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Intellectual property

in the innovative biopharmaceutical industry: a must for patients, society and the industry

October 2022

Intellectual property in the innovative biopharmaceutical industry: a must for patients, society and industry

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1. Introduction

Patents give companies a temporary monopoly on their invention. Patents are therefore an important **cornerstone of our innovation system**. During the COVID-19 pandemic, a **fierce debate** flared up **about vaccine patents**. Is it okay for life-saving vaccines to be protected by a patent? In general, are patents the right solution for an important industry such as the pharmaceutical sector? Do medicines not belong to everyone?

Placing reason and emotion as diametrically opposed, will not get us any further in the discussion. What can help, however, is to **overcome misunderstandings and start from a correct comprehension of the situation and its context.** With this publication, we wish to provide a first step in this direction.

a. Patents: hurdle or key to innovation?

- There are many misconceptions surrounding patents in the biopharmaceutical industry. Perhaps the **most persistent misconception** is that biopharmaceutical company **patents lead directly to limited access to new drugs and disproportionately high prices**. But this idea disregards a number of facts: Patents do indeed imply a temporary monopoly but they precisely enable innovation to be invested in and drugs to be created at all. **No patents, no new innovative drugs** (see 5).

- The alleged 'cashing in' of biopharmaceutical companies upon successful invention is just the tip of the iceberg. Underneath the water is an interplay of various actors, each rewarded for their contributions (see 4b). And what is also less visible are the many failures behind one success. So the chances of a 'reward' are rather small. Pharmaceutical development is actually **one long elimination- or attrition race**, where many leave but few reach the finish line (see 3d).

This misconception arises from a **'backwards-looking' approach**: one is looking back once the new innovative drug is effectively there. Author Jack Scannell uses the image of playing the lotto for this approach. If you just look at the winners, it does indeed seem incredibly lucrative: you spend one euro and you win as much as a million.1

Research and development (R&D) in the biopharmaceutical industry is all about looking **'forward'** at a time when the new innovative drug is not yet there: how do you make sure those new innovative drugs can get there in the first place? Ensuring biopharmaceutical companies still want to invest large sums of money when the chances of success are so slim? Because if nobody dares to invest, there are no new drugs and therefore no winners. With the lotto, you can still say you win by not playing (and thus not losing money), but **for medicines, not investing equals loss, both for patients, society and the industry.**

[1] https://www.forbes.com/sites/matthewherper/2015/10/13/four-reasons-drugs-are-expensive-of-which-two-are-false/?sh=4ad2a4a84c3b 1

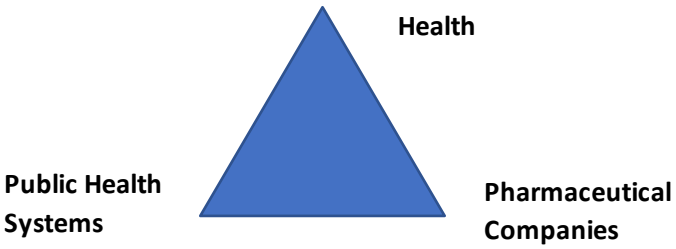
b. The context: an ethical-economic tension field

The fact that there are such persistent misunderstandings is linked to the **tension in which new innovative medicines are created.**

At the forefront of that tension is the **global fundamental right of everyone to health and healthcare**, including access to effective and affordable medicines. Governments create specific frameworks to ensure such access. They invest billions of euros of public funds in high-performing healthcare systems. Medicare reimbursement is part of this. In doing so, they put the health of their population at the centre but at the same time they have to balance this with financial and social feasibility/portability.

We largely owe the medicines needed to safeguard and improve health, to biopharmaceutical companies. Because of the complexity and scale required to develop, test and market a drug, these are often large, multinational groups. Where governments invest billions in high-performance healthcare systems, innovative **biopharmaceutical companies** invest billions in R&D worldwide.2
These efforts lead to more and better medicines, offering hope to patients. At the same time, these groups are driven by management and shareholders who expect returns. After all, it is part of the economic reality that the high investments companies make, eventually have to be matched by revenues so that they can stay afloat.

We find it problematic that we are largely dependent on such large conglomerates for the application of the right to health. As Jack Scannell points out: we may still find it taboo to put a price on issues such as health but **life-saving medicines do not exist in a parallel moral universe in which economics do not play a role**.3



This **ethical-economic trilemma** was very tangibly illustrated in June 2021 by the European Parliament (EP) resolution, *Dealing with the Challenge of the Global COVID-19 Pandemic*. With this resolution, the EP calls for a temporary waiver of intellectual property rights for corona vaccines. By doing so, the EP is responding to a loud-sounding demand to waive patents in order to address global production problems and supply shortages so that poorer countries would also have quick access to affordable corona vaccines.4

But at the same time, in the same resolution, the EP also recognises the importance and necessity of patents as an "important driver of innovation and research around the world" and that patents contribute rather than hinder the availability of vaccines.5

2 Before the COVID outbreak, global R&D investment by biopharmaceutical companies worldwide was estimated at USD 179 billion. Source: IFPMA Facts & Figures

3 https://www.forbes.com/sites/matthewherper/2015/10/13/four-reasons-drugs-are-expensive-of-which-two-are-false/?sh=4ad2a4a84c3b 1

4 https://www.europarl.europa.eu/news/nl/press-room/20210604IPR05514/ep-roept-op-tot-een-tijdelijke-ontheffing-van-patenten-op-coronavaccins EP calls for temporary waiver of patents on corona vaccines

2. What is a patent?

The government may grant a patent to someone at their request to protect their invention. A patent is thus **a right** - an intellectual property right - **protecting an invention**. In return, that invention must be disclosed. However, one does not obtain a patent just like that. The invention must meet a **number of conditions**: it must be new, inventive, industrially applicable and lawful.6 Patents must also be applied for, per country/region where protection for the invention is sought. If a patent application is approved, the inventor is given a **temporary legal monopoly**. He/She is, at that point, the only one allowed to exploit the invention in which he/she has invested time and resources; if someone else wants to do so, the inventor's permission is required. However, this right is time-limited: a patent is valid for 20 years from the day the application is filed. Via a supplementary protection certificate (SPC) that exists specifically for medicines, it can be extended for a maximum of 25 years.

