Professional MBA
Entrepreneurship &
Innovation

Innovation in the pharmaceutical industry in EU and USA: sources of new medicines over the period of 1996-2016

A Master's Thesis submitted for the degree of
"Master of Business Administration"

Supervised by Prof. Dr. Peter Keinz

Dr. med. Oleh Zagrijtschuk
Matr.Nr. 0109348

Vienna, May 27th,
2021

Affidavit

I, Oleh Zagrijtschuk, hereby declare

1. that I am the sole author of the present Master's Thesis, " Innovation in the pharmaceutical industry in EU and USA: the role of SMEs as source of novelty over the past decade", … pages, bound, and that I have not used any source or tool other than those referenced or any other illicit aid or tool, and

2. that I have not prior to this date submitted this Master's Thesis as an examination paper in any form in Austria or abroad.

Vienna, ….06.2021 Signature

Table of Content

Table of Figures

Table of Tables

1. Preface

1. Abstract

Productivity of pharmaceutical industry, calculated as the ratio of the number of new drugs introduced to the market (approved by the regulatory agencies) to the total R&D costs of the entire industry, then, declined since the 1950s (Lendrem et al, 2015). The number of approved innovative drugs has grown only insignificantly in recent decades globally, and R&D costs dramatically increased. This crisis has four main groups of reasons for such an adverse phenomenon in the industry (Scannell et al, 2012; Nosengo et al, 2016):

1. strategy of research and selection of the target diseases: the “low-hanging” disease have been exhausted,
2. high number of staff/FTEs specialists necessary for a full R&D and approval cycle of a single drug,
3. increase of regulatory control and scrutiny, and
4. imbalances in the management of pharmaceutical companies: huge amounts of money are spent on the development and introduction of new drugs, their increased cost does not always reflect the clinical benefits.

The four above mentioned reasons formed the basis for a powerful innovation shift in the activities of pharmaceutical companies - the transition to the field of biotech research. More and more attention is paid to biotech drugs, drugs for cancer and rare diseases, the treatment of which is difficult or unavailable, and therefore the corresponding drugs are much less prone to the problem of "low clinical benefits", and regulators practice approach of much lower resistance for these drugs to get to the market. Higher risk taking by more complex research

would be impossible without the underlying basic science research by Academia, a new emerging player in the field of pharmaceutical discovery. Large players have significantly less innovative potential and flexibility, prefer to focus on production, marketing and sales, therefore, to replenish their pipelines, they often do not invest in early discovery stages themselves, but buy innovative startups. The small companies are more efficient, they spend much less time and money on drug development, use capital and infrastructure more efficiently, and will be created under conditions of unmet medical need. For example, instead of purchasing equipment and reagents themselves, they conduct research - both preclinical (on biological models and laboratory animals) and clinical (testing the safety and efficacy of a new drug in patients), using the capabilities and resources of highly specialized contract research organizations. Innovative designs are more likely to be utilized in the comparable situations by SME rather than by big companies (Mesa, Zagrijtschuk et al, 2019).

In the light of the fact that big pharma became essentially dependent on external novelty to maintain their pipelines while being unable to come up with own innovation, academia emerged in the past decade from its usual role of basic research to looking for applicable tools and interventions against disease targets to investigate their therapeutic relevance. The novel targets and drugs will be acquired from universities prior to this investment, either directly via the license agreement, or passing the stage of a start-up or SME intermediate. Project managers and meeting the timelines, the usual industry standard, were common components to projects success of universities, alongside with the ability to publish research result in good journals. Over the time, this path became the mainstream of the industry. Thus, the principle questions about the origin of pharmaceutical innovation turns to become not *where* does the invention happen and makes its early steps, but rather ***if*** the invention is going to be done and noticed/explored by the party, able to create drugs, and if the supportive conditions will be created. Funnily, both big and small pharma create innovation – the latter ones develop innovative *models* to operate more efficiently, while the genuine innovation by discovery happes esewhere.

Knowing, understanding and positively influencing the factors is essential to positive guide and enhance the output of the whole pharmaceutical industry. USA based companies and universities used to be much more efficient in adopting and advancing the new model, as seen in faster market growth in the context of more competitive environment for faster research application. This work will focus on description of the differences between EU and USA in term of where does the innovation for novel drugs come from, and which stakeholder party was able to push the idea as a product to the market. The observation period covers the end of nineties (still, the golden age of a classic, big pharma dominated markets) through 2004, when the transformation occurred in form of market harmonization in the EU and the first wave of market consolidation in the USA until 2016 – a representative year for VC centric approach of early innovation funding, driven by the risk taking readiness and availability of early risk money as decisive factor for pharmaceutical success of academia and SMEs.

2. Acknowledgements

I want to thank to Prof. Dr. Peter Keinz for his supervision of this thesis and his valuable feedback and support. This work is also dedicated to my wife Helena and my two kids Markus and Julia.

3. *List of abbreviations*

R&D	Research and Development
EMA	European Medicines Agency
IP	Intellectual property
FDA	Food and Drug Administration, USA
M&A	Merger and acquisition
NAS	New active substance
NIH	National Institutes of Health, USA
PhRMA	American Pharmaceutical Research and Manufacturers Association
SME	Small or medium-sized enterprise
VC	Venture capital

2. Introduction

1. Problem statement and relevance of research

The pharmaceutical industry is special due to its dependence on scientific research progress (knowledge-based and knowledge-intensive industry) and regulation level. Globally, the industry has grown by 4-7% in recent decades, and the total volume of pharmaceutical products sold annually has already exceeded $1 trillion. The high level of scientific and technological development and the cost of launching new drugs to the market have led to the fact that pharmaceutical innovation today is almost entirely concentrated in the largest multinational companies (Ding et al, 2014).

In recent decades, the global costs of industry companies on innovative development (R&D) have increased significantly. Technological progress has facilitated the creation of drugs, but at the same time, the industry has faced a number of challenges. Firstly, it is declining productivity of R&D (when considered as the number of novel marketed products, introduced to the market in relation to the financial costs of innovative developments), since the 1950s, there has been a tendency of its significant decrease. Although the last 40 years have become an era of a breakthrough in the technologies used by the industry, the production and introduction of new drugs to the market has only become more expensive. Secondly, the weakening of patent protection and the market development for generics (i.e., cheaper analogues of patented brands) forced the largest companies to look for new models of making a profit. Third, the tightening of regulatory control led to an increased cost and bureaucratization of the industry, which also affected the decline in R&D productivity (DiMasi et al, 2016).

Innovative drugs continue to generate most of the profit for companies, and the final cost of drugs today is often remarkably high. The adoption of short-term measures to contain prices leads to the fact that the pharmaceutical industry is in a logic of conflict, and for its development, it is necessary to understand the mechanisms of transition to a new stage.

The listed challenges pose new challenges and problems of innovation policy, forcing the largest companies and the countries to look for ways to revise the existing mechanisms of innovation support.

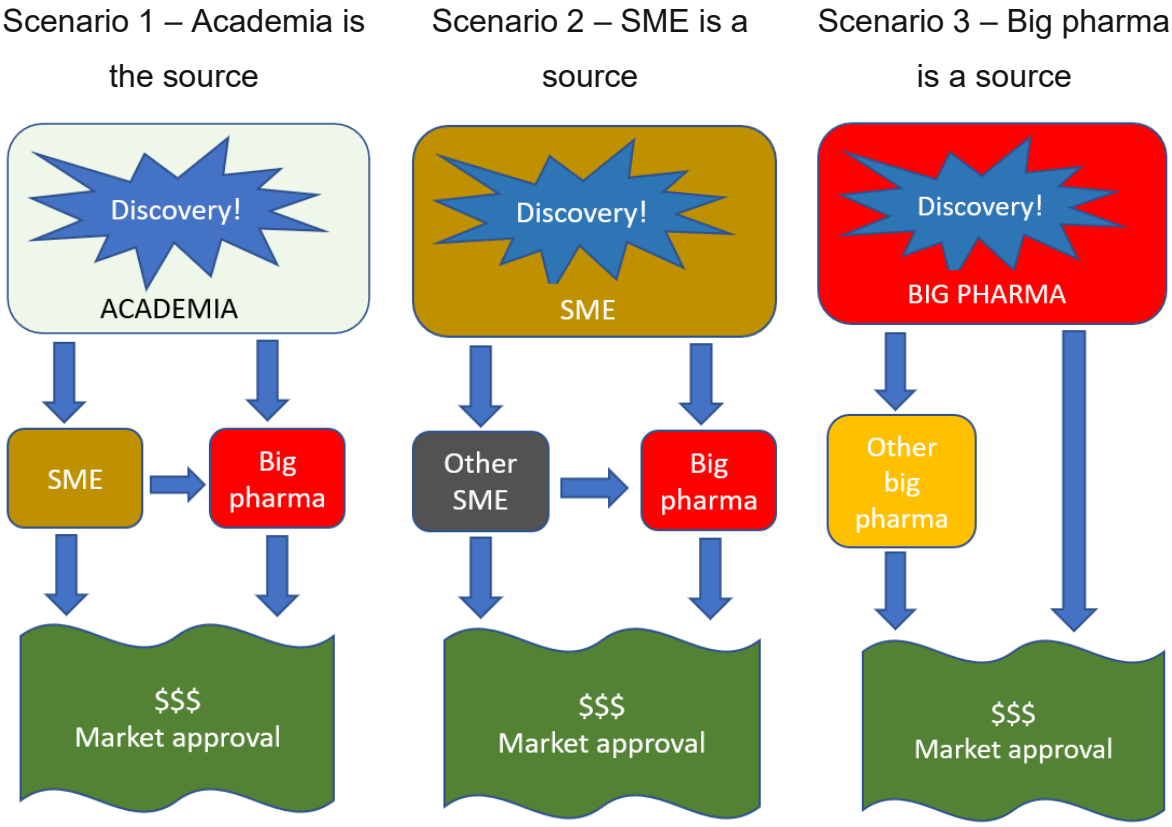
Among all sectors of the world economy, pharmaceutical industry is distinguished by its exceptional knowledge-intensiveness and therefore can be regarded as an example in the context of research on the dynamics of the development of global innovation processes. Indeed, drug research and development and related scientific research is an important component of national innovation systems (Fagerberg et al, 2008). At the same time innovative processes in pharmaceuticals have a number of unique features. In particular, pharmaceutical companies interact and hire a huge number of scientists, engineers and lawyers. The need for lawyers with relevant experience is caused by the increasingly complex regulatory system. Large companies also actively interact with small innovative businesses and large universities, and even help the venture investors to make decisions, that promotes innovative development of close coordination of venture capitalists with academia and SMEs. The presence of a strict patent laws, regulatory controls and competition from the side of the market generics are essential elements of the pharmaceutical industry, emphasizing its specificity (Lee et al, 2015). Most scientists, who investigated the formats of the development of pharmaceuticals and characteristic for its innovative dynamics, indicated, that in the last years, the industry experienced continuous extensive changes both in the business model, so in manufacturing (Garcia et al, 2017) and research activities (Light et al, 2012); Some researchers (Khanna et al, 2012) show an extremely important role of consolidating led by industry leading global companies. Others (Kesselheim et al, 2015) note the importance of in the R&D of new members - "open innovation sources", which in the case of pharmaceutical industry will be represented by Academia, doing applied research in the field of unmet medical need. Many scientists, in fact including Bachmann and John Cantwell, reitereated on the contribution of small companies in the development of the knowledge-dense industries, including in the pharmaceutical industry. Small companies, composed of both recently funded stat-ups and more mature but also dynymic and willing to accept the development risks, represent another

playing, outperforming the large pharma in efficiency and ability to utilize invested capital with higher % of return. As pointed out by Cantwell, in such unique situation and supported by observations from IT field the merging of technological competencies and knowledge among the high-tech giants is possible only by systematic adoption of external knowledge. Knowledge becomes more available for transfer, and the globalization and internationalization of global companies speed up the exchange of know how between companies from different regions of the world and that the more important, from a variety of related fields. If in the past the industrial companies simply passed the knowledge about the methods and processes from one manufacturing place and project to another, the information technology has created the environment in which there is the interpenetration of different competences, which gives a wide opportunity for innovative development beyond the originating company. It also opens up prospects for further global innovative jump, caused not so much a specific technology but due to emergence of a fundamentally new branch structure of the global economy. In such situation, changed sources of innovation and the ways of interaction with mature pharmaceutical companies make the growing role of pharmaceutical collaborations and joint enterprises, as well as small independent researchers and universities, inevitable for the durable success. Thus, innovative process ceases to be linear and goes beyond the scope of multinationals, opening opportunities for small businesses and innovative startups and underlying universities (Braunerhjelm and Svensson, 2010). An important role here also plays the competition between the developed and developing countries, as well as within-industry competition of producers of generics and leading multinationals focusing on innovative (non-generic) drugs. There is an ongoing discussion in the scientific community about the role of global pharma in innovation processes and peculiarities of their interaction with small innovative companies (Aghion et al, 2005).

