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Development of public financing initiatives in pharmaceutical R&D – is it the key to the future of medicine?

A gyógyszeripari kutatás-fejlesztés állami finanszírozási kezdeményezéseinek fejlesztése - ez az orvostudomány jövőjének kulcsa?

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Abstract

The pharmaceutical research and development process only begin if the drug holds the promise of being profitable. In the past pharmaceutical companies aimed to find solutions for common diseases with high prevalence. Meanwhile, the unmet medical need did not decrease in several therapeutic areas.

Public policy makers had to encourage pharmaceutical companies to invest in research and development in areas with high unmet medical need. Several public measures (including financing initiatives) were introduced. In this paper, we focus on the public research and development and regulatory incentives to accelerate investment.

In the past decades, there has been a considerable increase in public funding in the European Union, which diverted the attention of innovators to areas with public priorities. Still, there are areas where public funding alone could not lead to a prompt solution.

Keywords: pharmaceutical industry, R&D, public funding, Horizon Europe

Kulcsszavak: gyógyszeripar, K + F, állami finanszírozás, Európa Horizont

Background

In a world impacted by COVID-19 it is not necessary to emphasise the importance of pharmaceutical research and development (R&D). Developing solutions to such an impactful health challenge requires extraordinary commitment along with substantial human and financial resources.

Still, screening around 10,000 target molecules is needed to find one that would be available to patients[1]. The costs of drug development are enormous, considering the sunk costs of unsuccessful drug development phases. The estimated cost of developing a drug (including sunk costs) is in the range of 1 to 4 billion USD according to different studies.[2] [3] Hence, it is not surprising that the focus of pharmaceutical drug development has shifted during the last decades.

Shifting focus in pharmaceutical R&D

[1] https://www.magyosz.org/hu/oldal/gyogyszerfejlesztes (2021.03.20.)
[2] Wouters et al (2020)
[3] PricewaterhouseCoopers (PwC) (2012)

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In the past, pharmaceutical companies aimed to explore solutions for common diseases with high prevalence, which reduced the financial risks of drug development, but required strong promotional activities to maximize profit. This approach is often called as the 'blockbuster therapy' era of pharmaceutical R&D, because even relatively small market share in a large patient population could result in more than one billion USD of annual sales (which is the threshold of blockbuster medicines).

Figure 1 shows that the justifiable price determined by the economic value and disease rarity are inversely proportional. In the past, therapies were designed to reach blockbuster status in diseases with large population in Western countries in the majority of cases with minor added clinical value. Consequently, the unmet medical need did not decrease in rare diseases, small subgroups of more common diseases (e.g. patients with antimicrobial resistance in infectious diseases) or diseases in developing countries (e.g. malaria). The return on investment was less in these niche areas.