This **seems long**, but, **in practice,** for the biopharmaceutical sector, **this is not the case**, because patents for innovative drugs must be applied for at the beginning of the R&D cycle, when the drug is not yet there. Since it takes an average of 10 to 12 years before an innovative drug can be launched on the market (this is, of course, only if it has successfully passed all stages of further development), in the end - even including an extension via an SPC - the patent holder can enjoy that exclusivity for only about 10 years (and in any case never for more than 15 years). That is much shorter than in other sectors, where innovations can go to market faster.

If a biopharmaceutical company collaborated with a university or other research institution in the early stages of discovery and initial development, agreements on intellectual property rights were usually made at the same time. Today, well-developed knowledge transfer systems (tech transfer) are in place so public institutions that contribute to an innovation also see their efforts rewarded.

After those 20 or 25 years, the innovation becomes **public domain** anyway: once the patent expires, anybody who wants to do so can use that knowledge without the inventor's permission. Moreover, one can also only obtain a patent if the content of the invention is published. So a patent is in itself a **social contract**: you only obtain exclusivity on an invention on the condition that it is temporary and on the condition that you share the information about the invention with the world via publication.

Such publication must be effective no later than one and a half years after submission of the application. The importance of this should not be underestimated. It means that everyone can still use the invention as **inspiration** for **new, further developments** during the monopoly.
These, for their part, can lead to new inventions. Thanks to publication, companies know perfectly well what their competitors are doing and can use that knowledge to do better. We actually see that the time between a first and second drug in a new therapeutic class coming onto the market is shortening. So, a new drug gets competition much quicker; this puts the monopoly nature of the patent into perspective.

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[5] https://www.europarl.europa.eu/doceo/document/TA-9-2021-0283_NL.html: *"The European Parliament stresses that the protection of intellectual property is an **important driver of innovation and research** around the world; indicates that it provides the basis for voluntary licensing agreements and the transfer of know-how, **and therefore precisely contributes to (and does not hinder)** the availability of vaccines; warns that if patents were no longer enforceable, companies would have to resort to confidentiality or exclusivity to protect their innovations; stresses the threat that an indefinite "suspension" of the TRIPS Agreement would pose to research funding, particularly for researchers, investors, developers and clinical trials; emphasises that the protection of property rights, including intellectual property rights, is a constitutional obligation of the European Union and its member states.*

[6] https://economie.fgov.be/nl/themas/intellectuele-eigendom/intellectuele-eigendomsrechten/octrooien/moet-elke-uitvinding

3. How does a new, innovative drug emerge?

It is often said that biopharmaceutical companies quickly reap the benefits of academic or public research and generate huge sales. But apart from the fact that companies are also involved in research, this completely ignores the **second and third phases in the creation of new medicines: development and marketing**. Development is a crucial phase, and this is precisely the **exclusive core expertise of pharmaceutical companies**. They are the **only actor** in charge of this phase. **Without the D in R&D**, safe and effective drugs, that can cure patients, will not emerge.

Unfortunately, development is a long and complex process and success is anything but guaranteed.[7] Or as author Jeffrey S. Flier sums up: no matter how hopeful inventions may seem, biology remains complex, drug development is difficult, and it usually turns to failure.[8]

a. Research

The **research phase** focuses on **generating knowledge**. How to apply that knowledge will follow later. Basic research is done in public institutions, academic centres and at the companies themselves. Through basic research, we first try to gain new scientific insights and better understanding of how the human body functions, how diseases arise and develop, and which mechanisms and factors play a role in it.

Once we have these mapped out, we can look for ways to avoid the emergence of diseases, or to influence or stop their development. And we can start screening and identifying molecules that might help in this and deliver health benefits.

The key word in the research phase is 'possibly'. In the accumulation of knowledge, we are **not yet** immediately concerned about the **concrete and successful application** of that knowledge; it can still go either way, so to speak.

b. Development

In the development phase, on the other hand, it is all about **converting** those new insights and new knowledge **into promising molecules**. Then, these have to be **converted into new drugs** that have proven to be high-quality, safe, effective and have added value compared to existing drugs. To obtain that proof, there is a long and expensive road ahead.

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[7] Example https://www.science.org/content/blog-post/really-works

[8] *Academia and industry: allocating credit for discovery and development of new therapies*, Jeffrey S. Flier, May 20, 2019. J Clin Invest. 2019;129(6):2172-2174. https://doi.org/10.1172/JCI129122

Clinical trials, mostly conducted by or commissioned by biopharmaceutical companies, are essential in this. Clinical trials can only be conducted after government approval, in approved centres and according to a strictly defined protocol. They consist of a number of successive phases, all of which must be completed before a drug can be considered for approval. In the final stages, patients are given the chance to gain accelerated access to new innovative drugs.

- A **pre-clinical phase** involves testing the chemical, pharmaceutical and toxicological properties of promising molecules, including by animal testing. This research enables the determination of initial doses that can be safely tested on humans.

- **Phase 0: screening without therapeutic or diagnostic objectives**
  This phase includes exploratory studies on humans to confirm the biological mechanism of the drug, to characterise the disease and to establish clinical models for the next phases of research.

- **Phase 1: study with a limited group of healthy volunteers**
  This phase serves to analyse step by step the uptake of the new molecule in the human body and detect any undesirable effects.

- **Phase 2: study with a limited number of patients**
  The new molecule is tested for the first time in (a still limited group of) patients to determine the optimal dosage.