The pathway from discovery to approved pharmaceutical product organizationally requires certain skills to successfully complete respective stage – IP protection, completion of preclinical and clinical development, regulatory filing and commercial

launch of the product. Depending on source of the innovation (Academia, SME, Big Pharma), several transitions need to occur, as shown on the figure below.

Figure 1. Novelty transition scenarious depending on source of innovation (created by author).



In case of scenario 1, the key initial elements are: ability of academia to file IP (costs, competence, strategy aligned with publishing), contractual and legal infrastructure to negotiate license and technology transfer contract(s), presence of VC support if needed to form the idea as entity outside of the university. SME in this case may play a role of an intermediate (taking over the development part until the phase III) or introduce the drug to the market without any further support. Frequently, this decision will be met separately for different geographies and territories.

Scenario 2 requires from a SME to have a solid early R&D fundament and is usually facing much stronger capabilities in term of IP protection and professionalism of early steps (a common weakness of purely academic projects). SME frequently become

junior commercialization partners but want to keep key competences and knowledge of the core customers (physicians, hospitals, social securities and payers, but also patients). In many cases, SME "pass" the project to big pharma in case of initial failure and the need to re-do some or the whole development program and lack of finance or expertise to implement it.

Scenario 3, or the "classical" pathway of the pharmaceutical industry, does not require any additional partners or stakeholders, a company as integrated unit is able to launch a drug independently, limiting the SME role to potentially re-purpose the project if external conditions change or the market becomes less attractive/focus of the company shifts to another indications or diseases.

There are some significant differences between EU and and US business entities which can explain why the same factors act differently but also how the policies were historically created. American companies are more focused on short-term profits, have more stable management structures and prioritize stockholder satisfaction. European companies have multiple objectives, different (longer) time horizons and differences in corporate governance. In the US it is a standard to have a Board of Directors, while in Europe a dual system, with management board and supervisory board is commonly utilized.

Understanding the factors that have an impact on drug and pharmaceutical innovation, including the nature of the organizations involved, could definitely support the development of strategies to guide further advances.

2. Research questions

Two research questions were formulated:

Research Question 1. What are the sources of scientific innovation in the pharmaceutical industry in the EU and in the USA, and what is the structure of

ownership of approved drugs in the two major Western pharmaceutical markets (EU, USA), taken longitudinally in the time horizon of 1996-2016?

Research Question 2. What are the factors influencing the productivity and success rates of pharmaceutical innovation, how are they implemented differently in EU and USA, and how they can be improved to enable more efficient innovation processes?

3. Contribution

Existing literature does not provide a comparative view on pharmaceutical innovation process in the context of relative contribution of all involved parties (global pharmaceutical insdutry, SMEs and and academia/universities; start-ups formed for purpose of commercialization of the invention was considered and counted as part of academia for the purpose of this work). This thesis aims to close this gap of research to provide a comparative, data driven analysis over the period of time from 1996, 2006 and 2016 as representative timepoints, driven by external changes in the regulatory field, the way, how the companies operated and the innovation was created. The study topic of this thesis combines two separate fields, pharmaceutical regulatory science and innovation management. For better understanding of the factors, contributing to the innovation path, geography-specific environment influences were compared between EU and USA, the two largest pharmaceutical markets worldwide.

The research questions of this thesis have relevance for the strategists of the pharmaceutical companies, CEOs of SMEs and university-based technology transfer offices and entrepreneurs.

In addition, this work is also of relevance for deal making and licensing practitioners involved in development of drugs or in other high science background areas. Also, policy makers would be interested to learn the conclusions of this work.

4. Research structure

The research questions stated above are approached as follows.

First, a brief review of literature will focus on productivity factors of pharmaceutical industry and impact of different players is provided in chapter 3. The process of pharmaceutical discovery is reviewed in section 3.1. Further, it is shown (in section 3.2) that different external and internal factors contribute to the success of pharma R&D. Section 3.3 shows the important role of public innovation policies.

For the answering the research questions, a methodology was developed, which is explained in chapter 4. At first the methods and materials are explained, and sources of the data with endpoints are justified in section 4.1. Section 4.2 deals with the restrictions and limitations of the methodology and explains why the data obtained are still informative and generalizable.

Chapter 5 summarizes the results, obtained in the course of analysis.

Finally, chapter 6 provides the discussion of results (6.1), followed by section 6.2, which considers the limitations of the research and finally section 6.3 provides the conclusion and an outlook to future studies.

3. Review of the literature

1. Pharmaceutical research and development

Globally, the pharmaceutical industry is determined by three interrelated factors: the nature of new drug launches, the patenting system, and the generics market. Each of the factors has both direct and indirect effects on the others. The key factor can be considered a long period of development and market launch of industry products - the period can reach 12-15 years. Moreover, each next year of drug development costs companies more than the previous one. The fact is that any drug on the market must go through a full cycle from research to development and introduction to the market, and this cycle consists of several stages, each of which has its own characteristics with different levels of capital expenditure. Trials required to bring a drug to the market are divided into preclinical and clinical. Source of the novelty is usually a research lab (either industry-based or academic). Preclinical studies can last up to 8 years and are characterized by relatively low costs, which increase slightly over time. Clinical trials are divided into four phases46. In the phase I (up to 2 years), the drug is studied in a small number of patients with the aim of the phenomena of safe dosage, as well as therapeutic efficacy. In the phase II (up to 2 years), more complex and hypothesis-driven studies are carried out. In case of success, long-term (several years) studies are carried out in the third phase, which requires the greatest financial costs. In the third phase, clinical studies are carried out on many thousands of patients using a double-blind, randomized study design. It is the period of the phase II and III that most often becomes the moment when the drug has to be rejected for one or another clinical reason. The fourth phase begins in case of successful results of the third phase after sending an application for registration of a new drug by the regulatory authorities (this process can take up to 11.5yrs). The described cycle distinguishes the pharmaceutical industry from other innovative sectors of the economy, first

of all because the risks of abandoning the product remains very high precisely at the late stages of research and development. Costs for R&D increase during the first three clinical phases, followed by the growing uncertainty of the future success of the drug. The factor of complexity and capital intensity of the mechanism for bringing a drug to market is the main factor in the strategic and financial decisions of companies in the industry. Small companies (SMEs) developing drugs have the opportunity to sell more or less mature products to the global pharma in the research stage and focus on further early stage research projects. The presence of a developed system of government or venture financing, as especially present in the United States, contributes substantially to this. Another opportunity for both small companies and global pharma with a weak portfolio may be the mergers and acquisitions, or acquiring or in-licensing the products or product rights from the academia.

2. *External and internal factors of success of pharmaceutical R&D*

At company level, two structural variables are associated with innovation success, namely company size and the degree of diversification of a company. These structural parameters are difficult to influence by management in the short to medium term, but can be guided as part of strategic course through mergers or by focusing on selected indication areas. The idea that larger firms are more able to innovate is attributed to Schumpeter (1942; cited after Goodwin 1998) and has since been tested in countless empirical studies with varying results. The argument is that large companies from concentrated markets drive technical progress and are responsible for a disproportionate share of the innovative output: "What we have got to accept is that large scale establishment has come to be the most powerful engine of progress" (Joseph A. Schumpeter).

Tailoring this assumption to the pharmaceutical industry, it has been recognized that complementarities between R&D and other activities (e.g. marketing, finance, IT) that are more pronounced in large companies. A large company can also benefit from its marketing department in the R&D area, for example by being able to control innovation projects more precisely. On the other hand, large companies tend to suffer from organizational problems, as employees are more difficult to control by management and employees are also faced with fewer incentives, since their own efforts have neither significant effects on the company's success nor on their own remuneration. In the developmental stage of the project, the "not-invented-here" syndrome (Piller and Antons, 2020), which is more frequently observed in bigger companies, may play a significant role. Large companies are often less willing than small companies to take up inventions from outside and to develop them further. Large pharmaceutical companies are now trying to use the advantages of small units in the research process and are increasingly granting research departments more financial freedom and organizational independence in their organization by splitting their research departments into many small, entrepreneurial units that would then compete with specialized, independent companies and research institutions.

Large, global companies are favored if there are economies of scale in the R&D process, which e.g. result from high fixed costs in R&D projects. Until the 1990s, the prevailing drug search process was based on the trial and error principle, resulting in economies of scale in the research process, in which large companies had comparative advantages because they had high fixed costs on a large number of research projects. The research process itself was characterized by routine rather than creativity, which tends to benefit large companies (Arora, Gambardella 1994). Since the 1990s, however, the situation has fundamentally changed due to the increasing scientification of pharmaceutical research ("rational drug design") and the rapid technological advances in the devices and instruments used in research.

Response of big pharma to this challenge was the outsourcing of R&D. Since hardly any company can master the entire methodological spectrum from genetic engineering to combinatorial screening, research cooperations are there to get to know new methods without obligation, without a direct long-term financial commitment. Cooperations serve as a source of idea and expertise, and the company can carefully assess whether a new research method is promising or not. If projects fail, they can be dropped more quickly than if they were carried out “in-house”, which is why the research risk can be reduced to some extent. Cooperations can increase the motivation of employees by creating a competitive climate and making costs more transparent. The large number of alliances between the established pharmaceutical companies and small biotechnology companies seems to support the scenario of increasing division of labor. The startup/SME companies take on the role of supplying innovative activity. The result is a new type of supplier models, in which large companies, whose core expertise is in marketing and in coordination of development, contract the ideas and services of small research and development suppliers. The network of pharmaceutical companies is expanding rapidly and is structured in a strong hierarchical manner: newly added companies usually enter into collaborations with companies that have recently joined the network. The typical cooperation pattern of the network is that long-established companies (“big pharma”) as developers join forces with biotechnology companies of the 3rd generation as inventors (“originators”).