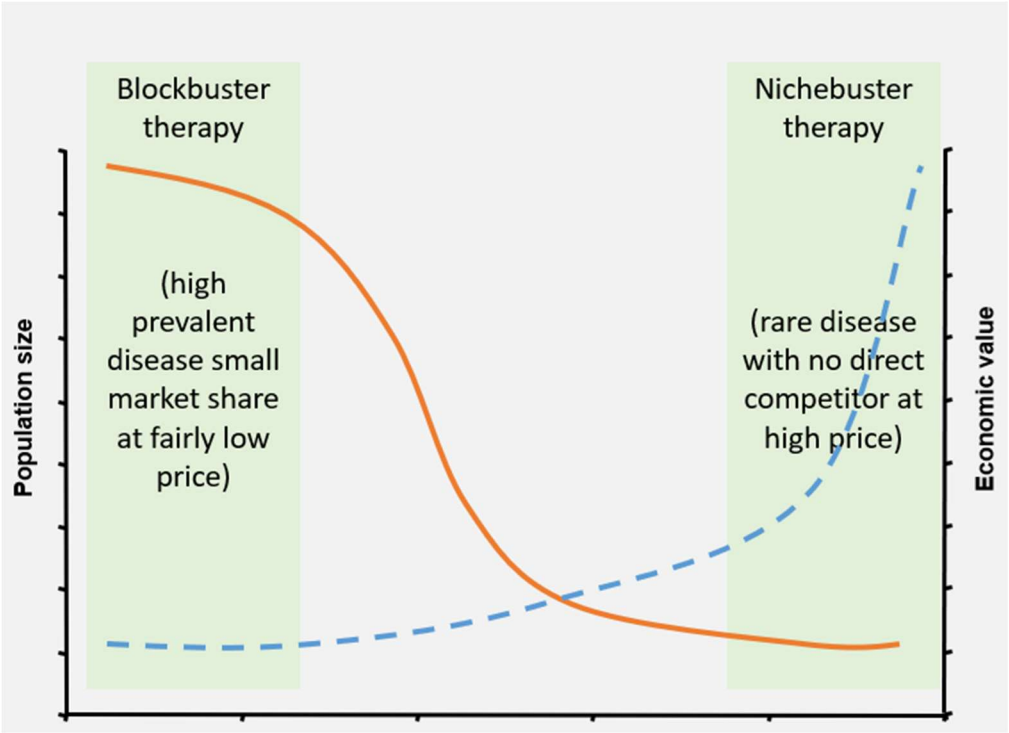

Figure 1. Shift in pharmaceutical R&D in the dimension of population size and economic value

In the private sector, the decision of investing into the development of a new drug candidate is a business decision, the pharmaceutical R&D process only begins if the drug holds the promise of being profitable, in other words, only if the project has positive net present value.

As the unmet medical need was typically higher in diseases with small population sizes, public policy makers had to encourage investment to pharmaceutical companies. This resulted in several public incentives in the most important markets. The initial R&D phase could be supported by public research grants and the establishment of supporting platforms, such as patient registries. Regulatory incentives were provided by several measures, such as granting extended market exclusivity, easing standard regulatory requirements, accelerating regulatory procedures, reducing regulatory fees, and providing assistance in designing clinical trial protocols. In the pricing and reimbursement decisions, automated reimbursement status, special

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reimbursement categories, or higher willingness-to-pay threshold for one unit of health gain support the market access of new medicines in neglected diseases. In this paper, we focus on the public R&D and regulatory incentives to accelerate investment in areas with high unmet medical needs.

Public incentives to facilitate pharmaceutical R&D in rare diseases

A legal framework that revolutionized pharmaceutical R&D in rare diseases is the Orphan Drug Act introduced in the USA in 1983. The Orphan Drug Act provided financial incentives, including a seven-year period of market exclusivity and tax credits up to 50% of R&D expenses to pharmaceutical companies who developed a drug for rare diseases. The definition of rare disease was defined as a disease affecting less than 200,000 people in the USA. Following this Act, by 1990, the U.S. Food and Drug Administration (FDA) designated 370 products for orphan status. By 2002, the number of orphan designations increased to almost 1,100. [4]

The European legal framework followed the American legislation and laid down the basic principles and stimulated orphan drug development in 2000. The European Union (EU) set multiple criteria for orphan designation, including:

- a treatment, prevention or diagnosis of a life-threatening or chronically debilitating disease,
- the prevalence of the condition in the EU is less than 5 in 10,000, or it is unlikely that marketing the medicine would generate sufficient return on investment due to the small population size,
- no satisfactory method of diagnosis, prevention, or treatment is available, or the new medicine results in significant benefit to patients [5].

The EU introduced several regulatory incentives, such as protocol assistance, or market exclusivity for a period of 10 years. In addition, there is a wide range of research grants in rare diseases by the European Commission. Figure 2 shows how the EU measures facilitated the orphan medicinal product authorisation at the European Medicines Agency (EMA). The number of authorised orphan drugs has been increasing since 2000.

The example of the Orphan Drug Act and the following EU legal framework proved that public initiatives can help fill the gaps of purely market-based solutions in pharmaceutical R&D.

[4] https://www.fda.gov/industry/orphan-products-development-events/story-behind-orphan-drug-act (2021.03.20.)
[5] https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview (2021.03.20.)