- **Phase 3: study with a large number of patients**
  The drug is now widely compared with existing treatments and/or a placebo in a randomised, double-blind study (neither the patient nor the doctor knows what is being administered).

At **each stage**, there is a fairly high **risk** that the potentially new drugs are not 'viable' and that the development process has to be stopped (see d, graph). Hence, just because a potential new drug passes the first phase well, it does not automatically survive phase 2 or phase 3.

c. Marketing

If the third phase does succeed, the European Medicines Agency (EMA) evaluates the results and decides **whether or not the new drug can be marketed**. The EMA assesses whether the benefits and, more specifically, the **efficacy** of the new medicine **sufficiently outweigh the potential risks**, in particular possible side effects. If the assessment is positive and the drug can indeed be sold, it can be further evaluated in a very large number of patients. This in turn provides information on its efficacy in real conditions of use and on its long-term effectiveness.

But that does not make the medicine eligible for **reimbursement**. That decision is taken by the public authorities (NIHDI) based on, among other things, the added therapeutic value and the price compared to already existing treatments. This requires appropriate studies that usually go further (and are more expensive) than what is needed to convince the EMA.

And **doctors and pharmacists**, of course, still have to know the drug, and be willing to prescribe and dispense it. Not every marketed medicine is a commercial success.

d. Risk during the proces

Because of a new drug needs to go through all these phases, it takes an **average of 10 to 12 years today to make it available to patients. Of the original amount of promising molecules, very few usually remain** after going through all the phases of clinical trials. A 2020 analysis by The Biotechnology Innovation Organisation (9) shows that just under 8% of the development projects launched effectively leads to a new drug. One in two projects fails after only phase 1. And even after phase 3 - the most expensive phase - four out of 10 remaining projects are discontinued:

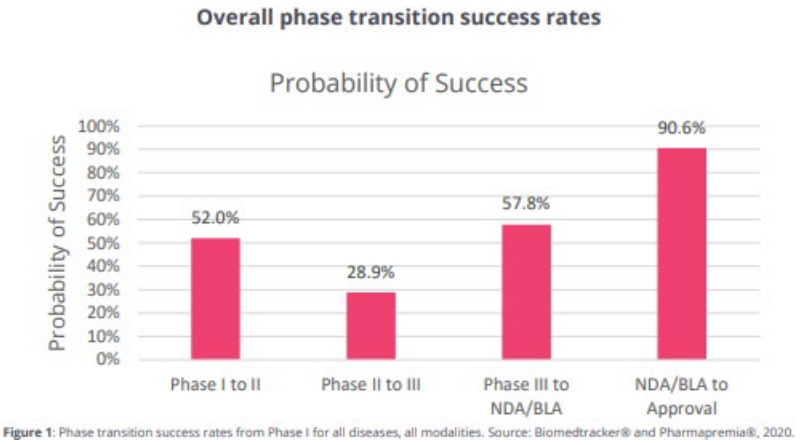


Figure 1: Phase transition success rates from Phase I for all diseases, all modalities. Source: Biomedtracker® and Pharmapremia®, 2020.

[10]

[9] https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf?_ga=2.178195500.828034807.1627993589-316997354.1627993589

[10] Companies seeking approval to market a new medicine in the US must submit either a New Drug Application (NDA) or a Biologic License Application (BLA) to the US Food & Drug Association (FDA).

4. Who is involved in the creation of new, innovative drugs?

a. The innovative biopharmaceutical companies

In many cases, the many efforts in development do not lead to new drugs. But the risks are mainly taken and borne by the **biopharmaceutical companies**. They are very active in generating new insights and new knowledge, alongside and together with public and academic institutions, but their **core business** is **converting those new insights and new knowledge into promising molecules, which in turn have to be converted into effective drugs.**

Therefore, they are pretty much exclusively in charge from the development stage. Whether they take full charge of development themselves or initiate and finance it: They are the ones who invest the necessary time and resources upfront with no guarantee of success afterwards.11

b. The ecosystem

Innovative biopharmaceutical companies do not work alone, of course. They are **part of a broader ecosystem**, which, incidentally, is very well developed in Belgium. Within this ecosystem, the various actors hook up with each other, each contributing from their background, mission and resources to the journey from inventions to drugs for patients. Besides companies, the ecosystem includes:

- **The State**. By subsidising research, supporting entrepreneurship and innovation, it has a highly developed and underpinned health system that guarantees quality, including through the extensive expertise of the Federal Agency for Medicines and Health Products (FAMHP).

- **The academic community**. It focuses on fundamental research, thereby building up ever more insights into the origin and course of diseases and helping to pave the way for innovative medicines.

- **Technology Transfer Offices** (TTOs). They ensure that the accumulated academic knowledge finds its way to private players, among others.

- Both privately and publicly funded **bio-incubators**. They provide financial, practical and substantive frameworks so that spin-offs and biotech start-ups can grow. Larger biopharmaceutical companies also do acquire start-ups to bring in additional innovation.

- **Contract Research Organisations** (CROs). Pharmaceutical companies regularly collaborate with CROs to set up and conduct clinical studies.

- These studies involve **academic hospitals**, and of course, **patients**.

[11] https://dolon.com/dolon/wp-content/uploads/2021/07/Addressing-unmet-needs-in-extremely-rare-and-paediatric-onset-diseases.pdf

The **dynamic interplay between all these actors** ensures that insights are built which lead to ideas, and that these ideas can be tested, developed and marketed by pharmaceutical companies.

Companies make the **most important financial efforts** in this process, which is evident from several studies. For instance, an analysis revealed that of the many projects financially supported by the US National Institute of Health (NIH) in 2000 eventually led to 18 FDA-licensed drugs by 2020. This analysis demonstrates the relationship between public and private resources: the 18 approved drugs could be made available to patients thanks to public investments by the NIH amounting to $670 million and to private investments by the industry amounting to a whopping $44.2 billion.12

5. What is the importance of patents in creating new, innovative medicines?

The fact that biopharmaceutical companies are **willing and able to continue making significant financial efforts** to develop new, innovative medicines is due to **intellectual property rights** such as patents.