There are essentially three disadvantages of cooperation type of research: research management is made more difficult because a network of different suppliers can be difficult to coordinate; there is a risk that the partner is given too much insight into their own competencies, and there is a risk of technological dependency on a partner if a company relies too much on outside knowledge.

However, there is also a “dark side” of the M&A strategy of the big pharma. Differing conceptions about how the life sciences ecosystem functions and the forces that drive biomedical innovation are recurring themes in the coming

months due to COVID-19 pandemics. These include proposals to exercise governmental rights to drug price controls, as well as the need to transform the frenzied response to COVID-19 into policies that promote long-term pandemic preparedness on the pharma development side. The pharmaceutical industry has undergone massive consolidation over the last decade and that an ever-smaller number of pharmas are swallowing biotechs whole, sucking out their innovation and spitting out the bones. Sometimes, this seems to be an extrapolation from criticisms of tech companies, from Google to Facebook, that The critical role of smaller companies which cultivate creativity and foster innovative thinking stop – "(…) as soon as these companies are acquired, the innovation stops. The small firm's vision is lost, and the big firm's profits become priority (…)". (Porter, 2021, as seen on https://www.vox.com/policy-and-politics/22256556/katie-porter-pharmaceutical-mergers-cancer-drug - accessed June 15, 2021).

3. Role of public innovation policies

Research of innovation processes in the pharmaceutical industry has shown a new wave of popularity in recent years. Scientists wonder about the effectiveness of existing mechanisms for supporting innovation from the corporate sector, while government mechanisms for managing the industry receive a relatively smaller share of attention. The topic of patenting is often considered separately from the regulators' activity and the corporate activities of industry players. In the early 1990s, the first large wave of research on innovation processes in pharmaceuticals was triggered by the first results of biotechnology research. Today biotechnology is often one of the main ways to overcome the crisis in the innovation effectiveness in the pharmaceutical industry. This implies the development of an entirely new market (biotechnological products), which will entail a large-scale change in the entire health care system (at the state level), which will require close

interaction of major players, governments, regulators and small innovative companies. Thus, today's research of the world economic processes is oriented to developing the future biopharmaceutical market, while the remaining problems of the industry remain unresolved and are often silent. Research on the pharma innovation processes is relatively rare; the strategic role of this industry requires much more attention to the structural changes taking place in it today. The mechanisms for supporting innovative processes in pharmaceuticals have mainly remained unchanged over the past decades, and only in recent years there has been a tendency to change the methods of evaluating the innovativeness levels of certain studies. The private and public sectors began to invest in new research in a much more conservative mode than before. Understanding of the pharma innovation processes on the example of developed countries is necessary to effectively stimulate the development of the industry in countries that are lagging behind the leaders in developing the latest drugs. Given the level of science intensity and market volume, the pharmaceutical industry's success is of strategic importance.

The most important elements of the public innovation policy in the pharmaceutical industry include: patenting and intellectual property protection, R&D support and providing access to the market.

World Intellectual Property Organization data revealed the dynamics of patenting pharmaceutical products in the largest leading countries of the industry. The role of patents, which remain an important source of financial stability for the largest companies and the basis for creating new drugs, is emphasized. In the case of pharmaceutical innovations, a significant part of the patent period is spent on clinical trials and obtaining regulatory approval for the drug. At the same time, competitors strive to produce analogs (generics) with the same chemical formula as the original drugs and sell them at much lower prices. The patent expiration allows any company to legally and cheaply produce generics of the patented drugs, which immediately collapses the profit from the sale of the "originals" (patent cliff).

The data are obtained from the study are structured as follows: first, there is a description of the current state of patenting in the pharmaceutical industry

on a global scale; secondly, the general role of regulators and the specifics of gaining market access for new drugs, as well as the related processes: the problem of low R&D efficiency and the emerging tendency to soften regulatory control is shown. The problems of low R&D efficiency and overpricing of new drugs emphasize the importance of analyzing innovation processes within the pharmaceutical industry, which could open the way to more efficient mechanisms of the industry. Government support of R&D in the United States is large, but participation in production and pricing is weak, making domestic drug prices in the country relatively high. Due to its size, the US market attracts global pharmaceutical companies, and the profit they receive allows them to finance R&D in large volumes, which helps to attract the best specialists from around the world. State structures support the industry indirectly, primarily intending to develop a scientific and technological base and the emergence of top specialists necessary for conducting pharmaceutical R&D. Generally, this happens through specialized government agencies and universities, which distribute budgetary funds in the form of grants, awards, project co-financing, and also conduct their own scientific activities in public research laboratories. In the European Union, the pharmaceutical industry is one of the most developed and competitive sectors in the economy. Many global multinational companies are concentrated in the EU. It is worth highlighting the UK, Germany, Italy, and France, and non-union Switzerland - the largest pharmaceutical manufacturer in Europe with a trade balance of +31.6 billion euros (excess of exports over imports). The added value per employee and the R&D intensity of the pharmaceutical industry remains the highest among all sectors of the EU economy.

4. Methodology

1. Methods, materials, data sources and endpoints

For the research question 1, the methodology, published by Lincker et al (2014) was used, with some modifications. Authors explored the profile and country origin of the organizations involved in the recent development of new medicines in the European Union (EU) and USA. The lists of human medicinal products with a new active substance (NAS), that received approval from the regulatory authorities – EMA (EU) and FDA (USA) for the years 1996, 2006 and 2016 were prepared based on information, disclosed by the respective competent authorities (for EMA: https://www.ema.europa.eu/en/about-us/annual-reports-work-programmes, for FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). A NAS is traditionally defined in the field and for such type pf the studies as a chemical, biological or radiopharmaceutical substance that has not been previously approved as a medicinal product (Lincker et al, 2014). For each approved drug, in line with the Lincker methodology, I profiled the originator organization (or organizations) from the ADIS insight database (https://adisinsight.springer.com/), taking into account company agreements and key development milestones. Each originator entity was then categorized as a large pharmaceutical company, a small or medium-sized enterprise (SME) or an academic/public body. Start-ups formed for purpose of commercialization of the invention was considered and counted as part of academia for the purpose of this work. The geographical origin of the organizations of the products was also analysed. Product transfers within the originator(s) and the later marketing authorization holders was considered if applicable. Licensing activity during the project stage was not considered. Lists of drugs per year and companies are ürpvided as the source data in the Annex to this thesis (section 8).

For the question 2, literature analysis of the main aspects of innovation policy in the US and the EU over time, focusing on big pharma, SMEs and Academia.

2. *Restrictions and limitations of the methodology*

Methodology provides quite precise quantitative analyses of the regulatory data. However, following restrictions should be considered while interpreting the results:

- Pharmaceutical innovation is a lengthy process: time from idea to a market product takes frequently up to 10 years or longer. Drug approval in e.g. 2016 required the development program to start in 2006 or potentially even earlier. Thus, time conclusions from the results may be retrospectively oriented and reflect the processes, which happen years ago before drug approval.
- EU geographically expended several times during the period of observation (2004 – 10 new members; 2007 – two new members; 2013 – new member Croatia), thus, potential sources of new drugs grew. However, new member states were not very active in term of drug approval via the centralized procedure and EMA. This, impact on the data analyzed remains limited.
- In Europe, the EMA centralized procedure is compulsory for majority of the innovative drugs (https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines) Thus, approval of less innovative medications by the national authorities in the individual member states would not change the results substantially, since the focus of this work is on the new active substances.
- Impact of COVID-19 effects on drugs approval (timelines, expectations, ability to facilitate review process and postpone delivery of long-term stability and toxicology data); simultaneously, enormous efficacy EMA and FDA demonstrated when reviewing and approving the COVID-19 vaccines demonstrated a new, fast pathway to approve drugs of high societal need within enormously short periods of time, believed not to be possible prior the pandemic situation. The real, long-term impact of this can be hardly foreseen now. The fact, that two most successful vaccine companies Moderna and BioNTech were founded

relatively shortly (2010 and 2008, respectivel) and are not part of the big pharma prior indicated clear advantage in the fast changing market for niche specialized providers.

Considering the highlighted above methodological restrictions, it still can be concluded that the results are trustable and generalizable and also allow to draw conclusions according to the scientific questions asked.

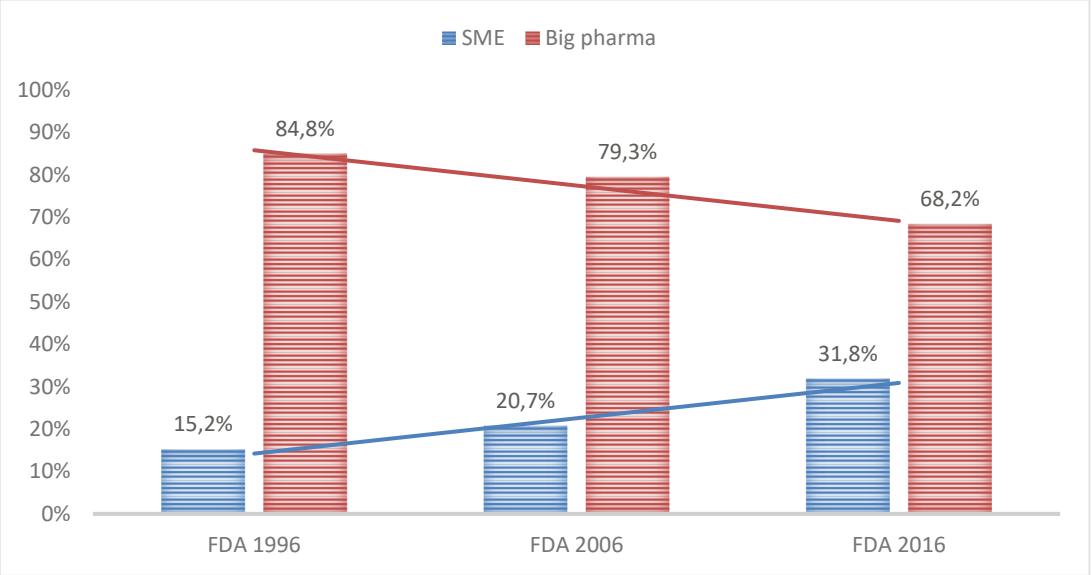
5. Results

1. Sources of scientific innovation in the pharmaceutical industry in the EU and in the USA

1. United States of America

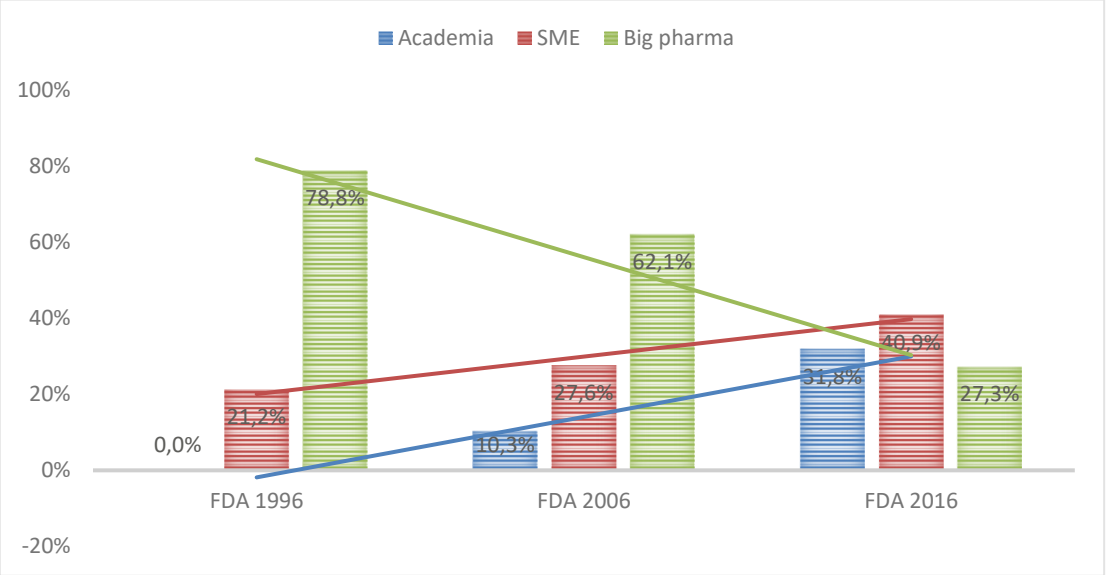
In USA, SME could maintain and increase their ability to bring the pharmaceuticals to the marketing stage: from 15% in 1996, 21% in 2006 up to the one third (32%) of all marketing authorizations in 2016.

