Received: 2 December 2020 | Revised: 8 June 2021 | Accepted: 15 June 2021

DOI: 10.1111/apce.12341

Annals of Public and Cooperative Economics
Annales de l'économie publique, sociale et coopérative

WILEY

SPECIAL ISSUE

Biomed Europa: After the coronavirus, a public infrastructure to overcome the pharmaceutical oligopoly

Massimo Florio | **Simona Gamba**

Department of Economics, Management and Quantitative Methods, University of Milan, Italy

Correspondence
Massimo Florio
Massimo.Florio@unimi.it

Abstract

After a brief analysis of the causes underlying the failure of both governments and the pharma industry in terms of preparedness for the COVID-19 pandemic, and after a discussion of further risks of health emergencies in the coming decades, this paper proposes a new public policy approach. The proposal aims at a major European initiative for the provision of research and development (R&D) in the biomedical field, based on public health priorities. A plan is discussed for an international, interconnected, transparent, science-informed and publicly funded research infrastructure for pharmaceutical and biomedical research combined with a public enterprise: Biomed Europa. The proposed platform aims to identify research priorities in the public health sector, focusing its efforts on the development of preventive and therapeutic strategies against those diseases that will pose the greatest threats to human and social welfare over future decades. Biomed Europa could be managed as both an international research infrastructure, along the model of CERN, or the EMBL (European Molecular Biology Laboratory, Heidelberg) and as a knowledge-intensive public enterprise with an industrial policy mission, such as the ESA (European Space Agency).

KEYWORDS
biomedical research, COVID-19, pharmaceutical industry, public research infrastructure

JEL CLASSIFICATION
H51, I11, L32, O32

1 | INTRODUCTION

As of 4 June 2021, the global outbreak of Severe Acute Respiratory Syndrome (SARS)-associated coronavirus 2 (SARS-CoV-2) has claimed more than 3.6 million lives out of 172 million cases.[1] It has been estimated that, in April 2020, half of the world's population has experienced some form of lockdown.[2] The disruption of economic activities in 2020 was more significant than any other slump since World War II, and the effects on growth and social welfare will possibly be felt for over a decade.

In this paper we try to answer two questions: Why were we so unprepared to deal with the pandemic? What can be done to avoid similar health emergencies in future?

The current COVID-19 pandemic provides a fundamental lesson about the lack of preparedness for infectious threats and other health challenges that we face globally and that exacerbate vulnerabilities associated with income inequality and health disparities. It can be argued that such a lack of preparedness arises from structural weaknesses in the public health system, rooted in excessive confidence of governments in market mechanisms in biomedical R&D and in the pharmaceutical industry.

In recent decades, the global health system in most countries relied heavily on the pro-profit private sector for the discovery, development and distribution of new drugs and other innovations in the biomedical field. This paper focuses particularly on pharmaceutical and vaccine research, but similar considerations apply to related biomedical sectors, such as diagnostics. Governments allocate public funds to health-related research—grants for the most part aimed at supporting basic and early-stage research. Rather, late-stage drug development is largely funded by the pharmaceutical industry, either by biotech start-ups supported by venture capital or large-sized companies, which are incentivized to invest by a system of patent monopolies. To maximize their financial returns, companies invest selectively in the most marketable and profitable biomedical sectors, where drugs command the highest profits (even though they sometimes offer marginal therapeutic improvements and have little impact on social welfare). Thus, critically important biomedical research sectors remain underfunded, and urgent public health needs are left unmet by the investment plans of the industry.

This was the case of vaccines against coronaviruses, for which the scientific community has been raising alarming concerns for almost 20 years, but it is also the case of orphan and neglected diseases. Both kind of diseases are characterized by an insufficient market to attract R&D investment by the pharmaceutical industry (Dimitri, 2012)—while the former only affect a small

[1] https://covid19.who.int/

[2] https://www.euronews.com/2020/04/02/coronavirus-in-europe-spain-s-death-toll-hits-10-000-after-record-950-new-deaths-in-24-hou

number of individuals,[3] the latter principally affect the world's poorest people. Moreover, the further we go towards precision medicine, the smaller the market size for each drug will be because of the gradually decreasing number of patients for each disease identified. For example, following the success of the Human Genome Project, the genetic basis of several diseases has been identified: many of these affect a limited number of individuals. However, the cumulative number of patients affected by 'rare' disease may be significant, particularly for cancer.

As it has been pointed out by the literature, medical innovation mainly responds to potential profits, and market size is a critical dimension for the allocation of resources. Dubois et al. (2015) and Acemoglu and Linn (2004) find significant elasticities of innovation to expected market size (0.25 and 6, respectively), while Barrenho et al. (2019) and Gamba et al. (2019) find that, among orphan diseases, innovation is concentrated on diseases with higher prevalence or greater willingness to pay. The importance of market size is confirmed by further studies evaluating the effect of variations in market size on R&D investments. On the one hand, positive exogenous demand shocks (Clemens & Rogers, 2020), the introduction of patent protection (Qian, 2007; Gamba, 2017), positive reimbursement decisions (Jobjörnsson et al., 2016), the expansion of health insurance coverage (Blume-Kohout & Sood, 2013; Clemens, 2013), and policies designed to increase usage of existing vaccines (Finkelstein, 2004) proved to stimulate R&D. On the other hand, delays in the approval process and uncertainty surrounding it (Stern, 2017), and as well as drug exclusions from insurance coverage (Agha et al., 2020) may reduce investments.

Thus, it is not surprising that both orphan and neglected diseases are characterized by a lack of treatments: a treatment is available for less than 10% of known orphan diseases (Melnikova, 2012; Tambuyzer, 2010). In 2018, total R&D investments for neglected diseases amounted to roughly US$4bn, with HIV, malaria and tuberculosis receiving more than two-thirds of these and neglected tropical diseases accounting for roughly 6.5% (G-Finder, 2019), as compared to a total global pharmaceutical spending for R&D of US$181bn.[4] More than three-quarters of R&D investments for neglected diseases, and more than 80% for neglected tropical ones, came from the public sector or the philanthropic one, despite the recent increase in industry investments. While more than half of public investments were for basic and early-stage research, 70% of multinational companies' investments were for clinical development and post-registration studies (G-Finder, 2019). In addition to public investments, in many developed countries the public sector also stimulates private investments for orphan (and genetic) diseases through several tools, such as lower fees for marketing authorization, market exclusivity and tax credits on R&D expenditures (Gamba et al., 2019).

Several motivations may be identified for encouraging pharmaceutical R&D investments in those biomedical research sectors currently underfunded. The first one is related to inequality aversion (McCabe et al., 2005; Claxton, & Tsuchiya, 2005; Nord et al., 1995); strictly related to this is the "fair innings" argument, according to which everyone has to be granted a minimum life-expectancy (Harris, 2006). Another rational is related to the positive insurance value of innovation: medical innovation is the main method of achieving smoothing in health across disease states, by lowering physical risks borne by healthy patients who might get sick (Philipson & Zanjani, 2014; Lakdawalla et al., 2017). This rationale also suggests that the insurance value of innovation is higher for those diseases characterized by a lack of treatments, given the severity of the

[3] The exact definition of an orphan disease changes from one institutional context to another, and may involve the number of people affected, the profitability of the disease and its seriousness (Gamba et al., 2019).

[4] https://www.statista.com/statistics/309466/global-r-and-d-expenditure-for-pharmaceuticals/

disease. Another motivation relates to the public good dimension of infectious diseases' surveillance (Chen et al., 1999), pandemic preparedness (Stein & Sridhar, 2017) and basic research (Kaul et al., 1999), which are non-excludable and non-rivalrous. As highlighted by the current epidemic, globalization has made the world heavily interconnected, and one nation's public health struggle affects also other countries, causing serious externalities. Concerning orphan and genetic diseases, it is important to recall the existence of positive externalities that R&D focusing on these diseases might have on others. Rare diseases make good models for common ones (Rodwell & Aymé, 2015), and the study of genetic mutations leading to rare genetic diseases might provide information on the role of altered protein. For example, the alteration of the Niemann–Pick C1 protein responsible for the rare degenerative disorder called Niemann–Pick disease was found to be responsible for the Ebola virus entry (Carette et al., 2011; Côté et al., 2011), suggesting a possible strategy to fight the virus. Thus, it is not surprising that 38% of transformative drugs—innovative and having a ground-breaking effect on patient care—approved by the Food and Drugs Administration (FDA), the US drug agency, between 1984 and 2009 were developed for rare diseases before their broader applicability was found (Kesselheim et al., 2015; Kesselheim & Avorn, 2013). In 2020 the goal to find vaccines for SARS-CoV-2 and, to a more limited extent, to study drugs or biological treatments to cure infected people, was eventually achieved by the industry at surprisingly high speed, but only after governments committed unprecedented amounts of subsidies and advance payments. The risk was mostly shifted to the public sector, but without any government claiming the capability to produce and distribute the vaccines on its own. Is this the right way to manage future emergencies? This paper explores alternatives and suggests designing a large-scale international platform for pharmaceutical and biomedical research. The proposed platform, Biomed Europa, which could be based on an intergovernmental treaty sponsored by the European Union (EU), but not restricted to EU Member States, should aim at identifying research priorities in the public health sector, focusing efforts on the development of preventive and therapeutic strategies against those diseases that pose the greatest threats to human and social welfare, but that are not high priority for the pharma industry.