The importance of patents cannot be underestimated: they help enable investment, facilitate collaboration with the other actors in the ecosystem, and, 'last' but certainly not 'least', they keep the whole engine of innovation in healthcare running.

a. Co-enabling investments

In contrast to the 'backwards-looking' approach (see 1a), where innovations are only considered when they are effectively successfully launched on the market, biopharmaceutical companies need to **think ahead**. At a time when there is zero certainty about the outcome, they have to take risks and invest in developing and marketing potential drugs.

That investment may lead to success but may just as well (or rather) turn out to be in vain. At the very least, **patents** offer companies a **guarantee** that, if their efforts, at best, yield some success and lead to a finished drug, they will be, for a limited time, the only ones allowed to use the information created during development. That way, they can still harvest the fruits of their investments.

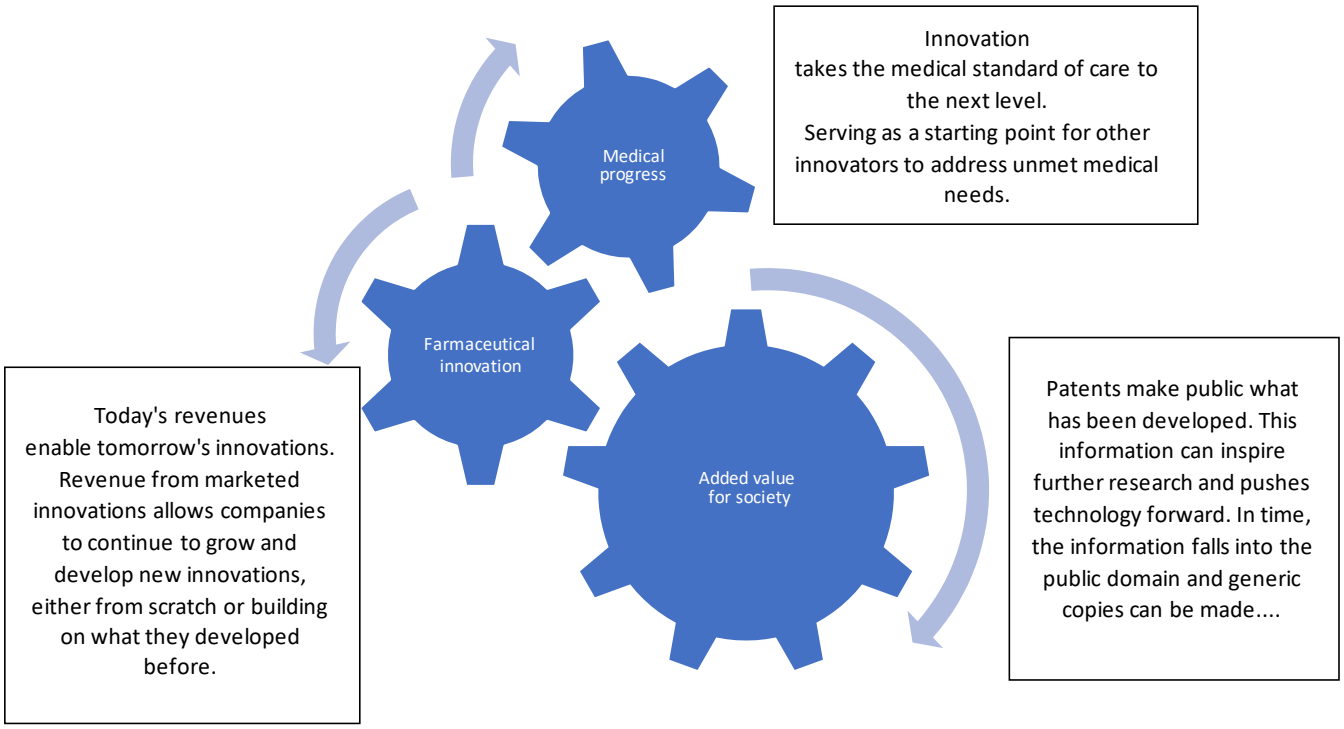
b. Facilitating collaboration

Development and marketing start from insights and knowledge that have emerged during the general research phase. Biopharmaceutical companies cannot simply use those insights and knowledge (unless they are the result of their own research). Intellectual property rights also come into play here.
For instance, much academic research is patented. Those patents then serve as **the basis for negotiations** between academia (through TTOs) and the biopharmaceutical industry, to further develop the ideas. This facilitates collaboration and ensures that each actor in the journey has their efforts rewarded.

[12] idem

c. Keeping the engine of innovation running

Patents keep the **engine of innovation** in healthcare running. The cogs of pharmaceutical innovation, medical progress, and added value for society interlock and propel each other forward, benefiting patients, society, industry and the economy alike.



- **Farmaceutical innovation**

  Patents that lead to successful developments generate revenue. These funds can be **reinvested** by the companies involved in R&D, which in turn can lead to new innovations. This allows individual pharmaceutical companies to continue to grow. For biotech start-ups, patents are possibly even more crucial. They usually have many ideas but no assets or customers yet. Thanks to patents the can **attract** the necessary **investors** to realise their ideas.

  At a macro level too, patents contribute to a **strong (knowledge) economy**. The biopharmaceutical sector invested over 14 million euros a day in R&D in Belgium in 2021, accounted for a total of 132,000 direct and indirect jobs, and generated a trade surplus of over 23 billion euros by exporting medicines and vaccines.