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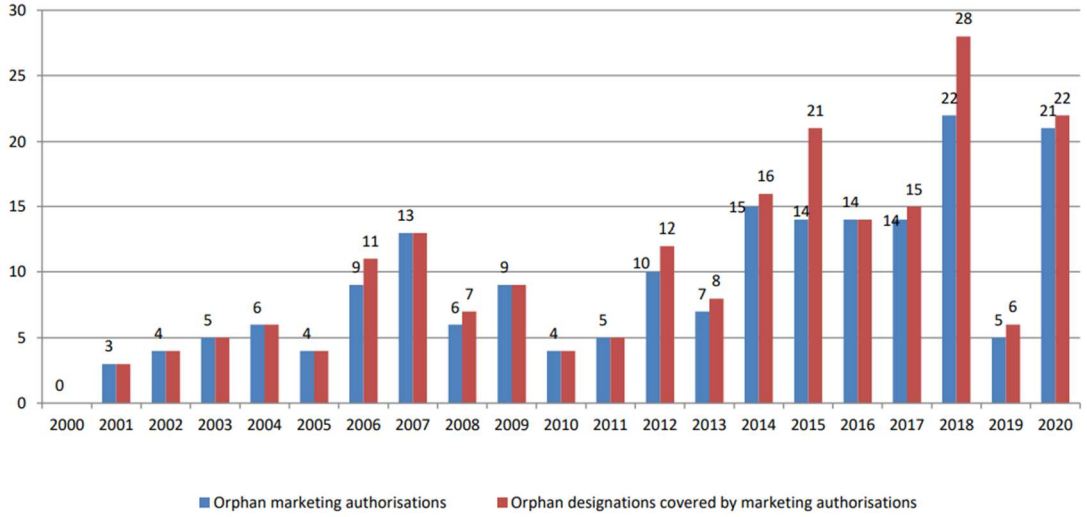

Figure 2. Authorised orphan medicinal products by EMA from 2000 to 2020[6]

An example of a prevailing challenge

Pharmaceutical R&D successfully provided solutions to the majority of bacterial infections in the ’80s and ’90s. The availability of cheap generic medicines prevented pharmaceutical companies from investing into new classes of antibiotics, consequently, antimicrobial resistance has become an emerging health challenge. The annual public EU investment into antibiotic R&D was 147 million EUR between 2007 and 2013, while the USA invested 260 million USD in 2015. As for the private investment, global venture capital in antimicrobial R&D plummeted by 28% between the two five-year periods of 2004-2008 and 2009-2013. [7]

In response to this trend, many public incentives were introduced to facilitate companies conducting R&D in the field of antibiotics. In 2016, there were 58 active R&D initiatives globally that directly subsidized antibiotics development.[8] Still, despite the numerous incentive opportunities, the issue of antimicrobial resistance is an emerging issue.

Triumph of public financing in pandemic control

The Ebola virus outbreak in West Africa in 2014 was the largest one recorded in history infecting 30,000 people by 2016 and causing the death of 11,000 people.[9] It put the spotlight on the importance of R&D in neglected diseases of low-income regions.

The total research funding for Ebola and Marburg virus was 1.035 billion USD, 42.0% of which was disbursed in 2014 and 2015 during the outbreak of the virus. The following graph summarizes the sources of investment in Ebola research funding.

[6] Orphan Medicines Figures 2000- 2020 (europa.eu) (2021.03.20.)
[7] RENWICK, MATTHEW J et al (2016)
[8] RENWICK, MATTHEW J et al (2016)
[9] FITCHETT JR ET AL (2016)

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The total funding is divided into three categories:

- public (e.g. National Institutes of Health, European Commission)
- philanthropic (e.g. Gates Foundation, Wellcome Trust),
- public-private partnership (PPP) [e.g. Innovative Medicines Initiative].[10]

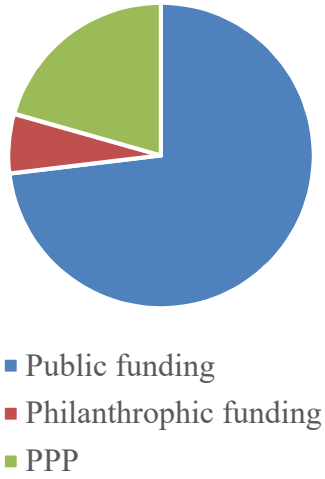

Figure 3. Funding awarded to Ebola research from 1997 to 2015 divided by the source of funding[11]

Ebola could not be stopped without public-private partnership, which indicates the importance of public interventions to provide answers to societal challenges.