Figure 2. Marketing authorization holders for pharmaceuticals, approved in USA by FDA (1996-2016)



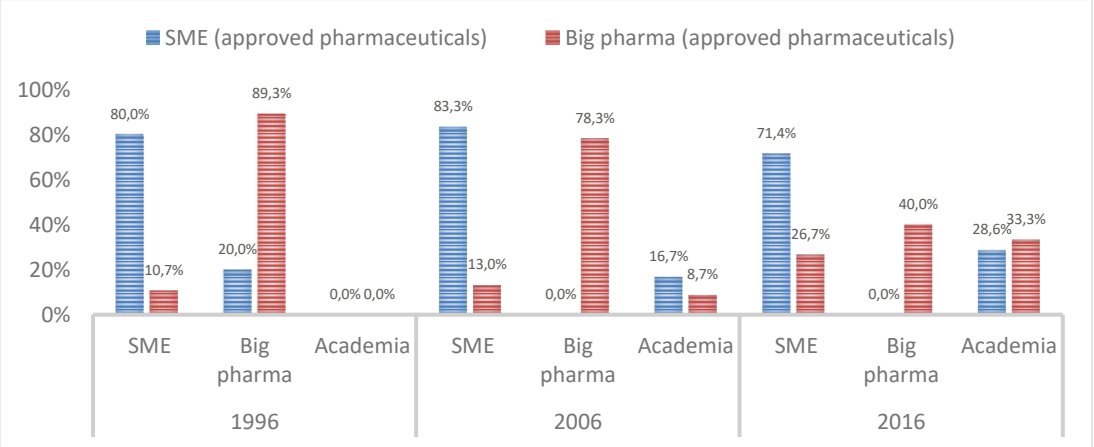
In 1996, there were no approved drugs with the novelty, originating from academia (Figure 1). In 2006, every 10th drug, approved in the USA was discovered in the academic setting, while in 2016 the percentage of academia-invented drugs jumped to 32%. While the role of SME in pharmaceutical discovery remained constant with steady growth over the period of observation (21% in 1996, 28% in 2006 and the dominant 41% in 2016), big pharma in the USA dramatically lost its pioneering role in being source of innovation from 78,8% in 1996 to <30% in 2016.

Figure 3. Sources of IP for pharmaceuticals, approved in USA by FDA (1996-2016)



Contribution of big pharma as source of innovation in the USA dropped from 89% in 1996 to 40% in 2016. SMEs remained active source of inhouse R&D (80% n 1996, 83% in 2006 and 71% in 2016), and could equally gain, alongside the big pharma, from the academic research (17% vs 9% in 2006, and 29% vs 33% in 2016 for SME and big pharma, respectively).

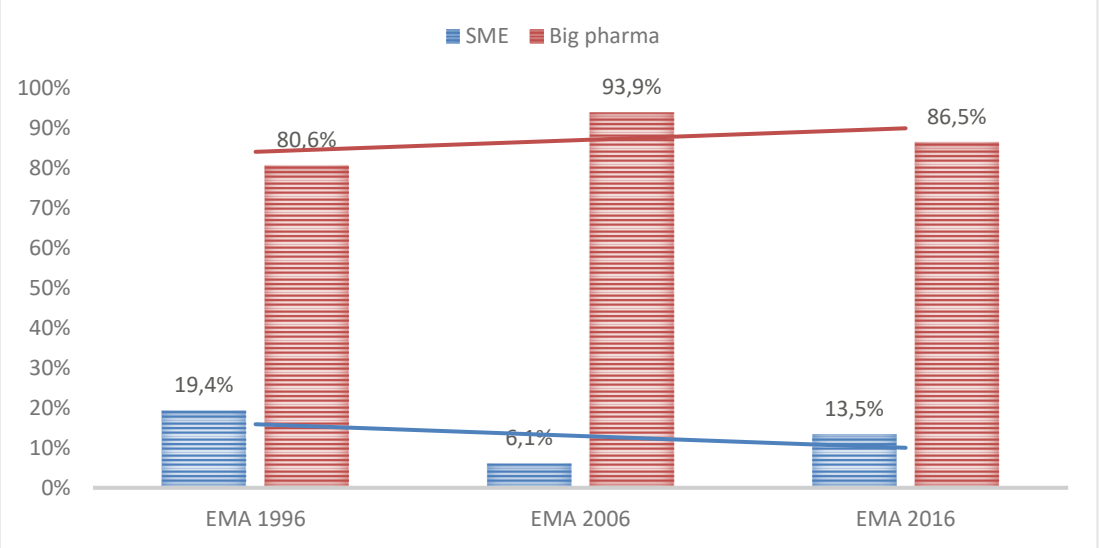
Figure 4. Sources of innovation for pharmaceuticals, approved in USA (1996-2016)



2. European Union

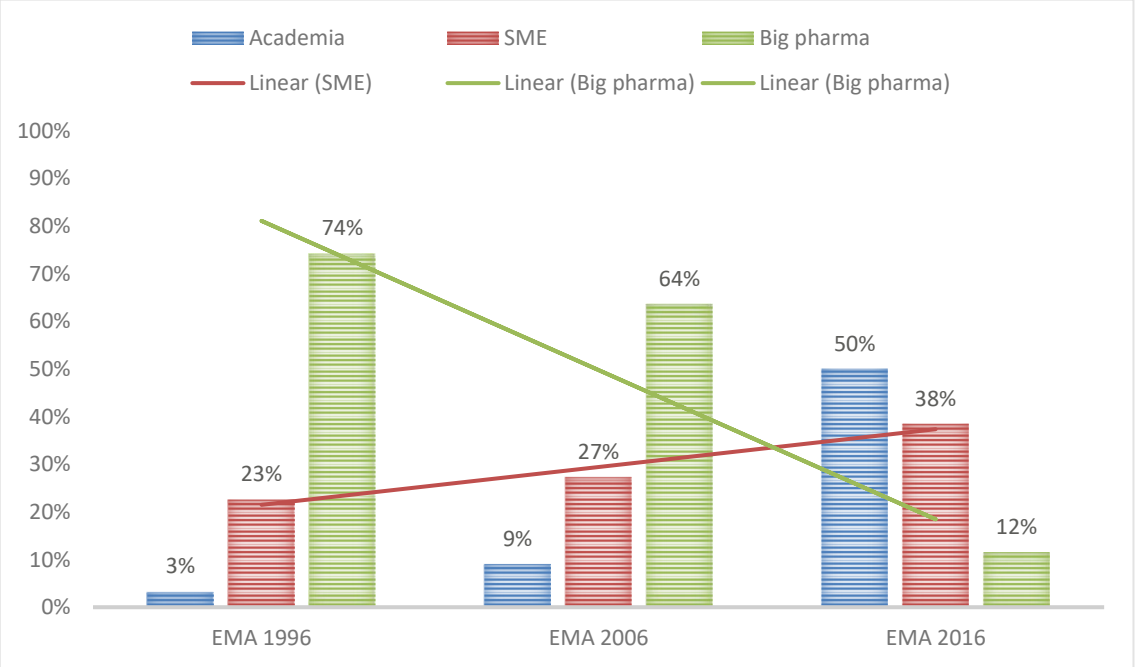
On the contrary to the USA, however, the big pharma positions in getting commercial authorization did not change significantly over time, indicating that the these market players could maintain their dominant role by acquiring or in-licensing projects, emerged from the SME or academia (Figure 2). While in 1996, SME were in a position to maintain marketing authorization of the drugs in almost 20% of the medications of the market, ownership of approvals decreased to 6% in 2006 and recovered slowly to 13,5% in 2016 to the values observed at the beginning of the observation period.

Figure 5. Marketing authorization holders in EU by European Medicines Agency (1996-2016)



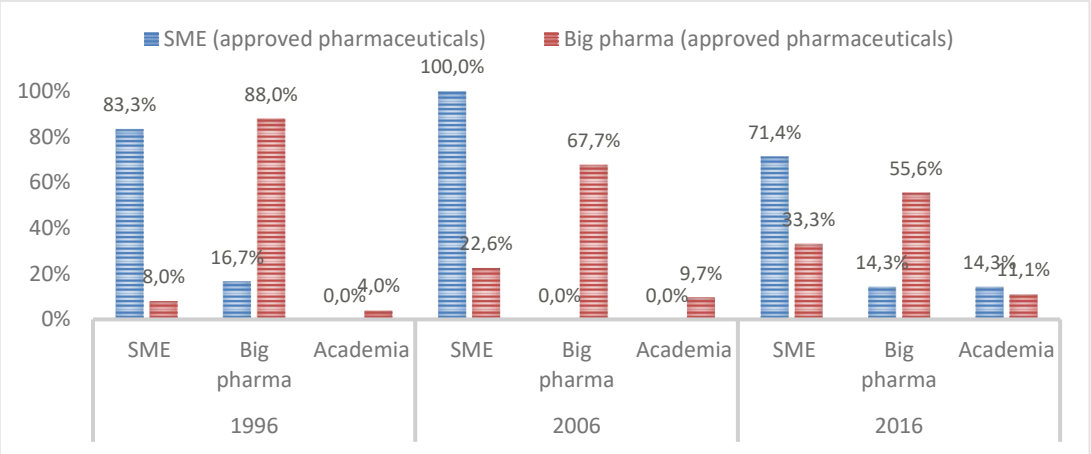
Big pharma played an important role in driving the innovation in the pharmaceutical research in the EU in the year 1996 (74% of all approved drugs patents were filed to big pharma). This figure dropped significantly over the time: 64% and 50% in 2006 and 2016, respectively, while the role of SMEs increased steadily (23%, 27% and 38%), same as academia (3%, 9% and 12%) in the years 1996, 2006 and 2016, respectively.

Figure 6. Sources of IP for pharmaceuticals, approved in EU (1996-2016)



From all pharmaceuticals (n=25), approved by big pharma in 1996, 88% (or 22 products) were invented by big pharma. Proportion of own, in-house invention for big pharma dropped during the upcoming observation periods to 68% in and 56% in 1996. Big pharma actively acquired novelty from SMEs and academia, resulting in the rates of 23% and 10% in 2006, and 33% and 11% in 2016 (for SMEs and Academia, respectively). SME remained the main source of novelty for themselves during the observation period, although the group could acquire significant amount of projects from Big pharma and Academia (for 2016 figures grew up to 33% and 14%, respectively).