The paper suggests that this approach is needed because of a structural misalignment between the industry and public health policies and because public policies based on subsidies and taxation, or on regulatory reforms alone, would not be able to correct market failures in this area. Historically, governments, in other fields and industries, particularly in Europe, have been able to correct market failures by building their own organizations (Bernier et al., 2020), often with success. They still do so largely in such essential fields as network industries (transport, energy, telecoms) and in services of general interest such as health and education. There is no compelling reason that prevents governments from stepping into the biomedical R&D arena as they have done elsewhere, even if the costs and risks of doing so need to be carefully assessed and discussed against the possible social benefits.

Table 1 summarizes the main current challenges and the possible solutions provided by Biomed Europa that will be further analyzed in the remaining of the paper, which is organized as follows. Firstly, we discuss why the current pandemic reveals a market failure (Section 2). The pandemic was a predicted major risk that was, however, considered low priority by investors in the pharmaceutical industry. The pandemic is also a policy failure, as governments ignored early warnings from the scientific community. Secondly, we briefly mention some features of the pharma industry, and discuss the incentive structure facing companies and management in the industry (Section 3). Then we turn to a discussion of biomedical R&D and show why the current public policy framework, based on grants to universities and research bodies, subsidies to firms, legal monopoly on innovations through patents, market authorizations through pharmaceutical

TABLE 1 Current challenges, and possible solutions provided by Biomed Europa

Main current challenges	Possible solution through Biomed Europa
Firms' incentives to invest in most marketable and profitable drugs (because of market forces driving their choices), leaving critically important public health needs (such as vaccines, antibiotics, drugs for orphan and neglected diseases) unmet	Research targets based on public health priorities
Unpreparedness in front of pandemics	Research targets based on scientific advice and priorities set by scientists
Externalities arising from infectious diseases not taken into account	Internalization of externalities
Public subsidies for early-stage research and regulatory reforms not able to influence the industry research targets	Public subsidies devoted to the development of drugs for unmet needs
Public subsidies (and advance payments by governments for COVID-19 vaccines) not linked to co-sharing of IPR	Ownership of IPR for drugs developed by the research infrastructure
High prices, low accessibility, shortages of essential drugs	Ownership of IPR and direct control of the whole drug life cycle, from R&D to distribution; supervision of the supply of raw materials; supply of equivalent drugs

agencies, regulatory testing data protection, and (limited) ex-post surveillance, despite having worked in some areas, has overall failed to address the misalignment of priorities between public health systems and the pharma industry (Section 4). In Section 5 the proposal of Biomed Europa as a new policy concept and public infrastructure is presented, with a discussion of public mission, operation, governance, intellectual property (IP) management, feasibility of the project in terms of budget, and funding. The social benefits and costs of different options are discussed. We also mention recent proposals by the European Commission and the need for further exploration of the policy options, as it is likely that concurring changes in other institutions and policies would enhance the probability of success of the proposal. In Section 6 we discuss possible objections to and concerns about the proposal.

2 | THE CORONAVIRUS PANDEMIC AS A MARKET AND POLICY FAILURE

The current pandemic shows a spectacular failure over the last 20 years in research into infectious diseases on the part of the pharmaceutical industry. At the same time, it points to a policy failure of the governments that mostly entrusted our defence against such diseases to pharma companies. Alarm bells were sounding but were ignored. In February 2018 the World Health Organization convened a panel of experts in order to identify a list of high-risk pathologies for human health. The panel suggested that the lack of vaccines or treatments for some infectious diseases posed a particularly high risk: along with the Ebola and Zika viruses, SARS-CoV-1 (Severe Acute Respiratory Syndrome associated with a coronavirus) was mentioned. The latter was identified as early as 2003. Moreover, the WHO panel warned that a new "pandemic X" could start any time.

The current SARS-CoV-2 is a coronavirus, a strand of viruses that have been known to experts for decades as the most likely candidates for a pandemic. Overall, at least 1,400 pathogens are

currently known to be able to infect humans. While so far only 20% of them are viruses, since 1940 two thirds of newly discovered pathogens have, in fact, been viruses of different groups (either DNA or RNA based, coronavirus being a subgroup of the latter). We are now aware that our planet hosts hundreds of thousands of different types of viruses. These replicate themselves within other forms of life, particularly in certain animals. Some of them can potentially jump into humans just like any other host. This mechanism, a zoonosis, is what happened with AIDS-HIV, Ebola, SARS and with the current SARS-Cov-2.[5]

Hence, the COVID-19 pandemic associated with SARS-Cov-2 was not just predictable, it was actually predicted by scientists. After SARS-CoV-1, then MERS (Middle East Respiratory Syndrome), caused by a strain of coronavirus, was identified in 2012. In 2012 the scientific journalist David Quammen (2017), author of the popular book "Spillover", interviewed dozens of experts, asking them two precise questions: is there a risk of a new pandemic such as AIDS or Spanish flu? What form will it take and where will it come from? The interviewees replied that a pandemic was likely and that a coronavirus was the best candidate for spreading it. Laboratory experiments in 2015 showed how another coronavirus hosted by certain species of bats could prove dangerous to man (Menachery et al., 2015).

Despite these alarm bells, for almost 18 years prior to the COVID-19 outbreak, the pharmaceutical industry had made very limited R&D investments in this direction, with only six clinical trials recorded by the WHO in 2019 and ten basic and pre-clinical studies for all types of coronaviruses, and no drugs were being registered on the part of the industry (Rizvi, 2020). This in spite of considerable National Institutes of Health (NIH, which are part of the US Department of Health and Human Services) and other public funders' grants, amounting to an estimated total of US$ 700 million since the first SARS outbreak (Mazzucato & Momenghalibaf, 2020). With the pandemic, by July 2020, the US government had spent more than US$ 13 billion to finance the development of a vaccine for COVID-19.[6] In the subsequent months another huge flood of money from governments to pharma companies was committed in the form of advance purchase agreements (APA) or, again, support for research. On 29 January 2021 the European Commission (EC) authorized six contracts for 2.3 billion doses of future vaccines and it is going to increase the orders. Through Horizon 2020 the EC has committed €660 million for COVID-19 research, and the European Investment Bank has provided large-scale loans to some pharma companies.[7]

A surprising aspect of the contracts for future vaccine doses in the US and Europe, as far as they have been disclosed, is that while most of the economic risks were shifted from the companies to the public sector, research grants were not linked to any co-sharing of intellectual property rights between the private and public sector. Moreover, it seems that no long-term price determination mechanisms were negotiated although the immunity offered by the vaccines probably lasts no more than 12 months, hence subsequent cycles will definitely be needed. Mechanisms for third-party production and distribution licenses were also omitted from the APAs. As a consequence, the production of vaccines is fragmented, depending on the capacity of each patent owner, instead of being allowed anywhere in the world where there is the capacity to do so. This strategy fully reveals how governments are currently unable and unwilling to countervail the market power of the pharma companies, in spite of the significant subsidies and other money they are giving them.

[5] The Economist, 27 June 2020, Pandemic-Proofing the Planet, p 61; The Economist, 22 August 2020, The Viral Universe, p. 13.

[6] The Economist, 18 July 2020, America First-Aid, p. 34.

[7] https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/overview-commissions-response_en

Let us restate that for around two decades the pharmaceutical industry deemed that research into a coronavirus vaccine was a pointless investment, despite the opinions of authoritative experts such as Peter Hotez, Baylor College of Medicine (Altman, 2020). On 5 March 2020 he testified before the US Congress that during the first SARS epidemic in 2003 his team developed the concept of a vaccine but was unable to secure enough funding to begin clinical trials.[8] Today, according to several experts, we regret having abandoned these tests because they would have provided a starting point, as Jason Schwartz of the Yale School of Public Health said recently: "Had we not set aside the SARS vaccine research program, we would have had a lot more foundational work that we could apply to this new, closely-related virus" (Buranyi, 2020). This was admitted also by the OECD General Secretary, Angel Gurrìa, in a letter to the G20: "Had a vaccine for the SARS-CoV-1 been developed at the time, it would have accelerated the development of one for the current outbreak given that the two viruses are 80% similar", Gurrìa (2020).[9]

Neither did the industry develop any research into antiviral drugs that may prevent the progress of this type of disease after infection. According to Professor Haseltine of Harvard Medical School, all coronaviruses have a common molecular structure and once the various types of genome have been sequenced, drugs that block the enzymes necessary for their growth are feasible and should be developed, produced and accumulated in anticipation of the next pandemic.[10] Professor Abrignani (2020) of the University of Milan suggested that research should start as soon as possible into the next pandemic, perhaps with a "universal" coronavirus vaccine project. In his opinion, considering the social contexts around the world that make a zoonosis possible, the question is not if there will be another coronavirus jumping from animals to men, but when, and looking at the previous episodes, it will again be in the current decade.