- **Medical progress**

  In the meanwhile, along with the new drugs and vaccines and the insights gained, the next generation of innovations is already being prepared. What was once state-of-the-art treatment is becoming standard medical practice. This higher standard serves as the starting point for new breakthrough searches. Patents enable individual innovations and ensure medical progress.

- **Added value for society**

  The innovative medicines made possible by patents, obviously benefit **individual patients** first and foremost. They lead to better or longer life or keep disease at bay. Patients and those around them regain perspective and their lives gain quality. This also has a **positive impact on society**. Just think of a decrease in the overall costs for the healthcare system.

  By publishing the patent, everyone can read what the innovation entails and use it as **inspiration for further research**. Thanks to the publication of patents, every company knows perfectly well what its competitors are working on.

  When the patent expires, the information generated falls into the public domain. Others can then use it to further produce and distribute the drug. The innovative medicines of today thus become the **generic medicines of tomorrow**.

6. Concluding

The attention given to the debate around patents in the pharmaceutical industry is justified. After all, new innovative medicines arise in a **complex** field of tension, in which ethical and economic perspectives come into play. The interests of individuals, society, and the economy must be carefully weighed, without touching the fundamental right to health and healthcare.

Assuming, however, that abolishing patents in the pharmaceutical sector will lead to broad and cheap access to new, innovative drugs is a false assumption. It is based on **'backwards-looking' thinking**, where you start from when there are already successful innovative drugs available.

In order to achieve such successful innovations, however, biopharmaceutical companies, the leading players in the phase of developing promising molecules into effective drugs, **have to think ahead as well as invest**. Even when this means that most of their investments will amount to nothing. After all, the path from idea to product in the pharmaceutical industry is long and complex and has few chances of success. At that point, when there is zero certainty, patents still offer companies the guarantee that they can benefit from their investments if the outcome turns out to be successful.

This enables biopharmaceutical companies to **keep investing and innovating.** This also enables others to use the information they developed. After all, patents are public and only offer exclusivity for a limited period of time. They are thus imply a **social contract**: the knowledge can be used by others, for the development of generic drugs afterwards, but also as a basis for new innovations. In **this way, patents keep the engine of innovation in healthcare running**.

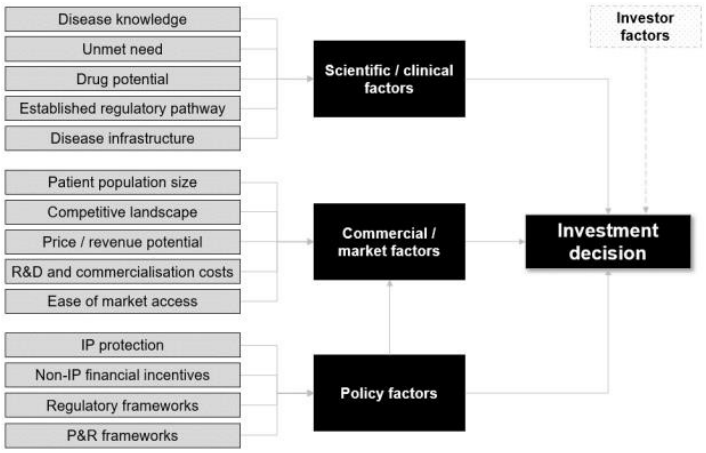
7. Appendices

Annex 1 - How does a biopharma company decide which new, innovative medicines to invest in?

The road from invention to a new, innovative medicine that is high-quality, safe, effective and adds value to existing drugs is long and expensive. Therefore biopharmaceutical companies do not start the development process of a new drug without thinking about it. And even during the process, they consider and weigh whether further investment in the development makes sense. **Various factors** come into play, and these factors differ depending on the stage of the development process.

In 2021, Dolon prepared a study for the European Federation of Pharmaceutical Industry Associations (EFPIA) on the role of the biopharmaceutical innovation model in finding solutions for very rare diseases and children's diseases. (13) This study clearly shows which **internal and external factors play a role in the decision whether or not to invest (further)**. These factors can be broadly categorised into **three types**: scientific/clinical factors, commercial/market factors, and policy factors. While all three types play a role in the decision-making process of biopharmaceutical companies, their importance varies depending on the stage of the development process.

Simplified taxonomy of factors involved in investment decisions (non-exhaustive) 14



Scientific/clinical factors

First and foremost, scientific/clinical factors weigh up long before commercial factors come into play. In the early, pre-clinical phase, companies look at what they are willing to invest in based on elements such as understanding (the mechanisms of) a disease, the presence/absence of promising targets and the extent to which there are unmet medical needs ("unmet needs").

Scientific knowledge and experience within the company also have a part to play. After all, companies often specialise in one or more therapeutic areas and thus build a knowledge advantage.

[13] https://dolon.com/dolon/wp-content/uploads/2021/07/Addressing-unmet-needs-in-extremely-rare-and-paediatric-onset-diseases.pdf

[14] Idem, figuur 1

In addition, biopharmaceutical companies work with patients and doctors to understand their needs and desires in terms of new treatments, and assess whether those expectations are feasible from a scientific point of view.

Only when clinical feasibility is demonstrated, biopharmaceutical companies consider additional factors.

Commercial/market factors

At this stage, companies start looking at the market: How many potential patients are involved? Do treatments for the same disease already exist or might soon be on the market? Will society be willing to pay for the added value of the new, innovative drug? And if so, how much will they be willing to pay? Again, this depends on the existence of alternative treatments and their price. There is also an examination of how similar benefits in other therapeutic areas are ultimately valued. Companies do not only investigate the Belgian market but always examine the global potential.

At this stage, companies review whether the new drug can offer a significant benefit to patients. After all, there is no point in developing new drugs that do not offer any added value.