Figure 7. Sources of innovation for pharmaceuticals, approved in EU (1996-2016)



Memo to the figures. The path of a pharmaceutical development starts with a discovery, followed promptly by a patent filing. IP is filed by originator of the invention and indicates the primary source of idea and underlying discovery for a drug. After IP filing, a development pathway starts (preclinical – clinical phase I – phase 2 – phase 3 – regulatory filing) with a marketing authorization/approval for commercial sales. The marketing authorization holdership identifies party, which was able to technically develop the drug according to the regulatory development standards.

2. *Productivity and success rates of pharmaceutical innovation in US vs EU*

1. The USA.

The success of the US pharmaceutical industry is based on a huge market, cutting-edge research, and the FDA's carefully crafted regulatory and supervisory framework. Private companies in the country conduct large volumes of research. As can be seen from the dynamics of R&D expenditures, since 2000, member companies of the American Pharmaceutical Research and Manufacturers Association (PhRMA), which unites more than 75 largest pharmaceutical and biotechnology companies,

have increased R&D expenditures by more than twice. Simultaneously, the number of new, annually approved drugs in the United States is growing much slower than the cost of R&D. With the strengthening of the patenting system and the practice of granting patents for slightly modified drugs, the largest corporations gain additional benefits. Because of the enormous resources, it is easier for corporations to commercialize patented results than for small and independent market players, which more closely locks industry innovation processes with multinational companies. Simultaneously, US patents remain the most important tool for obtaining grants and funding for small companies, start-ups, and university laboratories, as they are included in various performance indicators.

Conducting fundamental research is often not a priority for large corporations (risks and costs are high); therefore, in the USA, R&D is actively supported by the government, which also stimulates the growth of small companies. R&D expenditures related to pharmaceuticals, including biotechnology, in the United States account for the largest share (21% in 2011) of the total volume of private R&D expenditures in all sectors of the economy, almost twice ahead of software development (11% in 2011). A huge amount of funding comes from the National Institutes of Health (NIH), a government organization made up of 27 independent health research institutions (including pharmaceuticals) and the R&D Foundation. Pharmaceutical giants and small businesses work closely with NIH's. There are knowledge-sharing programs that allow NIH's to receive company-developed molecules for further fundamental research.

The US pharmaceutical industry attracted so much money that scientific breakthroughs began to occur more often, and technological development (primarily computerization) led to a reduction in the cost of basic research facilities (synthesis and analysis of molecular drugs). The largest corporations, whose activities have overextended, gradually lose out in R&D to small scientific enterprises, which is reflected today in the intensive growth of the number of biotechnological start-ups.

Biotechnology research is now carried out in many independent small

research enterprises that increasingly influence the industry and its traditional giants. In addition to the emergence and strengthening of interactions between major corporations and start-ups, biotechnology can also provide a new path to the emergence of blockbusters. Traditional blockbuster drugs of the molecular type have been maintained at high sales levels mainly by patent protection. The unique role of patents (most of them will be filed at the stage shortly after discovery, i.e. in the Academia stage of the invention), in this case, is due to the relatively easy copy of a molecular drug. For example, in the aviation industry, which, like the pharmaceutical industry, is characterized by extremely high science and capital intensity, the role of patents is significantly less, since the very process of copying a product of this industry would require a competitor to create complex elements: factories, machine tools, competencies. Thus, the difficulty of copying a product is a factor in protecting that product from competitors. In the case of biotechnological drugs, the creation of which takes place in completely different laboratory conditions and requires special processes, the complexity of copying increases, since even a slight change in scientific and production conditions has a significant effect on the resulting drug (and on its clinical effect). Therefore, the special "refinement" of new biotechnological drugs can become a factor in their transformation into new blockbusters.

2. European Union

Over the past 15 years, pharmaceutical production in Europe has almost doubled. The EU countries export a colossal volume of pharmaceutical products - in 2015, totaling 361.5 billion euros. Investments in innovative developments exceed 30 billion euros. However, government spending is several times less than in the United States.

The EU is characterized by uneven patent laws and a variety of monitoring mechanisms for intellectual property rights. Legislation in this area is being tightened. In addition to patents, certificates of additional protection, special conditions for drugs against rare and complex diseases are also

distributed. The political structures of the EU are slowly but purposefully pursuing a policy of leveling patent law, and the current system is much more unified than before. Due to internal agreements, the validity of a patent issued in one of the participating countries (applications can be filed not only with the single patent authority, where is a higher verification level but also with the local authorities of the countries). In the EU, there are mechanisms for an additional extension of the patents' term, depending on the R&D duration. (as a rule, by five years).

For a long time, the production of generics in the EU did not find adequate support. Although generics have been actively developing in the US since the late 1980s, in the EU, this process has intensified only in the last ten years. The share of generics in different EU member states differs significantly due to different clinical practices pre-joining the Union, market preferences, and different levels of development of intellectual property rights protection. In the EU, there are significant differences between countries in legislation, insurance reimbursement systems, and national health systems. For example, doctors in Greece, where the share of generics in the total volume of drugs sold is one of the lowest, society has a negative attitude towards generics, considering them less effective and even dangerous, especially if they are not produced in developed countries, which makes it challenging to implement government initiatives on the introduction of generics. Today, in most EU countries, production control and distribution of generics have become tighter and comparable to the requirements for conventional drugs.

Pharmaceutical R&Ds are funded in three main areas: corporate spending, EU-wide spending (framework programs), and national spending. Framework programs provide no more than 2% of total costs. Some countries allocate large funds, first of all, France and Germany. The share of corporate costs is relatively small in the Netherlands, Austria and Norway, and national support programs offset the costs. In countries with a large presence of multinational companies, generally, corporate expenses prevail (Switzerland, Ireland).

In the EU, more than a dozen instruments are regulating the industry. Most countries monitor retail pricing and lists of vital, authorized and prohibited

drugs are applied. Price caps are driving drug prices in the EU 40% lower than in the US. On the other hand, it reduces corporate investment in R&D. The EU is characterized by less participation of the academic sector in R&D than the USA. Universities are not sufficiently involved in the financial models of pharmaceutical companies, which reduces the R&D potential. Problems of supporting startups and small businesses have become traditional. The links between public research institutions and corporations are relatively weak, and the availability of venture capital is lower than in the United States. In fact, the EU pharmaceutical R&D sector suffers from underfunding. The European Commission seeks to solve this problem by allocating funds to develop the venture capital market (first of all, for the early stages of R&D and the life cycle of startups). The mechanism of public-private partnership (PPP) is also used. Insufficient activity of venture funds led to the fact that the intensively developing biotech direction became much less developed in the EU than in the USA. Since 2007, the European Commission has been trying to rectify the situation by working out development strategies, creating mechanisms for tax and credit incentives for small innovative companies, but state support for R&D capital is inactive.

Thus, the factors constraining innovation processes in the EU include imbalances in the patent system, a weak venture market, and a low level of cooperation between entities and transition from academic to startup/early commercial setting ("translational problem"). As a result, in comparison with the USA in the EU, the public policy on pharmaceuticals has an important additional aspect: support of small innovative enterprises through targeted state funding, as well as the adoption of additional measures to institutionalize the EU countries to facilitate trade, production - new activities and interaction of commercial and scientific sectors (Eger et al, 2014).

3. Europe 2017-2020

Europe experienced a very productinve year 2020 in term of funding new biotechs in 2020, but the speed of companies foundationslowed down, with a 20% decrease since 2017. Despite academia stayed last year to dominate in being source of the technology for start-ups, industry's contribution went up to almost one fourth of the new companies funded.

The trends indicate that Europe has still not addressed its translational problem — the gap between the high level of university research and the Europe's ability to transform innovative science into commercial enterprises. Based on the BioCentury data, who documented 62 companies headquartered in Europe that raised seed or series A funding in 2020, compared with 70 in 2019, and 57 and 78 in the two previous years. Most of the drop was due to fewer spinouts from academia; the number of newcos spun out of biopharmas grew by three to 14.

Still, academia continues to represent the main source of innovation in Europe, providing the technologies for about 80% of the companies raising early stage funding since 2017 (see Figure 7 below).

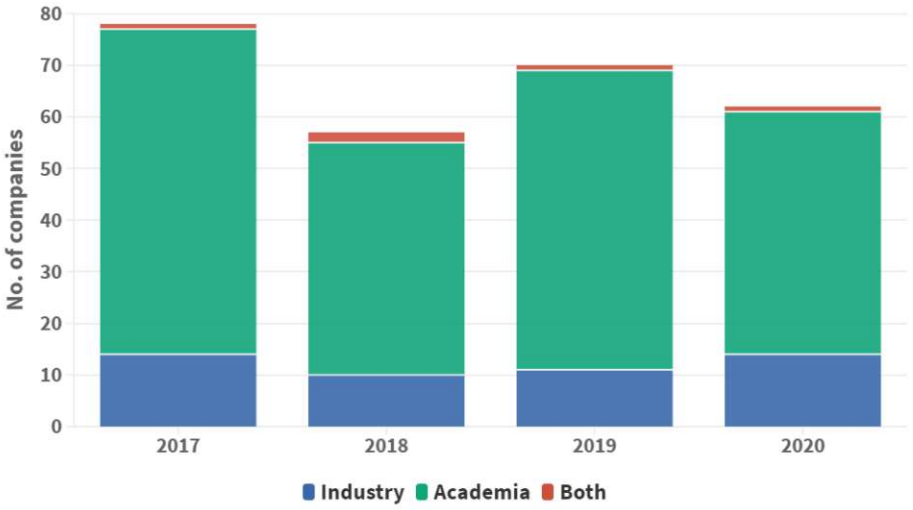


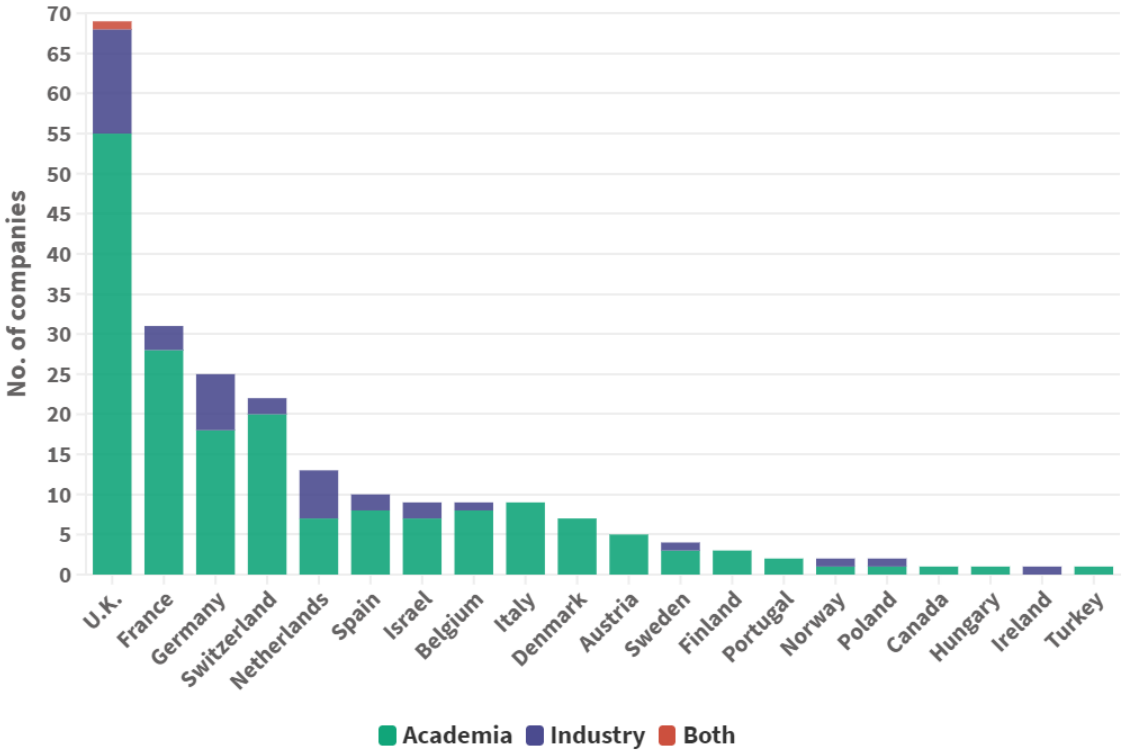
Figure 8. New company formation in Europe. Origins of technology for companies raising seed and series A funds.