However, in 2019 the Top 20 Pharma companies were busy carrying out research into about 400 new drugs, half of them anticancer (which currently sell for an average of US$195,000 per treatment), but only 65 projects involved infectious disease. Before the outbreak only very few of the Big Pharma firms had a stable research unit for vaccines. 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).

This did not happen by chance. The business model of the pharmaceutical industry focuses primarily on "blockbuster" drugs that bring in billions of dollars in annual turnover (Rea et al., 2018). The typical target markets for these drugs are chronic pathologies, such as high cholesterol, diabetes and hypertension. A cholesterol-combatting drug like Lipitor alone generated US$150 billion for Pfizer in less than 20 years. Certain types of cancer require long-term therapies that ensure high and lasting revenues and profits.

Rea et al. (2018) provide numerous other examples of how explorative drug research—with its related risks—is almost always initially carried out by teams in universities and small start-ups, often with critically important public funding. The Big Pharma companies only enter the arena when the investment appears promising in terms of a geographically broad market that is expected to increase over time (Chakravarthy et al., 2015; Prasad & Mailankody, 2017). Priority is not given to infectious diseases that give rise to local epidemics, often in areas with low spending power

[8] https://unfoundation.org/blog/post/qa-with-dr-peter-hotez-behind-the-scenes-of-covid-19-vaccine-research/

[9] https://www.oecd.org/about/secretary-general/Coronavirus-COVID-19-Joint-actions-to-win-the-war.pdf

[10] https://www.uschinahealthsummit.org/single-post/2020/02/21/What-Needs-to-be-Done-to-Deal-with-COVID-19-in-China-An-Interview-with-William-Haseltine

(as with Ebola in Africa), or those that once infection has been eradicated do not guarantee an interesting market that is commensurate with the risks of research into moving targets.

A pandemic like the present one offers a global market to authorized vaccines, with sales in the region of billions of dollars for a vaccine (Gard, 2020), or possibly to other drugs in future, but due to its nature, any pandemic, large as it may be, does not result in a chronic condition for patients. People recover and become immune, or they die within a relatively short period of time. It is not a stable market to invest in, unless governments offer pharmaceutical firms substantial subsidies to encourage them to do research (T'Hoen, 2020).

Thanks to their unrivalled lobbying activities, the pharmaceutical companies managed to get the US Congress to reject an amendment by the Democrats to the over US$2,000bn recovery bill, which was approved on 29 March 2020, to tackle the economic and social crisis provoked by coronavirus. The amendment aimed to control the prices of any vaccines or drugs obtained by private research institutes using public funds. Not only was the amendment rejected, but a ruling was introduced that explicitly forbids the government from limiting the prices demanded by the pharmaceutical firms that patent the COVID-19 drugs (Mazzucato & Momenghalibaf, 2020).

To sum-up this preliminary discussion: the pandemic was predicted, governments offered significant research grants to firms and to anybody interested in the topic, but the industry had different investment priorities. The pandemic eventually arrived, and governments offered emergency cash to incentivize R&D and production capacity. Vaccines were discovered in a surprisingly short time, leveraging different scientific approaches. This was done mostly not by Big Pharma themselves in the first place, but by researchers elsewhere, including in universities and small or medium-sized biotech laboratories. Governments disbursed huge sums of money for APAs and additional research, while some Big Pharma were able to step into the process, offering their capacity in large-scale clinical trials, production, and distribution, while governments allowed the game to be played according to the rules established by the industry.

Let us recall the standard definition of market failures as the violation of one or more of the assumptions for competitive markets (e.g. Atkinson & Stiglitz, 2015; Tresch, 2008; Florio, 2019): (a) large numbers of buyers and sellers for each product, so that market equilibria in terms of quantities and prices are not influenced by any of them; (b) homogeneous products; (c) information freely available to buyers and sellers; (d) no barriers to entry or exit. It seems evident that the economic history of the coronavirus vaccine cannot be framed as the outcome of a competitive market, as each of the four assumptions has been violated. In fact, such market failures apply to most of the pharma industry itself. Unfortunately, governments have not yet found ways to design an appropriate policy in this context, because they have mostly tried to find piecemeal remedies.

3 | STRUCTURE, INCENTIVES AND PERFORMANCE OF THE PHARMA INDUSTRY

According to some estimates, the revenue of the pharmaceutical industry in 2019 was US$1.25 trillion.[11] In the US, spending on drugs amounts to an average of 2% of GDP, one of the highest in the world, compared with France (1.5% of GDP) and possibly higher in Germany.[12] The average price of drugs is rising fast. Some studies predict that global spending on drugs will double over the period 2013–27.[13]

[11] https://www.statista.com/topics/1764/global-pharmaceutical-industry/

[12] OECD data 2018; The Economist 15 February 2020, Justin Trudeau's Drug Problem, p. 36.

[13] The Economist 22 June 2019, American drugmakers are raising prices. Again.; http://aswathdamodaran.blogspot.com/

The pharmaceutical industry is a complex ecosystem. At the top of the pyramid we find the Big Pharma. In 2021 the projected revenues of each of the Top Ten were in the region of US$ 30–50 billion, with Pfizer recording US$45.6 million, Roche US$51.3 million, and Johnson and Johnson US$46.9 million (excluding other sectors).

The Top Ten represented a market share of about 36% of the total in 2020.[14] This share does not imply per se a stable oligopoly: there are undoubtedly sectors like the automotive, to make a classic example, where the concentration is greater (well over 50%) and at the same time there are fewer chances for new arrivals. However, what is characteristic of the pharmaceutical industry is a peculiar combination of monopolistic legal protection of intellectual property (patents), a regime of exclusive authorization for release to the market (by the drug's advertising agency), a lengthy development times for innovations, a high risk in the initial phases of research, economies of variety (economies of scope: it is useful to have a diversified product portfolio), market power even after the expiry of the patent, due to a certain degree of inertia in the system induced by advertising and promotional expenses and, in the case of biologicals and genetic therapies, to fixed costs of setting up highly specialized manufacturing facilities (Conti et al., 2020). Thus, in reality, in the market segments defined in relation to specific pathologies the concentration is far higher than the aggregated data for the pharmaceutical market suggest. Often the therapeutic protocols adopted by health systems or recommended by the experts contemplate a single drug of first choice for a disease and a type of patient, defined as first-line therapy, and only when this cannot be administered for certain reasons, other drugs are used. This rigid market segmentation, and the fact that often patients cannot choose the treatment, are another peculiarity of the industry, which make it very different from other sectors with a high concentration of market shares.

The considerable time that elapses from basic research to mass production works in favor of market power. According to the EFPIA, the European Federation of Pharmaceutical Industries and Associations,[15] it typically takes six years from filing the patent to studying acute toxicity, the risks of chronic toxicity and pharmacology in stage 1, and a further two years of clinical trials in stage 2. Having completed stage 3, which entails trials on larger samples of participants, ten years have passed since the initial filing of the patent to the marketing authorization, and it takes another year to define prices and contracts for mass production. At this point pharmacovigilance for possible side effects starts and in the twentieth year (in certain cases the twenty-fifth) the patent expires. Obviously, such a long gestation period (although in practice it is not always so long in all fields) is not sustainable for a small business that wants to enter the market with a single innovation or family of related innovations, for which the risk of failure is mutually linked. It would not be easy to find the capital necessary to go beyond the early stages, even in contexts in which venture capital helps inventors. In this context, it becomes optimal to have a large organization that builds up a portfolio of patents and development projects over time (Cockburn & Henderson, 2001), each of them in a different stage of the cycle, so that already proven and profitable projects finance new, and initially riskier, ones. Hence the economies of scope.

If, to this policy of accumulation of projects especially through mergers and acquisitions by major companies (Danzon et al., 2007; Comanor & Sherer, 2013), we add the optimization of the management of relations with national regulators, financial investors, component suppliers and distributors, one can see why the oligopoly of Big Pharma prevails in the structure of the industry

[14] https://www.statista.com/statistics/1201485/top-pharmaceutical-companies-by-sales-forecast/

[15] EFPIA (2020) The Pharmaceutical Industry in Figures, https://efpia.eu/publications/downloads/efpia/2020-the-pharmaceutical-industry-in-figures/

without, however, excluding an increasing number of start-ups or firms specializing in a single drug, or in a single stage of the process (Malerba & Orsenigo, 2015).