Introducing a new drug to market requires serious investment. To demonstrate efficacy and safety, companies need to set up robust and expensive clinical studies, the success of which is very uncertain (see 3d). In addition, the drug must also be manufacturable in sufficient quantities; this requires significant investment in pharmaceutical development and building an adequate production capacity that meets all applicable (safety) requirements. Finally, a company must also consider the costs of complying with pharmacovigilance requirements, pricing and reimbursement procedures, distribution, medical education, etc.

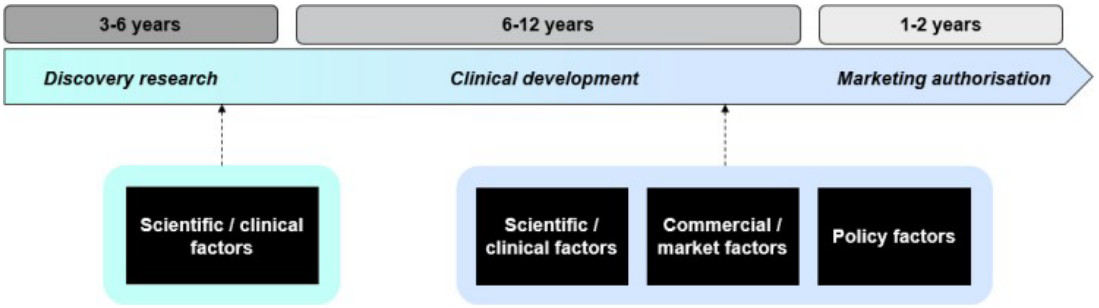
Policy drivers

Ultimately, investment decisions also depend on policy: the political and regulatory context in which drugs are developed and launched. A reliable regulation of intellectual property rights, for example, has been found to be a decisive factor for biopharmaceutical companies to invest or not. In addition, other incentives for innovation such as tax incentives may also be at play.

Besides incentives, companies also look at laws and regulations and the framework for pricing and reimbursement. These can vary greatly from country to country. For example, it may be economically less interesting to invest in a particular disease area if there is uncertainty about the regulatory requirements around marketing that will be imposed or if this is not a priority for certain governments when reimbursing medicines.

Importance of investment factors throughout the various phases of drug development [15]

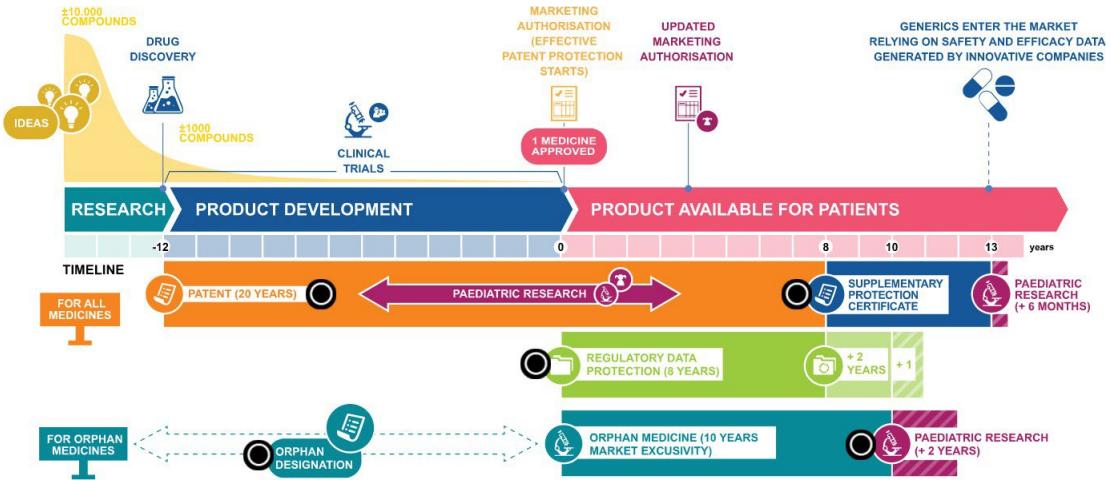
[15] Idem, figuur 2



The decision to (continue to) invest in the development of a new, innovative medicine is thus underpinned by an interplay of various factors throughout the journey. Even if these factors do not carry equal weight at every stage, at the end of the journey they combine to determine whether or not new, innovative drugs enter the market.

Annex 2 – Overview incentives for development of new innovative medicines

To encourage biopharmaceutical companies to keep investing in the often long and expensive road to new, innovative medicines, a **framework for incentives** has been developed within Europe. **Intellectual property rights (IPR) are the basic pillar in this**. IPR protect and encourage innovation. They also ensure that R&D investments are made for medical needs that remain unmet today.
Within this European framework, patents are the most common form of IPR. However, there are additional incentives specific to biopharmaceutical innovation. The European Federation of Pharmaceutical Industries and Associations (EFPIA) has mapped them: 16



The illustration clearly demonstrates that these incentives do not necessarily succeed each other in a linear fashion throughout the development process of new, innovative medicines. **They consist of a complementary mix of incentives that protect different aspects of innovation and are created for different purposes.** For example, some incentives are designed exclusively for medicines for childhood or orphan diseases. Others may in turn provide incentives where patents do not (or no longer) protect innovations. These incentives have all proven efficient and effective in encouraging innovation.

Besides patents and the supplementary protection certificate (SPC, see 2), the following incentives exist for the development of new, innovative medicines: 17

- **Regulatory Data Protection (RDP)**
  To market new, innovative medicines, biopharmaceutical companies have to prove their quality, efficacy and safety. To this end, they provide extensive data, collected from pre-clinical and clinical studies in which they have invested. These investments in data cannot be protected through a patent. Generic producers do not have to conduct the studies (and make the associated investment) to obtain their marketing authorisation; they may simply refer to the data of the original medicine they are copying.