The picture is not uniform across Europe. The U.K. is far and away the most prolific source of technology going into new companies, outpacing its closest competitor France by more than 100%.

U.K. technology gave rise to 69 companies from 2017-20 that raised seed or series A rounds, 55 of which came out of academia. The activity wasn't focused in any one year; U.K. technology was behind 16-20 companies per year, compared with a range of five to 10 for France and six to nine for Germany. Industry-sourced technology has come from a smaller spread of countries, primarily the U.K., France and Netherlands, with the Dutch newcos arising almost equally from industry and academia.

The countries shown in the chart below represent the source of the technology, rather than the headquarters of the company.

Figure 9. Technology origins of European start-ups. Seed and series A companies, 2017-2020



Europe has also made small steps, though not yet strides, in bringing technology from overseas to create start-ups in the region. US. innovation was behind 15 European start-ups from 2017-20, including eight from academia, all from different institutions.

The US-based newcos, including those spun out of industry, raised on aggregate $215.6 million, putting them in the same range as the Netherlands and Switzerland for number of companies and money raised, respectively. Six of the U.S.-derived companies were formed in the U.K., two each in Belgium, France and Israel, and the others in Austria, Denmark and the Netherlands.

Only five other companies came from outside Europe, with one industry spinout each from Korea and Japan, and one academic spinout each from Australia, New Zealand and Canada. The standout among them was Arvelle, whose technology came from SK Biopharmaceuticals Co. Ltd. Ireland's Priothera Ltd., raised a $35.5 million series A round last year to develop technology from Japan's Kyorin Pharmaceutical Co. Ltd. (Tokyo:4569) to develop a treatment for acute myelogenous leukemia.

The U.K.'s prominence is reflected in the number of universities producing multiple start-ups. Five of the top 15 academic institutions for newco creation are in the U.K., dominated by the Golden Triangle heavyweights of Oxford University, Cambridge University and the capital's University College London, Imperial College London and King's College London. The U.K. also kept all but three of its start-ups headquartered domestically.

France's INSERM and CNRS are high producers of translational talent, and likewise kept all but three of its start-ups in the country.

Germany's talent is not focused in specific institutions, by contrast. The most prolific were the Max Planck Institute and the University of Tübingen, which each produced three start-ups.

Barcelona's ICREA is starting to gain stride, producing four start-ups, including Ona Therapeutics, which raised a $33.8 million series A round in

2020 to develop an antibody targeting a lipid metabolism pathway for prevention of metastasis. ICREA — the Catalan Institute for Research and Advanced Studies — also produced three smaller companies with sub-$5 million raises.

Table 1.. Academic institution translational leaders. Source of funded start-ups, 2017-20

University	# of startups
Oxford University	17
Cambridge University	13
INSERM	11
CNRS	7
ETH Zurich	6
University College London	6
Technical University of Denmark	5
ICREA	4
Imperial College London	4
King's College London	4
KU Leuven	4
Leiden University	4
University of Basel	4
University of Strasbourg	4
VIB	4

4. USA 2017-2019

Starting 2017, 602 businesses had seed or series A financing where data could be collected via BioCentury (Source: Pharma spinouts: a snapshot of where and how pharmas spin out their assets). Source of technology was

identified (Biocentury) in 543 of these, 402 were created with assets licensed from academia.

Pharmas gave start to 43 new companies, 35 of which disclosed seed or series A funding. Additional 99 startups were spuspin offs of smaller companies (2017-19).

Academic startups continued to attract increasinglylaunch funding, they have been outstripped by the amounts raised by companies spun out of pharma. About one-third of pharma spinouts that disclosed initial funding raised more than $50M, with nine raising more than $100M.

Moreover, pharma spinouts raised on average $81.1M in series A funding, about four times the $20.8M average raise of academic startups and almost three times the $28.8M average raise for companies spun out of other biotechs. Pharma spinouts also lead in median raises, at $29.5M compared with $20M from other company spinouts and $12M for academic ones.

Figure 10. Total seed and series A funding by technology source.

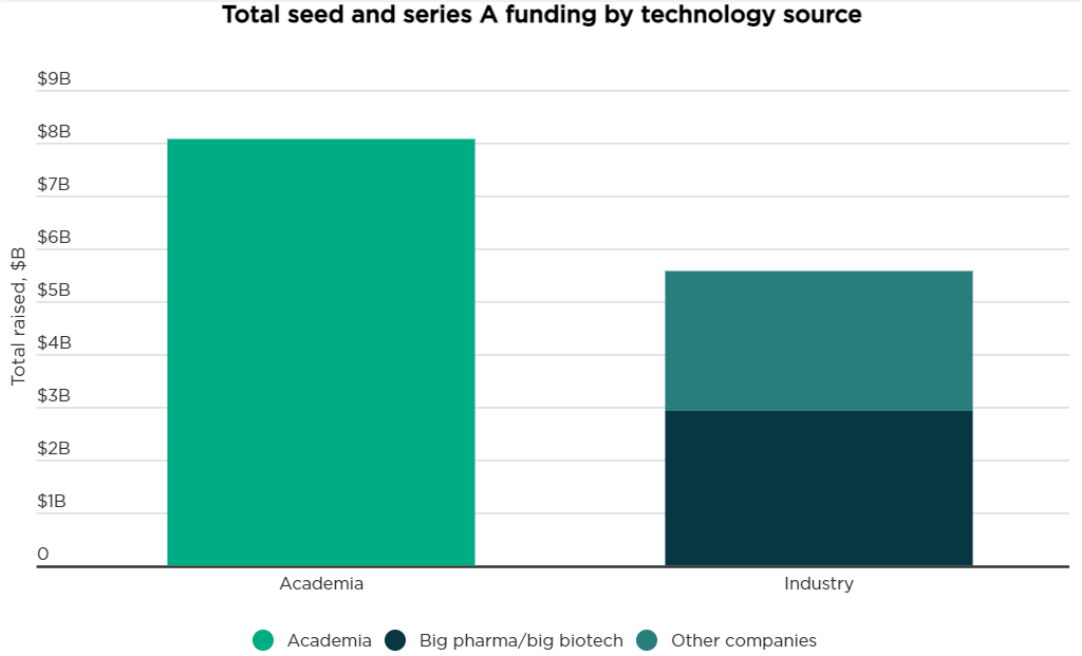
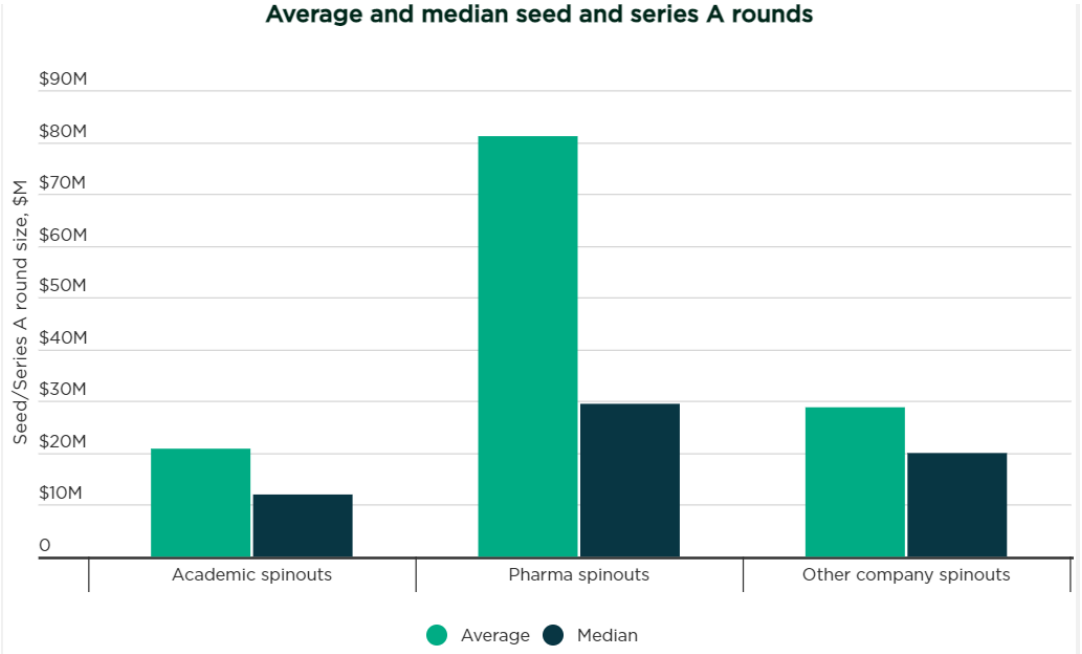


Figure 11. Average and median seed and series A rounds.



It's little surprise that cancer is the most dominant disease area, representing almost 29% of the total number of newcos, and more than one third of those spun out of pharma. However, three of the top disease areas -- neurology, infectious disease and cardiovascular -- represent areas where many pharmas have exited or wound down their activities. In neurology, 62 companies were created, including eight that spun out pharma assets, and in infectious disease, 41 companies, although only 2 from pharmas. That suggests that in those areas, there is a fair pipeline of opportunities in early stage development, and that investors are backing these opportunities. However, cardiovascular disease, an area of major public health need where many pharmas have exited, lags also in the newco lanscape. Only 16 of the total 543 companies, (3%), are in cardiovascular research as a lead indication, including four with assets spun out of pharmas.