In this complex context the value chain involves quite a strong division of labor (Malerba & Orsenigo, 2015). Today the large sector firms carry out increasingly less in-house research into discovering new molecules or developing new drugs, preferring to go shopping for projects (Schuhmacher et al., 2016), which are accounted for in their balance sheets as intangible assets and then presented as research and development (R&D). The larger firms increasingly often prefer to leverage relationships with small biotech companies, in order to use their innovative capabilities to develop new drugs. The extraction of value can take place in various ways: through licensing agreements whereby the large firms buy the molecules or drugs developed by the biotech companies; through the acquisition of promising start-ups or biotech companies with a portfolio of patents in specialist fields; or the large firms simply employ inventors and their groups (Newton, 2007; Mittra, 2007; Congressional Budget Office, 2021). Often the large firms do not even make the initial selection of ideas, leaving it to the venture capitalists or other specialists to hunt for promising biotech companies. Once the target is identified, the acquisition machine is set in motion: this combines legal aspects, market assessments and cost forecasts up to the decision based ultimately on the business case.

For the clinical trials, large firms often rely on intermediaries, such as the Contract Research Organizations (CRO), which deal with the recruitment of patients in health structures and other related activities (Mirowski & Van Horn, 2005). The presentation of the results of the trials and the dealings with public authorities, especially with drug agencies, is often also entrusted to specialists. Manufacturing, packaging, even the drafting of the accompanying instructions and product distribution are contracted to service providers, including the Contract Development and Manufacturing Organization (CDMO).

Given the actual concentration by segment, it is hardly surprising that the profitability of the sector is abnormally high compared to other industries. Oligopolistic market segmentation and high profits almost always go hand in hand.[16] According to a specialist in financial analysis, Aswath Damodaran (NYU Stern Business School),[17] the operating margin for the pharmaceutical industry after taxes (with the appropriate accounting adjustments for the capitalization of multiyear components such as R&D expenses and leases) is in the region of 24% of revenues, amongst the highest ever. Even more significantly, a study by the General Accountability Office (2017), the most authoritative US government agency for accounting analysis, showed that the average profitability of pharmaceutical firms is double that of the world's Top 500 companies. In addition to this the Big Pharma companies, as multinationals in general, can legally choose the most favorable tax regime in the various states in which they operate (Zachariadis, 2019).

4 | R&D, INNOVATION AND THE ROLE OF GOVERNMENT

Let's look in detail at the contribution to innovation. The R&D spending of the pharmaceutical industry in 2019[18] is estimated at over US$180bn compared to revenues of US$ 1,250bn,[19] including

[16] The Economist 22 June 2019, American drugmakers are raising prices. Again.; http://aswathdamodaran.blogspot.com/

[17] The Economist (2019) American drugmakers are raising prices. Again, 22 June 2019.

[18] https://www.statista.com/statistics/309466/global-r-and-d-expenditure-for-pharmaceuticals/

[19] https://www.statista.com/topics/1764/global-pharmaceutical-industry/

both traditional and biotechnological drugs.[20] The R&D spending on biomedical technologies is more than US$31bn. The analytical composition of this spending is not, however, known and could also include expenses for market research and other non-relevant items.

Looking only at the NIH grants, in 2019 every US citizen paid just less than US$120 a year to support biomedical research. Chakravarty et al. (2015) suggest that, through the NIH, the US public sector put up US$31.8bn every year to support, above all, basic research, to a lesser extent "translational" research,[21] and to an even lesser extent clinical research, while the private sector put up US$51.8bn with an inverted priority structure.[22] The numbers currently at stake would be different, since the NIH budget in 2020 was US$41bn. If the numbers in the above study were taken literally, the NIH channel alone would be worth 38% of total R&D spending in the sector. A similar percentage is reached considering the meticulous work of Cleary et al. (2018) on the 210 active ingredients (new molecular entities) approved by the FDA from 2010 to 2016. The authors calculated that the NIH had contributed an average US$840 million to research into each of these active ingredients. In turn, Wouters et al. (2020) study the costs of R&D for 63 products approved by the FDA between 2009 and 2018 for which R&D expenditures were available. They find a median value per new drug, capitalized at the real cost of capital rate of 10.5% per year and adjusted to account for frequent project failures, of US$985 million and a mean of US$1,336 million, but with great variability: double the average costs for oncology and immunology, around average for infectious diseases and gastrointestinal conditions, and below average for the nervous system and for dermatology. Gross of any duplications in the companies' balance sheets, if public and private money were added together to reach the market, then the public contribution would be 39% of the total. But the proportion could even be higher. Indeed, the NIH funds should be added to those of other US agencies such as the National Science Foundation and BARDA (Biomedical Advanced Research and Development Authority),[23] and of public and non-profit funders (which, in turn, are often fuelled by tax exemptions on upstream profits) from around the world. The grants rain down copiously on universities and other institutions, but then directly and indirectly drift to the firms.

Although it is difficult to make precise estimates, if we consider that, especially in Europe, it is the taxpayer who directly pays for the structural functioning of the university departments of pharmacy, pharmacology, biosciences and other disciplines that contribute to drug research, the public contribution to research could account for at least half of the total spending on research. Although some universities (for example MIT and the University of California in the United States) are owners or co-owners of pharmaceutical patents, generally speaking the public and non-profit sectors do not own a portfolio of patents proportionate to their contribution to the research.

Recent decades have also been characterized by a decline in the innovation productivity of the industry (Malerba & Orsenigo, 2015). Whilst in the decade 1950–60 the FDA approved around 50 new molecules for each billion dollars spent in R&D, in the 1980–90 decade this fell to about five molecules and since 2000 to less than one molecule per billion dollars a year.[24]

[20] https://www.statista.com/statistics/309471/randd-spending-share-of-top-pharmaceutical-companies/

[21] Translational research (or translational medicine) builds on basic research to create "real life" therapies, procedures, or diagnostics.

[22] The same priority structure for private and public investments is found, globally, for investments for neglected diseases (G-Finder, 2019).

[23] https://www.phe.gov/about/barda/Pages/default.aspx

[24] https://www.oecd-ilibrary.org/sites/9789264307391-3-en/index.html?itemId=/content/component/9789264307391-3-en; The Economist, 14 March 2020, Populations of one. Personalised medicine. Technology quarterly, p. 3.

5 | A NEW POLICY FRAMEWORK AND A PROPOSAL

Review different models for delinking R&D and the manufacture of drugs from profit incentives and instead prioritizing public health objectives. There are several possible approaches, including the involvement of philanthropic organizations, public–private partnerships, government funded centers, nationalization (Mazzucato & Li, 2020).

A public pharmaceutical initiative has been proposed for the US by the Democracy Collaborative think-tank to allow patients to access therapies and escape from the monopolistic market conditions that prevail today and that they end up paying for, either directly or indirectly (Brown, 2019). It contemplates (a) a drug research and development institute at federal level that is involved throughout the cycle of pharmacological research (including clinical trials); (b) a number of public manufacturing firms at regional, state or municipal level to produce new drugs or generics for sale at affordable prices; (c) wholesale distributors that are also public, such as the US Postal Service; (d) speedy delivery of the drugs supplied by the initiative at accessible prices to private retail pharmacies and hospitals. Senator Elizabeth Warren proposed to the US Congress the creation of an Office of Drug Manufacturing dependent on the Department of Health and Human Services.[25] The aim of this office would be to lower costs, improve access and reduce the shortage of essential drugs (Brown et al., 2019).

In the US, BARDA, which has been instrumental in speeding up research into COVID-19 vaccines, has also created three centers to develop and manufacture medical countermeasures, such as vaccines and other therapeutic products used to protect health in emergencies. These Department of Health and Human Services' Centers for Innovation in Advanced Development and Manufacturing (DHHS CIADM) can transition quickly and cost-effectively between products. They take the form of public–private partnerships, involving small biotech firms, universities, and large pharmaceutical companies. While mostly designed to rapidly respond to health emergencies, the centers "will also be used to explore emerging and innovative technologies that could be applied to current or future medical countermeasure development efforts to reduce risk, increase yield and ultimately to reduce total life-cycle costs through flexible manufacturing, consolidating other costly product development expenditures, or any other economy-of-scale opportunities".[26]

An example of a mostly philanthropic funded organization in the US is Civica Rx, a non-profit manufacturer founded in 2018 with the mission to reduce the shortage of essential drugs and to stabilize the supply of 14 essential drugs for sale to participating hospitals and for wholesale distribution. The project proved interesting and created a network of 800 hospitals that choose this alternative supply channel (Brown et al., 2019).