[16] https://www.efpia.eu/about-medicines/development-of-medicines/intellectual-property/#/
[17] More info: https://www.efpia.eu/about-medicines/development-of-medicines/intellectual-property/#/

In return, RDP ensures that the company of the original drug is recognised for its initial efforts for a certain period: only after 8 years, to be counted from the time the medicine was approved, can generic producers refer to those dates in their applications. This period is followed by 2 years of market exclusivity, during which generic producers are not permitted to enter the market for those products.

- **Orphan Regulation**

  These regulations, introduced by the EU in 2000, are the foundation of the strategy for ensuring that patients suffering from rare conditions (orphan diseases) receive the same high-quality treatment as all other patients in the EU. After all, innovation in orphan diseases is particularly challenging.18 The limited number of patients alone, for example, makes initiating statistically significant studies extremely difficult. The Orphan Regulation contains additional incentives to meet these challenges, nonetheless. Companies that invest in R&D for innovative treatments for orphan diseases, provided they meet the strict conditions, will be able to rely, among other things, on 10 years of market exclusivity. As a result, other medicines for the same condition can only receive market authorisation if there is significant added value. Additional incentives are provided for SMEs.

  This European regulation is delivering results. It has already resulted in the fact that 6.3 million patients with a rare disorder can now be treated.19

- **Paediatric Regulation**

  This framework was introduced in 2007 to support the development and availability of quality medicines suitable for children. Similar to innovation in orphan diseases, innovation in medicines for children collides with many specific challenges. For example, the ethical aspects that understandably weigh heavily in the design of clinical trials involving children. A child's physiology also works significantly differently from that of an adult and, moreover, changes occur throughout the period of a clinical trial as children grow. Thanks in part to this regulation, paediatric drug research is now an integral part of general medicine development.

  Companies that develop and obtain approval for a Paediatric Investigation Plan (PIP) can either extend their SPC by 6 months or, if it is a drug for an orphan disease, get an additional 2 years of market exclusivity on top of the first 10 years under the Orphan Regulation.

  This extra incentive makes a difference. Since the introduction of the Paediatric Regulation, almost 300 new medicines for children have been approved in Europe and the proportion of clinical trials that include children has increased by 50%.20

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[18] https://dolon.com/dolon/wp-content/uploads/2021/07/Addressing-unmet-needs-in-extremely-rare-and-paediatric-onset-diseases.pdf

[19] EFPIA, 'How to back Innovation – Protecting the spark of an idea for tomorrow's patients'

[20] Infographic https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/stimulating-the-development-of-new-medicines-for-children/. Figures on new medicines for children cover the period 2007-2019, figures on clinical trials cover the period 2006-2016.

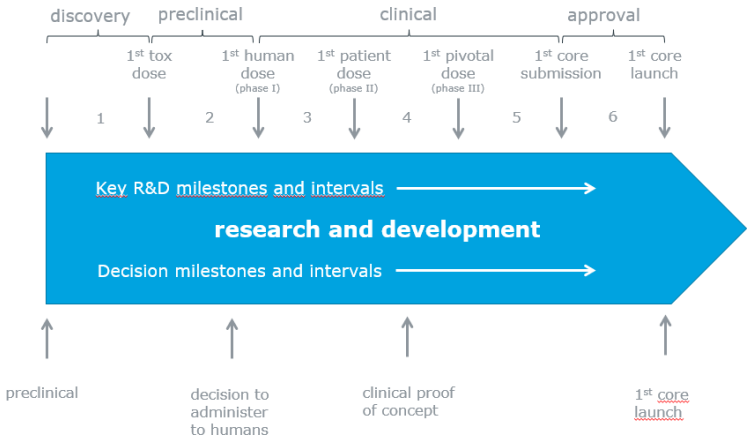
Annex 3 – What are the costs of an R&D trajectory?

IPR, and patents in particular, are an important incentive for biopharmaceutical companies to (continue to) invest in new, innovative medicines. IPR offer the guarantee that, if companies manage to bring such a medicine successfully to the market, they will be rewarded for the high investments they have made and the risks they have taken. But how significant are those investments and risks?

In fact, it is clear that a **mere accounting calculation** of expenditures and revenues will not get us to assess the investments and risks of new, innovative medicines. In late 2012, the Office of Health Economics (OHE) therefore released a study on the R&D costs of a new drug. (21) In this study, OHE intended to feed the, even then, lively debate on the "reasonableness" of drug prices and the (increase in) size of the long-term investments needed with insights into what new medication costs on average.

However, as the study shows, being able to estimate the "average" development cost of a new medicine is no easy task, as many variables come into play. Existing methodologies did not always or sufficiently take these into account. The researchers therefore developed their own methodology incorporating the complexity of a biopharmaceutical R&D project. To do so, they relied on, up until then, unpublished data collected by Centre for Medicines Research International (CMRI).

CMRI divides the R&D pathway into six milestones, leading to six intervals or phases:



The researchers set the calculation of R&D costs up against these intervals or phases. In doing so, they assume four basic components for which they have calculated an average value:

- The out-of-pocket costs for each phase
- The success rate to successfully complete the phase; these success rates vary by phase (see also 3b)
- The development time to complete the phase (this also varies by phase)
- The cost of capital, which has a large impact on the final cost of a successful new medicine due to the long development time.

