs for emerging infectious diseases.

While an advantage of companies is that they 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, the other side of the coin is that negotiations can take a long time as partners may dislike funding a legal entity that is controlled by 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). None of the interviewees mentioned neither the company nor the foundation models the most suitable legal form for the European Medicines Infrastructure.

Intergovernmental treaties. Organisations established through intergovernmental agreement/treaty have international legal personality which is governed by international law. The first European research organisation based on an intergovernmental agreement was the European Organisation for Nuclear Research (CERN). It then became 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, 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 servant or United Nation types), with privileges and immunities, makes it possible to attract very highly skilled collaborators (EC, 2008).

The successful experiences of CERN, ESA, EMBL, and the European Southern Observatory makes 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 establish 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, in particular to implement the ESFRI Roadmaps, triggered discussions about an appropriate legal framework to establish and operate pan-European infrastructures. Such discussion conveyed into 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. ERIC as a legal person 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 the liability of ERIC members is limited to the financial contributions they make (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 that are 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 neither as members nor 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 States²⁶. 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 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

²⁶ 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).

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 in nature 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 that they do not jeopardise the achievement thereof. 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 that has been 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, at the national level, ministerial support is sufficient, without the necessity of engaging in potentially lengthy and complex parliamentary processes required for establishing an intergovernmental organisation (OECD, 2014). Despite this, ERIC still have 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 not clear 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 co-operative research across Europe in fields of key importance for industrial research, where there are clearly 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.²⁷ Clearly, another possible disadvantage of JTIs concerns the difficulty for non-European Countries to join.

²⁷ 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.

Agency. Beyond the above discussed legal forms, which are typically adopted for Research Infrastructures, the present study considers the option of 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 States across the EU. The members of EU agencies are all Member States but also other states may become members by means of agreements concluded between them and the EU.

At the moment, there is no general legal basis to create EU agencies²⁸ 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) the way in which 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 purely 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 the type of act, the decision require 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 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 prior consultation with the Commission, and (iii) agencies that can autonomously exercise their powers. As a result, there is not a unique agency model.

Funding

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* or a combination of fees and voluntary contributions by Member States. This is for instance the case of ECDC.

²⁸ 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.

- 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 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 or 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 with a usage hourly fee of €30 (€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 will be involved in the research and marketing authorisation of new treatment, e.g. for a neglected disease or a 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, public or private research institutes/organisations in Europe can benefit from 'InnovFin Science' made available by the EIB in the form of debt or equity-type financing. The aim is supporting R&I investments, including the financing of 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 €100 million in debt financing for COVID-19 vaccine development and manufacturing (EIB Press, 2020).

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With a focus on research and development in the area of innovative medicines, this study 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 such European medicines infrastructure should focus on threats and areas of research and development that are underinvested under the current business model. More specifically, the study uses an extensive literature review and a targeted survey of international experts from science, industry, public health and government institutions, 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.

On the basis of their research, the authors present a range of policy options. The most ambitious of these considers a Europe-wide public infrastructure equipped 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 the course of 30 years, in partnership with third-party research centres at national or European level and with companies. It would be the most important global player in biomedical innovation in the world.

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