In Europe, the biomedical research framework is more fragmented and research spending is lower in both absolute and relative terms than in the US (Bouillon et al., 2015). However, the European Commission has recently (November 2020) launched a European Pharmaceutical Strategy based on four pillars:

1. "ensuring access to affordable medicines for patients, and addressing unmet medical needs (in the areas of antimicrobial resistance and rare diseases, for example)
2. supporting the competitiveness, innovation and sustainability of the EU's pharmaceutical industry and the development of high quality, safe, effective and greener medicines

[25] https://www.globaljustice.org.uk/sites/default/files/files/resources/democratic_public_ownership_in_uk_pharmaceutical_sector_sept_2019.pdf

[26] https://www.medicalcountermeasures.gov/barda/core-services/ciadm.aspx

3. enhancing crisis preparedness and response mechanisms, diversified and secure supply chains, addressing medicines shortages
4. ensuring a strong EU voice in the world, by promoting a high level of quality, efficacy and safety standards."[27]

As part of this strategy some institutional changes have been proposed in relation to two existing agencies: the European Centre for Disease Control (ECDC) and the European Medicines Agency (EMA). The EC suggests to reinforce the ECDC mandate so that it may support the Commission and Member States in the following areas: epidemiological surveillance via integrated systems; preparedness and response planning, reporting and auditing; provision of non-binding recommendations and options for risk management; capacity to mobilise and deploy an EU Health Task Force to assist local response in Member States; building a network of EU reference laboratories and a network for substances of human origin. Concerning EMA, the EC proposes to reinforce its mandate so that EMA can facilitate a coordinated Union-level response to health crises by: monitoring and mitigating the risk of shortages of critical medicines and medical devices; providing scientific advice on medicines that may have the potential to treat, prevent or diagnose the diseases causing health crises; coordinating studies to monitor the effectiveness and safety of vaccines; coordinating clinical trials.

In addition to this, the EC has proposed to create a new agency, the Health Emergency Response Authority (HERA), inspired by BARDA in the US. Its mission will be

> to enable the EU and its Member States to rapidly deploy the most advanced medical and other measures in the event of a health emergency, by covering the whole value chain from conception to distribution and use. To that effect, it will, for example, undertake horizon scanning and foresight exercises to anticipate specific threats, identify promising potential countermeasures and underpinning competencies, and generate and disseminate knowledge of these. It will monitor and pool production capacity and development facilities, raw material requirements and availability, and ensure that supply chain vulnerabilities are addressed. It will support the development of crosscutting technologies and solutions sustaining multiple potential future threat responses (e.g. vaccine platform technologies, or the application of digital tools and artificial intelligence) as well as the development of specific countermeasures, including through clinical trials and data infrastructure. It will ensure that sufficient production capacity is available when necessary, as well as arranging for stockpiling and distribution. The European authority will plan, co-ordinate and assemble ecosystems of public and private capabilities that jointly enable a rapid response when the need arises. When an EU health emergency is declared, it will acquire the specific additional resources required to adequately react in the interest of all Member States. (European Commission, 11/11/2020).

While some of these proposals by the EC may go in the right direction, so far they are still limited in terms of scope, undefined in terms of resources, and lacking a coordinating mechanism. A more ambitious proposal to be explored is the creation of a large-scale public infrastructure that should operate throughout the whole drug life cycle (research, development, production and distribution) in critical areas where the industry is not interested in investing, not only when there

[27] https://ec.europa.eu/health/human-use/strategy_en

is an emergency. This new actor will not be another regulator of funding agency, but a knowledge-intensive public infrastructure (Castelnovo & Florio, 2020; Bernier et al., 2020) that may have the following characteristics:

a. Mission

The body managing the biomed infrastructure should decide on its own priorities according to the recommendations of the scientific community and health authorities. The strategic objective of Biomed Europa could be defined as follows: to build, over a 20-year period, a portfolio of innovative R&D projects in the biomedical area, which are not offered by the industry, but cover top priority for health in the 21st century. Biomed Europa could also usefully carry out clinical studies on drugs already authorized or whose patents have expired, with the goal of studying comparative effectiveness of existing treatments. Additional missions could involve the supervision of the supply of raw materials, which, for traditional drugs, are often imported from outside the EU, and the selection and supply (possibly entrusted to selected CDMOs) of equivalent drugs for which an unsatisfactory market equilibrium has been created, with unjustifiably high prices or with poorly verifiable quality as they are produced outside the EU.

b. Operation

A technological hub would be needed to coordinate the distribution system. It would also be necessary to imagine a functionally integrated complex of laboratories, which include facilities of the highest level of security for the study of lethal pathogens, and units accessible in rotation to different groups.

The activities downstream of basic and preclinical research could be managed by the infrastructure itself or through agreements with one or more CROs that contractually manage the manufacturing of the final product or aspects of its development. Some pharmaceutical firms or their consortia could be invited to co-develop a few projects. Thus, the definition of the technological base would depend on the configuration of the use of existing public and private structures. Perhaps the most important point of the Biomed Europa proposal is the large-scale attraction of human capital of excellence. Worldwide, the life sciences community presumably has the largest relative share of the approximately 7.8 million researchers estimated by UNESCO, with more female participation than in other fields.[28] Biomed Europa would serve to stimulate the labor market for European researchers, offering an alternative to employment in industry and universities, through in-house positions and in the form of international collaboration. By way of comparison, the scientific community of CERN and its international collaborations involve about 10,000 researchers, while EMBL (which covers only some of the topics that would be needed for Biomed Europa) has 1,700 employees over 80 research groups in six locations.

c. Legal base and governance

The legal status of any infrastructure is particularly relevant since it might affect the possibility to enter into contracts, to develop relationship with the industry, to hire staff, to hold central funds, to submit proposals or to receive grants, as well as to commercialize the research work or to transfer technology (OECD, 2014).

[28] http://uis.unesco.org/sites/default/files/documents/unesco-science-report-towards-2030-part1.pdf

Given its goals, Biomed Europa could be based on an inter-governmental treaty that gives rise to a supranational institution, with its headquarters adjoining, for example, the EMBL in Heidelberg, which is already a supranational structure, or the future Human Technopole campus,[29] or any of the excellent, but too fragmented, research infrastructures that already exist in Europe (Florio, 2019). International organizations, created through inter-governmental treaties, are governed by international law and their legal form usually allows to enter into contracts, to develop relationship with the industry, as well as it provides significant advantages in terms of tax exemptions, procurement regulations and favorable staff policy that makes it possible to attract very highly skilled collaborators (European Commission, 2008; Berberich et al., 2008). For these reasons, many European scientific organizations, such as EMBL, CERN or ESA, have been created through inter-governmental treaties. However, it is important to note that negotiating international treaties is not simple, as it often requires the approval of each parliament. Given the length and complexity of this parliamentary process, intergovernmental agreements are usually justified only for large research infrastructure (Jahreiss, 2006), as it would be Biomed Europa. The governance model of already existing European scientific international organizations could be duly adapted, combining a Council where the Member States are represented, and an Advisory Board where scientists and health authorities may draft the strategies and action plans.

Drug manufacture could be managed with appropriate facilities (owned or rented) that may be organized in collaboration with industrial partners or CDMOs. It might be critically important to devise a system of conventions with the national health authorities for the development of clinical trials (possibly involving the services of CROs through transparent competitive tendering). The infrastructure could also build a logistics distribution network through the national public postal systems or through tenders open to private firms.

In the European context, the governance model of EMBL, CERN or ESA could be duly adapted, combining a Council where the Member States are represented, and an Advisory Board where scientists and health authorities may draft the strategies and action plans.

d. IP management

Accessibility to drugs, which includes both affordability and availability, has to be one of the main goals of Biomed Europa. To grant it, several options for the management of innovations are available: these go from the traditional form of protection through intellectual property rights (IPRs), to a flexible and responsible intellectual property management (Access to Medicine Foundation, 2021), to the free accessibility to innovation. The choice of the best option should consider two main aspects: the financial structure of Biomed Europa, and the steps of the lifecycles in which Biomed is involved.

The advantage of a profit-oriented management of IPRs is the possibility to finance R&D through IP rent revenues. Moreover, patents strength the ability to ensure control of the development process and to negotiate with partners: this is particularly relevant in order to transfer innovations to the private sectors for further development and commercialisation (Stevens, Van Overwalle, Van Looy, & Huys, 2016). Patents might also be necessary to ensure accessibility of the end product (Drugs for Neglected Diseases initiative, 2018): for these reasons, also some access-oriented organizations, such as the Drugs for Neglected Diseases initiative, the NIH, or some public–private partnership—defined "partnership-focused" by Stevens et al. (2016)—resort to patenting.

[29] https://www.humantechnopole.it

To allow for a public-oriented use of IP, Biomed Europa may stimulate further innovation by sharing its IP 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, such as the Infectious Diseases Data Observatory, the Joint European Compound Library, WIPO Re:Search, the Global Health Innovative Technology Fund, TrasCelerate, and the National Center for Advancing Translational Sciences. IP assets sharing may also take place in the context of public–private partnerships, which also allow to pool the risks of R&D projects.