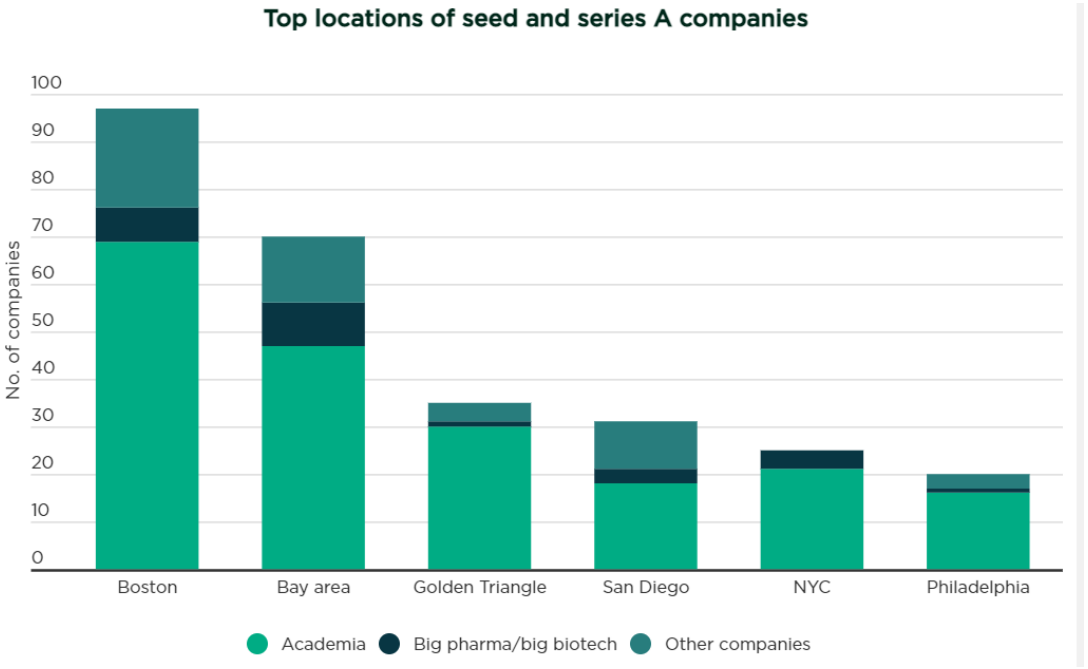
Figure 12. Top disease areas of 2017-19 new companies.

Top disease areas

	Academia	Big pharma/big biotech	Other companies	Total
Cancer	116	12	30	158
Neurology	45	8	9	62
Infectious	31	2	8	41
Autoimmune	19	4	10	33
Endocrine/metabolic	14	0	3	17
Cardiovascular	12	4	0	16
Ophthalmic	11	0	5	16

Pharmas are spinning out their companies in the standard hubs, although the Bay Area has snagged nine, against Boston's seven. That order is reversed among all the newcos, where a total of 97 were placed in Boston, versus 70 in the Bay Area. But pharmas have yet to dive into the U.K.'s Golden Triangle of Cambridge-Oxford-London, which globally represents the third biggest hub for newco creation, based on number of companies, but only attracted a single pharma spinout.

Figure 13. Location of seed and series A companies.



6. Summary and discussion

1. Summary of findings

Three major components were identified as main influencors of the development of the industry and will be elaborated in this thesis:

- governmental regulation of the industry,
- the system of patenting of drugs, and
- financing of scientific and investigations (venture, corporate, public funding of pharmaceutical R&D).

Differences between sources of innovation and originators of approved drugs were observed between US and EU.

In USA, SME could maintain and increase their ability to bring the pharmaceuticals to the marketing stage: from 15% in 1996, 21% in 2006 up to the one third (32%) of all marketing authorizations in 2016. In 1996, there were no approved drugs with the novelty, originating from academia. In 2006, every 10th drug, approved in the USA was discovered in the academic

setting, while in 2016 the percentage of academia-invented drugs jumped to 32%. While the role of SME in pharmaceutical discovery remained constant with steady growth over the period of observation (21% in 1996, 28% in 2006 and the dominant 41% in 2016), big pharma in the USA dramatically lost its pioneering role in being source of innovation from 78,8% in 1996 to <30% in 2016. Contribution of big pharma as source of innovation in the USA dropped from 89% in 1996 to 40% in 2016. SMEs remainedactive source of in house R&D (80% n 1996, 83% in 2006 and 71% in 2016), and could equally gain, alongside the big pharma, from the academic research (17% vs 9% in 2006, and 29% vs 33% in 2016 for SME and big pharma, respectively).

In the European Union 0n the contrary to the USA, however, the big pharma positions in getting commercial authorization did not change significantly over time, indicating that the these market players could maintain their dominant role by acquiring or in-licensing projects, emerged from the SME or academia. While in 1996, SME were in a position to maintain marketing authorization of the drugs in almost 20% of the medications of the market, ownership of approvals decreased to 6% in 2006 and recovered slowly to 13,5% in 2016 to the values observed at the beginning of the observation period. Big pharma played an important role in driving the innovation in the pharmaceutical research in the EU in the year 1996 (74% of all approved drugs patents were filed to big pharma). This figure dropped significantly over the time: 64% and 50% in 2006 and 2016, respectively, while the role of SMEs increased steadily (23%, 27% and 38%), same as academia (3%, 9% and 12%) in the years 1996, 2006 and 2016, respectively. From all pharmaceuticals (n=25), approved by big pharma in 1996, 88% (or 22 products) were invented by big pharma. Proportion of own, in-house invention for big pharma dropped during the upcoming observation periods to 68% in and 56% in 1996. Big pharma actively acquired novelty from SMEs and academia, resulting in the rates of 23% and 10% in 2006, and 33% and 11% in 2016 (for SMEs and Academia, respectively). SME remained the main source of novelty for themselves during the observation period, although the

group could acquire significant amount of projects from Big pharma and Academia (for 2016 figures grew up to 33% and 14%, respectively).

2. *Limitations of the research*

The following limitations apply to this work:
The work did not consider the major economical (e.g. world economic crisis of 2008) and regulatory (major changes of the legislations in the EU and USA) Impact of presence and access to the venture capital, believed to be an important factor for academic and SME innovation was not considered
However, the numbers of approvals and their origin as major outcome of pharmaceutical innovation, cumulated all potential effects, mentioned above, as final, consolidatedproduct. Thus, the generated data have their one standalone information value.

3. *Conclusion and outlook*

Support for pharmaceutical innovations overall continues to be associated with simple financial support for R&D. Today, companies are striving to increase the R&D focus and move from quantitative R&D indicators to qualitative ones. It is becoming clear that simply increasing the share of R&D does not necessarily entail innovation. However, global spending on industry R&D continues to grow.
The first wave of biotechnological drugs in the 1990s had already slowed down the decline rate in R&D productivity, but by now, the valuation of production efficiency has decreased more than halved than the average values of the 1990s. World pharmaceutical companies, amid falling profitability, are now working to improve efficiency and are highly conservative about new research projects.
There has been increased focus on biotech drugs, cancer drugs and orphan drugs, which are much less susceptible to the problem of "low clinical

benefit". New drugs target rare diseases, most of which are genetic nature, and, therefore, the mechanisms of production of such drugs are significantly different from the production of classical molecular drugs. As molecular drugs increasingly enter the generic market, the question arises about the financial future of the pharmaceutical industry as a whole. Managers of the largest companies are aware of the industry's challenges and now actively seeking to introduce new business models that would allow companies to remain financially stable in the new paradigm.

Governments in Western countries, in particularly in EU and USA, are focusing on strengthening patenting and trying to be flexible in regulating market access. Patent law is becoming more global and uniform. Most likely, developed countries will maintain a prudent and balanced approach to patent law, and in the medium term, patents will retain their status quo.

In the discourse on patenting today, it is necessary to emphasize the existence of indirect opportunities for improving the mechanisms of the industry's functioning, including:

- licensing of existing patents to third parties;
- transition to the open data paradigm;
- improving the quality of patents, that is, increasing the share of patents for unique drugs, rather than modifications;
- creating research areas free from patent restrictions, providing access to the entire spectrum of knowledge (research exemptions).

Academia–pharma collaborations are basic to overcoming the pharmaceutical development shortfall and bringing publicly supported novel discoveries to the patients (Palmer and Chaguturu, 2017). The rate of disclosure of novel modes of actions, empowering innovations, and novel translational models are expanding year over year. Pharmaceutical research siloed inside a company, the standard of yesterday, is not the fruitful case any longer. Moreover, keeping disclosure closed in a university setting will not be considered ethical and plausible any more.

Regulators in developed countries today pursue a liberal policy towards small businesses, support access to the market for generics, but at the same time tighten requirements for their production. Government funding for R&D in most developed countries has reached stable levels (growth has stopped), while in the United States, taking into account inflation, the role of the state in R&D is declining.

In an attempt to maintain the status quo, the largest corporations are pursuing a policy of mergers and acquisitions - their number has reached record levels in recent years. Cooperation with small businesses, start-ups, independent gamblers, and the academic sector is intensifying. Companies are trying to open new markets and lobby for better conditions (primarily in developing countries) while paying more and more attention to breakthrough areas - telemedicine, medical services, biotechnology, and personalized drugs. Market participants and government agencies have yet to come to understand the new realities of the pharmaceutical industry. The search for effective mechanisms to support pharmaceutical innovation and the subsequent reassessment of the concept of innovation in the industry is just beginning.

7. Bibliography

Aghion, P. and Bloom, N. and Blundell, R. and Griffith, R. and Howitt, P. (2002) Competition and innovation: an inverted U relationship. Working paper. NBER Working Papers (9269). National Bureau of Economic Research, Cambridge, US.. 120. 10.1093/qje/120.2.701.

Arora, Ashish and Gambardella, Alfonso, (1994), The changing technology of technological change: general and abstract knowledge and the division of innovative labour, Research Policy, 23, issue 5, p. 523-532.

Cantwell J.A., Bachmann A (1998). Changing patterns in technological leadership – evidence from the pharmaceutical industry. International Journal of Technology Management. 1998. Vol. 21. P. 45–77.

European translation sees more money but fewer start-ups in 2020 (BioCentury, 2021). Accessed under**: https://www.biocentury.com/article/636035 on June 15**, 2021

Pharma spinouts: a snapshot of where and how pharmas spin out their assets (BioCentury, 2019). Accessed under https://www.biocentury.com/article/304099/pharma-spinouts-account-for-small-percentage-of-total-newcos-but-large-share-of-capital-raised on June 15, 2021

DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ. 2016 May;47:20-33. doi: 10.1016/j.jhealeco.2016.01.012. Epub 2016 Feb 12. PMID: 26928437.

Ding M., Eliashberg J., Stremersch S., editors. Innovation and Marketing in the Pharmaceutical Industry. International Series in Quantitative Marketing. 2014. DOI: http://dx.doi. org/10.1007/978-1-4614-7801-0

Eger S., Mahlich J.C. Pharmaceutical regulation in Europe and its impact on corporate R&D. Health Economics Review. 2014; 4(1):1. DOI: http://dx.doi.org/10.1186/s13561-014-0023-5

Fagerberg J., Srholec M. National innovation systems, capabilities and economic development. Research policy. 2008. Vol 37;9: 1417–1435. https://doi.org/10.1016/j.respol.2008.06.003

Garcia FA, Vandiver MW. Throughput Optimization of Continuous Biopharmaceutical Manufacturing Facilities. PDA J Pharm Sci Technol. 2017 May-Jun;71(3):189-205. doi: 10.5731/pdajpst.2016.006882. Epub 2016 Dec 14. PMID: 27974629.