European public grants

The European Union has dedicated Framework Programmes to R&D with a growing budget since 1984. The 7th Framework Programme (FP7) represented a new level of funding, as its budget was over EUR 50 billion, EUR 6 billion of which was dedicated to health R&D. [12]

A recent study showed that approximately 80% of funded Health projects in FP7 lack evaluation. Hence, the EU introduced a program to capture the results of the projects funded by the initiatives.[13]

Horizon 2020 became the largest ever publicly financed research programme. The budget was almost EUR 80 billion throughout the 7-year cycle (2014-2020). 38.5% (EUR 29.68 billion) of the overall budget targeted societal challenges, among which health, demographic change, and wellbeing represented the highest proportion. [14]

[10] https://www.imi.europa.eu/projects-results/project-factsheets?programmes=ebola (2021.03.11)
[11] FITCHETT JR et al. (2016)
[12] https://ec.europa.eu/research/fp7/pdf/fp7-inbrief_en.pdf (2021.03.11.)
[13] https://cordis.europa.eu/project/id/733266 (2021.03.11.)
[14] untitled (europa.eu) (2021.03.11.)

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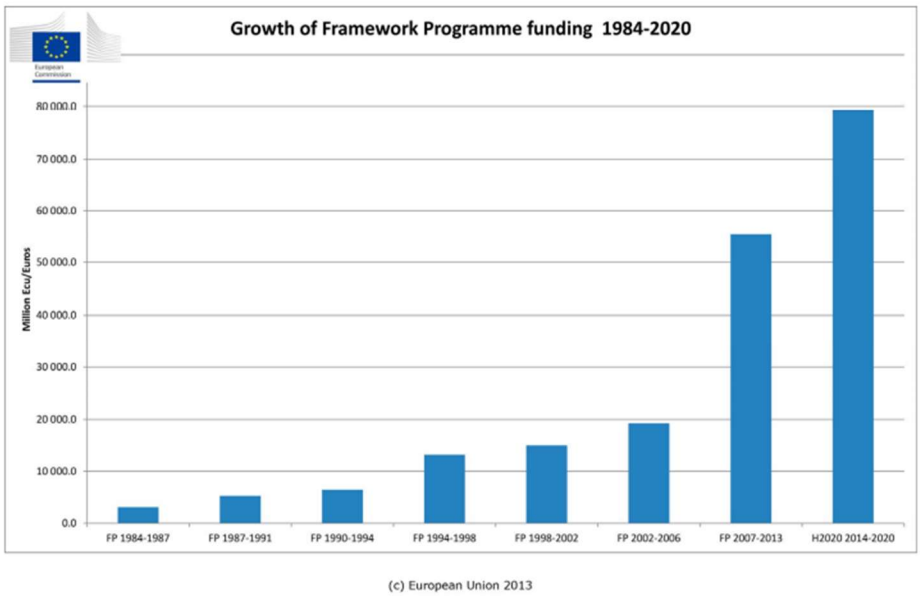

4. Figure EU Framework Programme budget from 1983 to 2020[15]

The Innovative Medicines Initiative (IMI) is an example of how public-private partnership can provide incentives to market-based solutions in areas with public importance. IMI is financed by the European Union (represented by the European Commission) and the European pharmaceutical industry (represented by the European Federation of Pharmaceutical Industries and Associations). The budget of the first IMI programme (IMI1) was EUR 2 billion between 2008 and 2013. During that time, it was the most significant PPP. The IMI2 programme ran with an extended budget of EUR 3.3 billion from 2014 to 2020.