To maintain the right to the IP of the discoveries, and to facilitate access to patented medicines at affordable prices, the public infrastructure may resort to patent waivers or to non-exclusive voluntary licencing. 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, while with a non-exclusive voluntary license the patent holder voluntary grants multiple manufacturers permission to develop and manufacture generic versions of the drug. These licenses may be granted directly to manufacturers, through bilateral licenses, or might be managed through NGOs or international organizations, such as the WHO, which organize a patent pool, a portfolio of patents held by various actors but that relate to the use of a same technology (OECD, 2011). While patent pools have existed for more than a hundred years in other fields of technology, they are a relatively new concept in public health (Burrone, 2018), with the Medicines Patent Pool established in 2010 being the first effective (and efficient) attempt (Juneja et al., 2017; Lampe & Moser, 2016; Martinelli et al., 2020; Galassso & Schankerman, 2020; Wang, 2020).

Finally, innovation by Biomed Europa may be freely accessible: potential advantages of this choice have been analyzed by Balasegaram and coauthors (Balasegaram et al., 2017) and Murray et al. (2016). In this case, accessibility and usage of the innovations may or may not (as in the case of Open Source Malaria) be limited by some boundaries, such as the acceptance of some agreements forecasting, for example, that subsequent knowledge has to be contributed back (as in the case of Open Source Drug Discovery; Sugumaran, 2012). To ensure free access to innovation, Biomed Europa may patent its innovations, as a mechanism to keep knowledge free for use, and resort to non-exclusive licenses (as it is done, for example, by Open Source Drug Discovery), or might decide not to patent them, following an open model framework (as the one followed by the Structural Genomics Consortium). This framework is usually adopted when the project outcome involves databases, models, research tools and platform technologies, but not a drug itself: for these IP assets, the patenting cost represent a clear obstacle (Stevens et al., 2016). Some exceptions, characterized by the absence of patent protection even on the results of late stages of the R&D process, are currently represented by the Agora Open Science Trust (which nevertheless benefits from the market exclusivity granted to orphan drugs) and the Istituto di Ricerche Farmacologiche Mario Negri. In some cases, deep technology transfer from Biomed Europa to third parties should be part of its policy.

e. Funding

The public infrastructure should have an annual budget sufficient to launch a significant portfolio of R&D projects over 20 years, in order to cover areas that are under-researched or where the outcomes in terms of price are socially unacceptable. Taking as a benchmark the above mentioned figures for the R&D cost per drug of about €1bn per project, an infrastructure with an annual budget similar to the in-house R&D of the NIH (about €5–6bn per year) would be able to manage about 100 projects in 20 years. These might include, for example, studies into vaccines, new

antibiotics, new antiviral treatments, biological therapies, drugs for some neurological disorders, orphan drugs, repurposing and comparative risk–benefit studies and cost profiles.

Financial sustainability could be ensured through two complementary mechanisms, in proportions yet to be studied:

- a base of transfers from the budgets of member states, channelling into Biomed Europa the numerous inadequate streams of national public funds supporting research, currently captured directly or indirectly by private firms, at times with the mediation of the universities;
- a market component of revenues deriving from production licences and from the distribution at cost of new drugs (and biomedical technologies in general) and certified high-quality generic drugs to national health systems.[30]

Moreover, one may consider for some start-up years a special purpose levy (or other similar mechanism) on pharma companies with marketing authorization in Europe, in order to ask them to pay back to the public sector for the subsidies and incentives they have enjoyed with limited compensation or profit-sharing over the decades: a public dividend to jump-start public investment in R&D for public health.

f. Cost–benefit analysis

As a social benefit, the greatest return of Biomed Europa would come from the lower economic impact of severe pathologies, better quality of life, social cohesion and greater security, since there is little doubt about the possible recurrence of pandemics (Fan et al., 2018). What is it costing us to have been caught by surprise by the new coronavirus, totally unprepared despite predictions that there was a high probability of a pandemic? Before COVID-19 the World Bank[31] estimated that a pandemic similar to the Spanish flu could reduce global GDP by 5%, an order of magnitude that—added to the economic value of the years of "statistical life" lost, without counting the suffering that the losses cause in those who survive—would be of the same size as the consequences deriving from climate change. Because of the current pandemic, according to the World Bank (World Bank, 2021) the level of global GDP in 2021 could be 5.3% below pre-pandemic projections.

If the scientists are right, every ten years there is a high probability of a pandemic (between 2010 and 2019 there were two potential, and one actual pandemic, Abrignani 2020). Let us suppose that the accumulated economic value of GDP definitively lost in the EU over a decade (compared to the long-term trend) was one percentage point of GDP, and let us also ignore the economic value of the "statistical lives" lost and the psycho-physical suffering connected to the disease itself and to bereavement. In this case, public spending of 0.10% of GDP each year for the research and development of vaccines, drugs and any other tool that is useful in preventing or managing a pandemic episode would be fully recovered in terms of risk avoided, without counting the impact on other diseases currently not covered by the industry, or the savings for consumers of a price-calming effect. An infrastructure such as the one proposed would, therefore, be recoverable as a sort of social insurance for health risks worth one percentage point of GDP every 10 years.

[30] Price affordability for consumers would of course also depend on the reimbursement mechanism adopted by the national health systems.

[31] https://www.worldbank.org/content/dam/Worldbank/document/HDN/Health/WDR14_bp_Pandemic_Risk_Jonas.pdf

6 | CONCLUDING REMARKS

The biomedical research system is suffering from an irreconcilable contradiction between the priorities of science for health and science for profit. This illness can be cured by a radical R&D policy change, similar to what governments in Europe have done when the provision of essential services, including health services, were stuck in underinvestment and social exclusion. We need a new public policy for pharmaceuticals and other biomedical innovations.

The current system is characterized by the companies' investments mainly limited to most profitable diseases: consequently, several sectors do not benefit from adequate R&D investments.

Governments have tried to solve the problem through subsidies. The NIH experience is revealing. For decades, it has distributed tens of billions of dollars every year in research grants. Ultimately, the results of a large share of this research have been incorporated into innovations by the pharmaceutical industry and other for-profit biomedical industries. Although the scientific results of such generous public funding have often been good, there is a built-in inefficiency in this mechanism. Directly or indirectly subsidising the R&D budgets of pharma companies with public funds is not enough to permanently change the orientation of research priorities that is at the root of the failure with the novel coronavirus and other pathologies.

It is not just a policy based on subsidies that is inadequate, but also the IP system. The traditional Schumpeterian argument that monopoly spurs innovation (see, for example, McKenzie & Lee, 2008) do not take into account the global externalities arising from infectious diseases. Both suppliers of R&D, and eventually of vaccines and drugs, on the one hand, and potential patients, on the other, are unable to internalize the huge social costs and benefits related to a possible pandemic.

Another issue arising with the COVID-19 pandemic is the IP of biologics. According to the definition by FDA:

> Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. … Biologics are isolated from a variety of natural sources—human, animal or microorganism—and may be produced by biotechnology methods and other cutting-edge technologies.[32]

In this context it is debated to what extent IPRs apply to something that is not invented and is not the typical small-scale molecular entity (Acetylsalicylic acid (ASA) in Aspirin is 21 atoms, an engineered antibody may be 20,000 atoms) but is, at least in part, a therapeutic innovation based on certain properties of molecules or combinations of molecules existing in nature. With billions of dollars per year invested in the US (US$8.95bn in 2015) and elsewhere in biotech start-ups, and biologics and biosimilars, the industry also welcomes the usually over 10 years of data protection combined with patents (20 years) whenever this is possible.[33] Moreover, given the particular nature of biologics and genetic treatments, their production process requires extremely high infrastructure costs and there are plenty of structural barriers to entry: this allows the manufacturers to abuse their monopoly on the drugs even after the patent expires (Conti et al., 2020).

[32] https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers

[33] https://www.wipo.int/wipo_magazine/en/2017/03/article_0007.html

In this paper we have proposed a corrective public intervention: the creation of an international, science-informed and publicly funded research infrastructure for pharmaceutical and biomedical research, Biomed Europa, whose goal is to focus on those diseases that will pose the greatest threats to human and social welfare over future decades.

Of course, this infrastructure may also suffer from some limitations. Public organizations can be captured by private interests or political groups, have difficulties in matching technical and political deadlines, show inefficiency and problems of incentives, decision-making and prioritization among the interests of countries, allocation of benefits and externalities, etc. This criticism in principle may apply to all branches of government. For example, lawmakers can be lobbied by the pharma companies. According to Wouters et al. (2020):

> 1999 to 2018 … the pharmaceutical and health product industry spent $4.7 billion… on lobbying the US federal government… (including) contributions to presidential and congressional electoral candidates, national party committees, and outside spending groups, and contributions to state candidates and committees. Contributions were targeted at senior legislators in Congress involved in drafting health care laws and state committees that opposed or supported key referenda on drug pricing and regulation.