Goodwin, Melissa (1998) "Firm Size and R&D; Testing the Schumpeterian Hypothesis," University Avenue Undergraduate Journal of Economics: Vol. 2 : Iss. 1 , Article 4. Available at: https://digitalcommons.iwu.edu/uauje/vol2/iss1/4

John Cantwell & Astrid Bachmann, 1998. "Changing Patterns of Technological Leadership: Evidence from the Pharma Ceutical Industry," International Journal of Innovation Management (ijim), World Scientific Publishing Co. Pte. Ltd., vol. 2(01), pages 45-77. https://ideas.repec.org/a/wsi/ijimxx/v02y1998i01ns1363919698000031.html

Justin S. Bryans, Catherine A. Kettleborough & Roberto Solari (2019) Are academic drug discovery efforts receiving more recognition with declining industry efficiency?, Expert Opinion on Drug Discovery, 14:7, 605-607, DOI: 10.1080/17460441.2019.1596080

Kesselheim AS, Tan YT, Avorn J. The roles of academia, rare diseases, and repurposing in the development of the most transformative drugs. Health Aff (Millwood). 2015 Feb;34(2):286-93. doi: 10.1377/hlthaff.2014.1038. PMID: 25646109.

Khanna I. Drug discovery in pharmaceutical industry: productivity challenges and trends. Drug Discov Today. 2012 Oct;17(19-20):1088-102. doi: 10.1016/j.drudis.2012.05.007. Epub 2012 May 22. PMID: 22627006.

Lee, Sau & O'Connor, Thomas & Yang, Xiaochuan & Cruz, Celia & Chatterjee, Sharmista & Madurawe, Rapti & Moore, Christine & Yu, Lawrence & Woodcock, Janet. (2015). Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production. Journal of Pharmaceutical Innovation. 10. 10.1007/s12247-015-9215-8.

Lendrem D, Senn SJ, Lendrem BC, Isaacs JD. R&D productivity rides again? Pharm Stat. 2015 Jan-Feb;14(1):1-3. doi: 10.1002/pst.1653. Epub 2014 Oct 22. PMID: 25336017.

Light DW, Lexchin JR. Pharmaceutical research and development: what do we get for all that money? BMJ. 2012 Aug 7;345:e4348. doi: 10.1136/bmj.e4348. PMID: 22872694.

Lincker H, Ziogas C, Carr M, Porta N, Eichler HG. Regulatory watch: Where do new medicines originate from in the EU? Nat Rev Drug Discov. 2014 Feb;13(2):92-3. doi: 10.1038/nrd4232. PMID: 24481298.

Ruben A. Mesa, Craig Zimmerman, Lih Lisa Kang, Albert Qin, Chungwei Lee, Weichung (Joe) Shih, **Oleh Zagrijtschuk**, Norio Komatsu, Zhi-Jian Xiao, Hsin-An Hou, Chih-Cheng Chen, and Srdan Verstovsek (2019). Journal of Clinical Oncology 37:15_suppl, 7055.

Nosengo N. Can you teach old drugs new tricks? Nature. 2016 Jun 16;534(7607):314-6. doi: 10.1038/534314a. PMID: 27306171.

Michelle Palmer & Rathnam Chaguturu (2017) Academia–pharma partnerships for novel drug discovery: essential or nice to have?, Expert Opinion on Drug Discovery, 12:6, 537-540, DOI: 10.1080/17460441.2017.1318124

Piller, Frank & Antons, David. (2015). Opening the Black Box of "Not Invented Here": Attitudes, Decision Biases, and Behavioral Consequences. Academy of Management Executive. 29. 193-217. 10.5465/amp.2013.0091.

Pontus Braunerhjelm & Roger Svensson, 2010. The inventor's role: was Schumpeter right? Journal of Evolutionary Economics, Springer, vol. 20(3), pages 413-444, June. https://ideas.repec.org/a/spr/joevec/v20y2010i3p413-444.html

Scannell, J., Blanckley, A., Boldon, H. *et al.* Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov* **11,** 191–200 (2012). https://doi.org/10.1038/nrd3681

8. Annex. Source data, used for analysis.

Table 2. Drugs, approved by EMA in 2016.

Trade name	Non-proprietary name
Aerivio Spiromax	salmeterol / fluticasone propionate
Afstyla	lonoctocog alfa
Airexar Spiromax	salmeterol / fluticasone propionate
Alecensa	alectinib
Alprolix	eftrenonacog alfa
CABOMETYX	cabozantinib
Chenodeoxycholic acid sigma-tau	chenodeoxycholic acid
Cinqaero	reslizumab
Coagadex	human coagulation factor X
Cystadrops	mercaptamine
Darzalex	daratumumab
Descovy	emtricitabine / tenofovir alafenamide
Empliciti	elotuzumab
EndolucinBeta	lutetium (177 Lu) chloride
Enzepi	pancreas powder
Epclusa	sofosbuvir / velpatasvir
Fiasp	insulin aspart
Flixabi	infliximab
Galafold	migalastat
Glyxambi	empagliflozin / linagliptin
IBRANCE	palbociclib
IDELVION	albutrepenonacog alfa
Kisplyx	lenvatinib
Lartruvo	olaratumab
LEDAGA	chlormethine
Lonsurf	trifluridine / tipiracil
Neparvis	sacubitril / valsartan
NINLARO*	ixazomib
OCALIVA	obeticholic acid
Odefsey	emtricitabine / rilpivirine / tenofovir alafenamide
Olumiant	baricitinib
Ongentys	opicapone
Onivyde	irinotecan hydrochloride trihydrate
Vaccine H5N1	pandemic influenza vaccine (H5N1) (live attenuated, nasal)
Parsabiv	etelcalcetide
Pregabalin Zentiva k.s.	pregabalin
Qtern	saxagliptin / dapagliflozin
Rekovelle	follitropin delta
Sialanar*	glycopyrronium
SomaKit TOC	edotreotide
Strimvelis	autologous CD34+ enriched cell fraction
Suliqua	insulin glargine / lixisenatide
Taltz	ixekizumab
Truberzi	eluxadoline
Vemlidy	tenofovir alafenamide

Venclyxto	venetoclax
Vihuma	simoctocog alfa
Zalmoxis	allogeneic t cells genetically modified
Zavicefta	ceftazidime / avibactam
Zepatier	elbasvir / grazoprevir
Zinbryta	daclizumab
Zinplava	bezlotoxumab

Table 3. Drugs, approved by EMA, in 2006.

Product Name	Company
Proquad	Sanofi Pasteur MSD
Preotact parathyroid hormone	Nycomed Danmark
M-M-RVAXPRO	Sanofi Pasteur MSD
Duotrav travopost/ timolol maleate	Alcon Laboratories
Tygacil tigecycline	Wyeth Europa
Ganfort	Allergan
Zostavax varicella - zoster live virus	Sanofi Pasteur MSD
Avaglim	SmithKline Beecham
RotaTeq	Sanofi Pasteur MSD
Baraclude	Bristol Myers Squibb Pharma
Tysabri	Elan Pharma International
Zimulti	Sanofi-Synthelabo
Acomplia	Sanofi-Synthelabo
Intrinsa	Procter & Gamble
Livensa	Procter & Gamble Pharmaceuticals
Competact	Takeda Europe
Atryn	Genzyme Europe
Exjade	Novartis Europharm
Champix	Pfizer
Silgard	Merck Sharp &Dohme
Gardasil	Sanofi
Suboxone	Schering Plough Europe
Luminity	Bristol-Myers Squibb Pharma
Byetta	Eli Lilly and Company
Tandemact	Takeda Europe R&D Centre
Adrovance	Merck Sharp & Dohme
Lucentis	Novartis Europharm
Exforge	Novartis Europharm
Dafiro	Novartis Europharm
Copalia	Novartis Europharm
Imprida	Novartis Europharm
Prezist	Tibotec
Daronrix	GlaxoSmithKline Biologicals

Table 4. Drugs, approved by EMA, in 1996.

Drug	Company
Gonal F	Merch serono
Betaferon	Serono Laboratories
Taxotere	Rhone Poulenc
NovoSeven	Novo Nordisc
CellCept	Roche
Fareston	Orion
Humalog	Eli Lilly
Puregon	Oregon
Stavudine	BMS
Rilutek	Rhone Poulenc
Caelyx	Sequus Pharm Inc
Bondronat	Boehringer Mannheim
Bonviva	Gallenus Mannheim
Tritanrix	SmithKline
Epivir	Glaxo
Arcitumomab	Immunomedics
Tecnemab	Sorin
Rapilysin	Roche
Ecokinase	Gallenus Mannheim
Twinrix Adult	GSK
Norvir	Abbot
Indimacis 125	Cis Bio International
Invirase	Roche
Zyprexa	Eli Lilly
Olanzek	Eli Lilly
Crixivan	Merck
Hycamtin	GSK
Evotopin	GSK
Leukoscan	Immunomedics
Insuman	Hoechst
Twinrix Paediatric	GSK

Table 5. Drugs, approved by FDA in 2016.

Drug	Company
Zepatier	Merck
Briviact	UCB
Anthim	Elusys Therapeutics
Taltz	Eli Lilly
Cinqair	Shering
Defitelio	Jazz Pharma
Venclexta	Abbott
Nuplazid	Acadia Pharma
Tecentriq	Genentech
Axumin	Genentech
Ocaliva	GSK
Zinbryta	Biogen
Netspot	advanced accelerator applications
Epclusa	Gilead
Xiidra	Takeda

Adlyxin	Sanofi
Exondys 51	AVI BioPharma
Lartruvo	ImClone
Zinplava	Medarex
Eucrisa	Anacor Phamraceuticals
Rubraca	Pfizer
Spiraza	Genzyme

Table 6. Drugs, approved by FDA in 2006.

Drug	Company
Ranexa	CV Therapeutics, Gilead
Elestrin	Antares
Januvia	Merck
Eraxis	Pfizer
Noxafil	Schering Plau
Prezista	Tibotec
Vectibix	Amgen
Vivitrol	Alkermes
Amitiza	Sucampo/Takeda
Dacogen	Indiana Univ./SuperGen
Tyzeka	Centre National de la Recherche Scientifique
Eraxis	Eli Lilly
Gardasil	Merck
Noxafil	Merck
Prezista	Johnson & Johnson
Rotateq	Merck
Veregen	AbbVie
Eraxis	Eli Lilly
Invega	Johnson & Johnson
Elestrin	Antares Pharma
Sprycel	BMS
Sutent	Pfizer
Vectibix	Amgen
Lucentis	Genentech
Desonate	Dow Pharmaceutical Sciences
Elaprase	Shire
Myozyme	Genzyme
Chantix	Pfizer
Brovana	Sepracor

Table 7. Drugs, approved by FDA in 1996.

Drug	Company
Lipitor	Pfizer
Mavik	Sanofi
Muse	Vivus
ProAmatine	Robert
Retavase	Roche
Visipague	Nycomed
Aredia	Gador
Arimidex	Astra Zeneca

CEA-Scan	Immunimedics
Desmopressin acetate	Rhone Polulenc
Gemzar	Eli Lilly
Glyset	Bayer
Humalog	Eli Lilly
Humatrop	Eli Lilly
Hycamtin	GSK
Lupron depot	Wyeth
Nascoban	Questcor
Nutropin	Genentech
Redux	Wyeth/Servier
Remeron	Organon
Saizen	Merck Serono
Aricept	Eisai
Atrovent	Boehringer Ingleheim
Augmentin	GSK
Azmacort	Aventis
Crixivan	Merck
Elmiron	bene arzneimittel; IVAX
Viramune	Boehringer Ingelheim
Prilosec	Astra/Merck
Pulmozyme	Genentech
Leukine	Amgen
Havrix	GSK
Zithromax	Prizer