[21] https://www.ohe.org/publications/rd-cost-new-medicine

By doing so, they estimate, interval by interval, the average cost of a new drug:

Interval	Mean out-of-pocket costs (Mio $)	Probability of getting to the next +interval	# compounds needed for 1 successful NME	Costs per successfull NME (Mio $)	Time until launch (years)	Capital cost	Capitalized cost per successfull NME (Mio $)
1: pre 1st tox dose	-	-	-	76,5	9,6	11%	207,4
2: from 1st tox dose to 1st human dose	6,5	0,70	13,3	86,8	7,2	11%	184,1
3: from 1st human dose to 1st patient dose	16,0	0,63	9,3	149,5	6,2	11%	284,0
4: from 1st patient dose to 1st pivotal dose	53,9	0,31	5,9	316,9	4,4	11%	501,6
5: from 1st pivotal dose to 1st core submission	129,3	0,63	1,8	235,9	2,1	11%	293,8
6: from 1st core submission to 1st core launch	29,0	0,87	1,1	33,3	0,5	11%	34,9
TOTAL	**234,6**	**0,075**		**899,0**	**11,5**		**1.506,0**

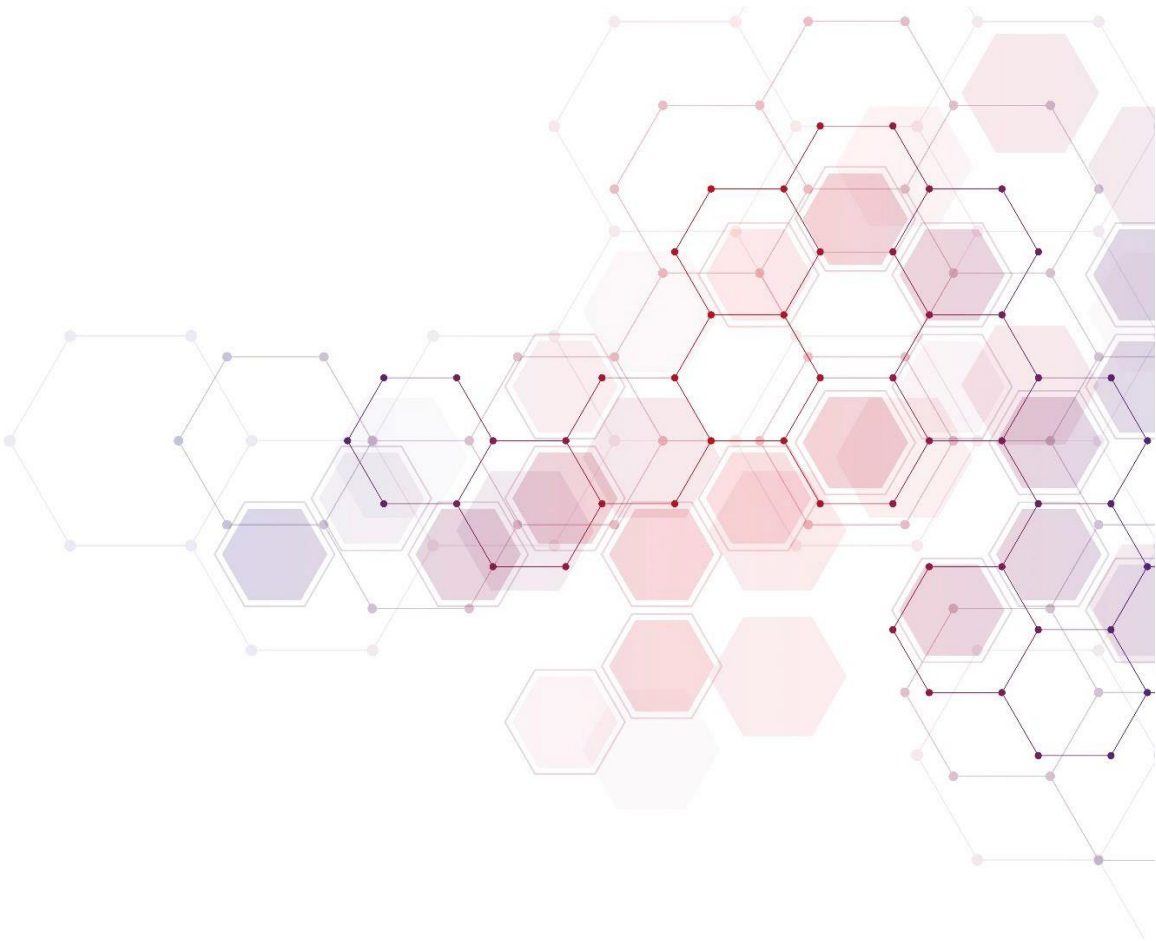
This table already shows that calculating the average cost for a new medicine is much more complex and nuanced than just looking at what a specific new medicine has cost at the end (or $234.6 million versus $1,506.0 million). Yet researchers admit even this methodology has its limitations. After all, behind an average R&D cost, there can be a considerable amount of differences per medicine. Factors involved include:

- **Therapeutic domain**: there are clear differences in R&D costs by (sub)therapeutic domain. For example, new treatments for neurological disorders typically cost more than anti-parasitic medicines. This is mainly related to success rates and development time required.
- **Proprietary molecules versus licensed molecules**: clinical success rates tend to be higher for medicines starting from licensed/acquired molecules.
- **Company size**: not all companies are “big pharma”; there are also many SMEs and start-ups. Although studies do not provide unambiguous results, company size does seem to have an impact on R&D productivity and costs.
- **Biopharmaceuticals**: in general, success rates for biotechnology molecules are higher compared to classical chemical molecules; however, the latter appear to require less development time.

This OHE study dates from the end of 2012. Although the context today is different from 10 years ago and average costs per interval or phase have increased, the basic elements of this methodology remain intact. In fact, researchers themselves also indicated which drivers may cause trends/evolutions in new medicines' R&D costs:

- **Drivers of out-of-pocket costs** include the cost of clinical trials, depending on the cost per patient and the number of patients required.
- **Drivers of failure rates** include rising risk aversion among regulatory/approval bodies or insufficiently rigorous preclinical screenings.
- Among the **drivers of development time**, rising risk aversion among regulatory bodies also appears here, alongside, for example, the growing complexity of clinical trials.

The results of the study thus remain relevant today to fuel the debate around the R&D costs of a new medicine.



Published by pharma.be vzw/asbl
Terhulpsesteenweg 166 1170 Brussels
October 2022 Resp. Editor: C. Ven
Depot nummer: D/2022/4021/08