Regulators are also exposed to asymmetric information, managers of state-owned enterprises can be badly hired, loyal to a policymaker and not to the public interest. However, this journal has often discussed counter-arguments and counter-examples to this widespread argument against public ownership, and several recent special issues and articles in international journals about the return of state-owned enterprises after decades of privatization. Bernier et al. (2020) provide a wide overview of recent literature that points to the conditions for efficiency of government-owned organizations, including certain features of the quality of government.

The property structures should respond to specific contexts and demands (Hansmann, 1996, 2006), according to social efficiency considerations. For this reason, the proposal presented in this paper is flexible, and it suggests redefining the optimal combination of contracts (Ayotte and Hansmann, 2015). It does not amount to outright nationalization of the industry: Biomed Europa should also consider public–private partnerships in order to increase flexibility of its approach. After all, the system of health care provision we have built in Europe is overall successful and based on a large public sector combined with regulated private markets. It seems time to extend the merit of such a model to biomedical R&D, by introducing a new public player in the arena.

ACKNOWLEDGEMENTS

Some of the ideas presented in this paper are based on presentations made at the Diseguaglianze e Diversità Forum meetings in 2019 and in 2020, seminars and conferences organized by Università Bocconi, Università degli Studi di Milano, Gran Sasso Science Institute and the Società Italiana degli Economisti. We are grateful to Martina Dalmolin, Letizia Giorgetti, Laura Iacovone and Chiara Pancotti for comments on earlier versions.

Massimo Florio is currently (2021) involved in a study for the European Parliament "European pharmaceutical research and development: Could a public infrastructure overcome market failures?" Procedure: EPRS/STOA/SER/20/228N, but this paper was written in a personal capacity before the current assignment and no EU institution or any third party is in any way involved in the opinions expressed here.

ORCID

Massimo Florio https://orcid.org/0000-0001-9315-3580
Simona Gamba https://orcid.org/0000-0002-5538-2873

REFERENCES

Abrignani, S. (2020). Si deve realizzare un vaccino per tutti i coronavirus. *Corriere della Sera*, 11 November 2020, p. 27.

Access to Medicine Foundation (2021). *Access to medicine index 2021*. Amsterdam: Access to Medicine Foundation.

Acemoglu, D., & Linn, J. (2004). Market size in innovation: Theory and evidence from the pharmaceutical industry. *Quarterly Journal of Economics*, 1049–1090.

Agha, L., Kim, S., & Li, D. (2020). *Insurance design and pharmaceutical innovation*. NBER Working Paper w27563.

Altman, M. J. (2020). Q&A with Dr. Peter Hotez: Behind the scenes of COVID-19 vaccine research. United Nations Foundation, 15 May, https://unfoundation.org/blog/post/qa-with-dr-peter-hotez-behind-the-scenes-of-covid-19-vaccine-research/

Atkinson, A. B., & Stiglitz, J. E. (2015). *Lectures on Public Economics Updated edition*, Economics Books, Princeton University Press, edition 1, 1990, edition 2, 2015.

Ayotte, K., & Hansmann, H. (2015). A nexus of contracts theory of legal entities. *International Review of Law and Economics*, *42*, 1–12.

Balasegaram, M., Kolb, P., McKew, J., Menon, J., Olliaro, P., Sablinski, T., … Wilbanks, J. (2017). An open source pharma roadmap. *PLOS Medicine*.

Barrenho, E., Miraldo, M., & Smith, P. C. (2019). Does global drug innovation correspond to burden of disease? The neglected diseases in developed and developing countries. *Health Economics*, 123–143.

Berberich, F., Griffiths, E., Lichnewsky, A., Brunel, E., Mahdi, V., Schwemmer, K., … Subirada, F. (2008). *Report on options for a legal entity*. PRACE Consortium Partners.

Bernier, L., Florio, M., & Bance, P. (2020). *The Routledge handbook of state-owned enterprises*. Routledge.

Blume-Kohout, M. E., & Sood, N. (2013). Market size and innovation: Effects of Medicare part D on pharmaceutical research and development. *Journal of Public Economics*, 327–336.

Bouillon, R., Slordahl, S., Nogueira, M. M., S K., Varela-Nieto, I., Pacini, G., … Syka, J. (2015). Public investment in biomedical research in Europe. *The Lancet: correspondence*, 1135.

Brown, D. (2019). Medicine for all. The case for a public option in the pharmaceutical industry. *Democracy Collaborative*, 31 August.

Brown D., Chow H., Hanna T. M., & McDonald D. (2019). *Democratic public ownership in the UK pharmaceutical sector*, Working Paper, The Democracy Collaborative, Global Justice Now, and Just Treatment.

Buranyi, S. (2020). How profit makes the fight for a coronavirus vaccine harder, *The Guardian*, 4 March.

Burrone, E. (2018). Patent pooling in public health. In M. Chon, P. Roffe, & A. Abdel-Latif, *The Cambridge handbook of public–private partnerships, intellectual property governance, and sustainable development* (pp. 93–108). Cambridge University Press.

Carette, J. E., Raaben, M., Wong, A. C., Herbert, A. S., Obernosterer, G., Mulherkar, N., Kuehne, A. I., Kranzusch, P. J., Griffin, A. M., Ruthel, G., Dal Cin, P., Dye, J. M., Whelan, S. P., Chandran, K., & Brummelkamp, T. R. (2011). Ebola virus entry requires the cholesterol transporter Niemann–Pick C1. *Nature*, *477*(7364), 340–343.

Castelnovo, P., & Florio, M. (2020). Mission-oriented public organizations for knowledge creation. In Bernier L., Florio M., & Bance P. (Eds.), *The Routledge handbook of state-owned enterprises*. Routledge.

Chakravarthy, R., Cotter, K., Dimasi, J., Milne, C. P., & Wendel, N. (2015). Public and private sector contributions to the research & development of the most transformational drugs of the last 25 years: From theory to therapy. *Therapeutic Innovation & Regulatory Science*, *50*(6), 759–768.

Chen, L. C., Evans, T. G., & Cash, R. A. (1999). Health as a global public good. In I. Kaul, I. Grunberg, & M. Stern, *Global public goods* (pp. 284–304). Oxford University Press.

Cleary et al. (2018). Contribution of NIH funding to new drug approvals 2010–2016. *Proceedings of the National Academy of Sciences*, *115*(10), 2329–2334.

Clemens, J. (2013). *The effect of US health insurance expansions on medical innovation*. NBER Working Paper w19761.

Clemens, J., & Rogers, P. (2020). *Demand shocks, procurement policies, and the nature of medical innovation: Evidence from wartime prosthetic device patents*. NBER Working Paper w26679.

Cockburn, I., & Henderson, R. (2001). Scale and scope in drug development: Unpacking the advantages of size in pharmaceutical research. *Journal of Health Economics*, 1033–1057.

Comanor, W., & Sherer, F. (2013). Mergers and innovation in the pharmaceutical industry. *Journal of Health Economics*, 106–113.

Congressional Budget Office. (2021). *Research and development in the pharmaceutical industry*. Congressional Budget Office.

Conti, R., Gruber, J., Ollendorf, D., & Neumann, P. (2020). *Valuing rare pediatric drugs: An economic perspective*. NBER Working Paper w27978.

Côté, M., Misasi, J., Ren, T., Bruchez, A., Lee, K., Filone, C. M., Hensley, L., Li, Q., Ory, D., Chandran, K., & Cunningham, J. (2011). Small molecule inhibitors reveal Niemann–Pick C1 is essential for Ebola virus infection. *Nature*, *477*(7364), 344–348.

Danzon, P., Epstein, A., & Nicholson, S. (2007). Mergers and acquisitions in the pharmaceutical and Biotech industries. *Managerial and Decision Economics*, 307–328.

Dimitri, N. (2012). R&D Incentives for neglected diseases. *PLoS One*.

Drugs for Neglected Diseases initiative. (2018). *Intellectual property policy*. Drugs for Neglected Diseases initiative.

Dubois, P., De Mouzon, O., Scott-Morton, F., & Seabright, P. (2015). Market size and pharmaceutical innovation. *RAND Journal of Economics*, 844–871.

European Commission (11/11/ 2020). *Building a European Health Union: Reinforcing the EU's resilience for cross-border health threats*. Brussels: European Commission.

European Commission (2008). *Commission Staff Working Document. Accompanyng document to the Proposal for a Council Regulation on the Community legal framework for a European Research Infrastructure*. Brussels: European Commission.

Fan, V. Y., Jamison, D. T., & Summers, L. H. (2018). Pandemic risk: how large are the expected losses? *Bulletin of the World Health Organization*, *96*(2), 129–134.

Finkelstein, A. (2004). Static and dynamic effects of health policy: Evidence from the vaccine industry. *Quarterly Journal of Economics*, 527–564.