Besides the budget increase, it is important to note that during the IMI2 programme, other life sciences organisations also had the chance to contribute to the funding as associated partners. The IMI programme budgets were available to universities, research organisations, patient organisations, and small and medium-sized enterprises (SME). [16]

The objective of IMI is to develop the next generation of vaccines, medicines, and treatment, such as new antibiotics or treatment to rare diseases. The IMI plays an essential role in facilitating research on fields where stand-alone organisations or companies would not start research due to the lack of resources, anticipated profit level, etc. The strategic research agenda of the IMI focuses on '*priority disease areas, where safe, effective treatments are lacking, and/or where the impact on public health is greatest'*.[17]

The projects funded by the IMI stimulate the cooperation between international organisations and corporations. By 2021, 167 projects were started, to which more than 5,000 participants contributed. [18]

The below graph summarizes the funding provided via the IMI1 and IMI2 funds, divided by regions.

[15] untitled (europa.eu) (2021.03.11.)
[16] https://www.imi.europa.eu/about-imi/imi-funding-model (2021.03.25.)
[17] https://www.imi.europa.eu/about-imi/strategic-research-agenda (2021.03.25.)
[18] https://www.imi.europa.eu/ (2021.03.25.)

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Figure 5. IMI project budgets across Europe[19]

Based on this figure, the vast majority of funding is spent in wealthier Western-European countries. This trend is in line with the landscape of other EU programmes. Healthcare-related FP7 and H2020 research funds were disproportionally allocated to the EU-15 versus the EU-13, as 96.9% of the total healthcare grants were assigned to EU-15 countries.[20] This leads to the conclusion that a higher burden of disease (common in Eastern European countries) is not in correlation with distributing more research funding in these countries.

The next EU funding programme would be Horizon Europe. Its budget – being EUR 95.5 billion – is even higher than that of Horizon 2020. Pillar II covers Global challenges and European Industrial Competitiveness, including the Health area. Its proposed budget is EUR 52.7 billion. The key areas of planned interventions include:

- health across life span,
- non-communicable and rare diseases,
- personalised medicine,
- infectious diseases, including neglected and poverty-related diseases, etc.[21]

[19] https://www.imi.europa.eu/projects-results/maps-statistics (2021.03.25.)
[20] KALÓ et al. (2019)
[21] horizon_europe_en_investing_to_shape_our_future.pdf (europa.eu) (2021.03.11.)

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Among Research & Innovation mission areas, cancer is highlighted[22]. The EU's mission is to save 3 million lives and to ensure longer and better living in connection with cancer by 2030. A mission is a set of actions across disciplines to achieve a goal within a specified timeframe, while making an impact on the society. In terms of the Mission on Cancer, equitable access, prevention, and optimised diagnostics are the essential tools to reach the goal.[23]

Health innovations are considered as key among industrialized European partnerships. For such partnerships, commitment to financial and in-kind contribution is essential.

The aim of Horizon Europe is to make a comprehensive impact in several areas, not only in science, but also in the economy and the society. Table 1 summarizes the main attributes in the different fields where the EU wants to make an impact via Horizon Europe.

SCIENTIFIC IMPACT	SOCIETAL IMPACT	ECONOMIC IMPACT
Creating high-quality new knowledge	Addressing EU policy priorities & global challenges through R&I	Generating innovation-based growth
Strengthening human capital in R&I	Delivering benefits & impact via R&I missions	Creating more and better jobs
Fostering diffusion of knowledge and Open Science	Strengthening the uptake of R&I in society	Leveraging investments in R&I

Table 1. Key impact pathways in Horizon Europe[24]

Conclusion

In the past decades, there has been a considerable increase in public funding for pharmaceutical R&D in the European Union, which diverted the attention of innovators to areas with public priorities.

However, the problem of antimicrobial resistance indicates that there are areas where public funding alone could not lead to a prompt solution. In such situations, a broad range of public incentives may provide better solution, just like in the case of orphan medicines.

Besides the better coordination of parallel public research funding, the methods of allocating research funds should be also revised. As the burden of disease is higher in Eastern European countries, involving organisations from these countries to defeat public health challenges would be essential in the future.

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[22] Mission area: Cancer | European Commission (europa.eu) (2021.03.11.)
[23] Conquering cancer - Publications Office of the EU (europa.eu) (2021.03.11.)
[24] horizon_europe_en_investing_to_shape_our_future.pdf (europa.eu) (2021.03.20.)

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