Florio, M. (2019). *Investing in science. Social cost-benefit analysis of research infrastructures*. MIT Press.

Galassso, A., & Schankerman, M. (2020). *Licensing life-saving drugs for developing countries: Evidence from the Medicines Patent Pool*. CEPR Discussion Paper No. DP15544.

Gamba, S. (2017). The effect of intellectual property rights on domestic innovation in the pharmaceutical sector. *World Development*, 15–27.

Gamba, S., Magazzini, L., & Pertile, P. (2019). *R&D and market size: Who benefits from orphan drug legislation?* Working Paper Series, University of Verona.

GAO (2017). *Drug industry: Profits, research and development spending, and merger and acquisition deals*. GAO.

Gard, D. (2020). An updated guide to the coronavirus drugs and vaccines in development, *STAT*, 19 March.

G-Finder. (2019). G-FINDER: Global Funding of Innovation for Neglected Diseases. G-Finder.

Gurrìa, A. (2020). *Coronavirus (COVID-19): Joint actions to win the war*, OECD.

Hansmann, H. (2012). Ownership and organizational form. In *The handbook of organizational economics* (pp. 891–917). Princeton University Press.

Hansmann, H. (1996). *The ownership of enterprise*. Harvard University Press.

Harris, J. (2006). *The value of life: An introduction to medical ethics*. Routledge.

Jahreiss, H. (2006). Report of the Workshop on the "Legal forms of research infrastructures of pan-European interest". Brussels: ESFRI, European Commission.

Jobjörnsson, S., Forster, M., Pertile, P., & Burman, C.-F. (2016). Late-stage pharmaceutical R&D and pricing policies under two-stage regulation. *Journal of Health Economics*, 298–311.

Juneja, S., Gupta, A., Moon, S., & Resch, S. (2017). Projected savings through public health voluntary licences of HIV drugs negotiated by the Medicines Patent Pool (MPP). *Plos One*.

Kaul, I., Grunberg, I., & Stern, M. (1999). Global public goods: concepts, policies and strategies. In I. Kaul, I. Grunberg, & M. Stern, *Global public goods* (pp. 450–508). Oxford University Press.

Kesselheim, A., & Avorn, J. (2013). The most transformative drugs of the past 25 years: A survey of physicians. *Nature Perspectives*, 425–431.

Kesselheim, A., Tan, Y., & Avorn, J. (2015). The roles of academia, rare diseases, and repurposing in the development of the most transformative drugs. *Health Affairs*, 286–293.

Lakdawalla, D., Malani, A., & Reif, J. (2017). The insurance value of medical innovation. *Journal of Public Economics*, 94–102.

Lampe, R., & Moser, P. (2016). Patent pools, competition, and innovation—evidence from 20 US industries under the new deal. *Journal of Law, Economics, and Organization*, 1–36.

Malerba, F., & Orsenigo, L. (2015). The evolution of the pharmaceutical industry. *Business History*, 664–687.

Martinelli, A., Mina, A., & Romito, E. (2020). *Collective licensing and asymmetric information: The double effect of the Medicine Patent Pool on generic drug markets*. Scuola Superiore Sant'Anna Working Paper.

Mazzucato, M., & Li, H. (2020). Is it time to nationalise the pharmaceutical industry? *BMJ*.

Mazzucato, M. and Momenghalibaf, A. (2020). Drug companies will make a killing from coronavirus. *New York Times*, 18 March.

Melnikova, I. (2012). Rare diseases and orphan drugs. *Nature Reviews Drug Discovery*, *11*(4), 267–268. https://doi.org/10.1038/nrd3654

McCabe, C., Claxton, K., & Tsuchiya, A. (2005). Orphan drugs and the NHS: should we value rarity? *BMJ*, 1016–1019.

McKenzie, R. B., & Lee, D. R. (2008). *In defense of monopoly, how market power fosters creative knowledge*. University of Michigan Press.

Menachery, V., Yount, B., Debbink, K., et al. (2015). A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nature Medicine*, *21*, 1508–1513.

Mirowski, P., & Van Horn, R. (2005). The contract research organization and the commercialization of scientific research. *Social Studies of Science*, 503–548.

Mittra, J. (2007). Life science innovation and the restructuring of the pharmaceutical industry: Merger, acquisition and strategic alliance behaviour of large firms. *Technology Analysis & Strategic Management*, 279–301.

Murray, F., Aghion, P., Dewatripont, M., Kolev, J., & Stern, S. (2016). Of mice and academics: Examining the effect of openess on innovation. *American Economic Journal: Economic Policy*, 212–252.

Newton, C. (2007). The role of small- or medium-sized enterprises in drug discovery. *Comprehensive medicinal chemistry II*, 489–525.

Nord, E., Richardson, J., Street, A., Kuhse, H., & Singer, P. (1995). Maximizing health benefits vs egalitarianism: An Australian survey of health issues. *Social Science and Medicine*, 1429–1437.

OECD. (2011). *Collaborative mechanisms for intellectual property management in the life sciences*. OECD.

OECD. (2014). *International distributed research infrastructures: Issues and options*. OECD.

O'Neill, J. (2016). Tackling drug-resistant infections globally: Final report and recommendations, May. *Review on Antimicrobial Resistance*.

Philipson, T. J., & Zanjani, G. (2014). Economic analysis of risk and uncertainty induced by health shocks: A review and extension. *Handbook of the Economics of Risk and Uncertainty*, 453–491.

Prasad, V., & Mailankody, S. (2017). Research and development spending to bring a single cancer drug to market and revenues after approval. *JAMA Internal Medicine*, *177*(11), 1569–1575.

Qian, Y. (2007). Do national patent laws stimulate domestic innovation in a global patenting environment? A cross-country analysis of pharmaceutical patent protection, 1978–2002. *Review of Economics and Statistics*, 436–453.

Quammen, D. (2017). *Spillover. L'evoluzione delle pandemie*, 12th edition, trans. L. Civalleri, Adelphi.

Rea, P. A., Pauly, M. V., & Burns, L. R. (2018). *Managing discovery in the life sciences. Harnessing creativity to drive the biomedical innovation*. Cambridge University Press.

Rizvi, Z. (2020). How the COVID-19 outbreak shows the limits of pharma's monopoly model, *Public Citizen*, 20 February.

Rodwell, C., & Aymé, S. (2015). Rare disease policies to improve care for patients in Europe. *Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease*, 2329–2335.

Schuhmacher, A., Gassmann, O., & Hinder, M. (2016). Changing R&D models in research-based pharmaceutical companies. *Journal of Translational Medicine*.

Stein, F., & Sridhar, D. (2017). Health as a "global public good": Creating a market for pandemic risk. *BMJ*.

Stern, A. D. (2017). Innovation under regulatory uncertainty: Evidence from medical technology. *Journal of Public Economics*, 181–200.

Stevens, H., Van Overwalle, G., Van Looy, B., & Huys, I. (2016). Intellectual property policies in early-phase research in public–private partnerships. *Nature Biotechnology*, 504–510.

Sugumaran, G. (2012). Open source drug discovery—redefining IPR through open source innovations. *Current Science*, 1637–1639.

Tambuyzer, E. (2010). Rare diseases, orphan drugs and their regulation: questions and misconceptions. *Nature Reviews Drug Discov*, *9*(12), 921–929. https://doi.org/10.1038/nrd3275. Epub 2010 Nov 9.
The Economist 15 February 2020, Justin Trudeau's Drug Problem, p. 36.
The Economist, 14 March 2020, Populations of one. Personalised medicine. *Technology quarterly*, p. 3
The Economist 22 June 2019, American drugmakers are raising prices. Again.
The Economist, 27 June 2020, Pandemic-proofing the planet, p. 61.
The Economist, 18 July 2020, America first-aid, p. 34.
The Economist, 22 August 2020, The viral universe, p. 13.
T'Hoen, H. (2020). Coronavirus. The latest problem Big Pharma won't solve. *Barron's*, 7 February.
Tresch, R. W. (2008). *Public Sector Economics*, Routledge.
Wang, L. X. (2020). *Global drug diffusion and innovation with a patent pool: The case of HIV drug cocktails*. Max Planck Institute for Innovation and Competition Working Paper.
World Bank (2021). Global economic prospects.
Wouters, O. J., McKee, M., & Luyten, J. (2020). Estimated research and development investment needed to bring a new medicine to market, 2009–2018. *JAMA*, *323*(9), 844–853.
Zachariadis, I. (2019). Multinational enterprises, value creation and taxation. *European Parliament Research Service*.

How to cite this article: Florio, M., & Gamba, S. Biomed Europa: After the coronavirus, a public infrastructure to overcome the pharmaceutical oligopoly. *Ann Public Coop Econ*. 2021;*92*:387–409. https://doi.org/10.1111/apce.12341