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VALUE-ADDED CHAIN OF A NEW PHARMACEUTICAL PRODUCT

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Abstract

The aim of our study is to present the value-added chain for a new pharmaceutical product. Shifts in society are setting new expectations to pharmaceutical products. By critically using the results of leading researchers, we form the modern value-added chain.

The results of our study determine the most complex value-added chain for a new pharmaceutical product. The requirements by competent authorities for safe, efficient and quality pharmaceutical products determine the dynamics of value-added chain steps. The safety and efficacy of a new pharmaceutical product reduce the importance of other factors such as innovative and affordable product.

Keywords: *pharmaceutical industry; step-by-step production*
JEL Codes: *I11, L23, L65*

Introduction

The pharmaceutical industry has the most complex value-added chain. Each pharmaceutical product starts with R&D in the field of chemistry and biology, goes through a number of stages of development for added value and has been launched after a decision of a competent authority for the effectiveness and safety of the product. Each of the value-added stages has a characteristic term, a certain limit of financial resources and a separate risk of success for a pharmaceutical product.

The pharmaceutical industry is the crossroads of a number of sciences: chemistry, biology, medicine, economics, statistics, state regulation, and intellectual property. The

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interdisciplinary of creating a new pharmaceutical product determines both the interest in many sciences and the complexity of analyzing the pharmaceutical industry. The interface of the individual sciences in the pharmaceutical industry is the creation of an effective, safe and affordable product.

Pharmaceutical industry dynamics

The pharmaceutical industry is a phenomenon in modern society (Ilieva-Tonova, Stoimenova, & Pencheva, 2016, 366). Until 1925, the pharmaceutical industry was not present as an independent industry in Moody's first annual analysis and was reported as part of the chemical industry and cosmetics companies (Younkin, 2015, 14). Just three years later, the pharmaceutical industry was already ranked 16th as a profitable industry (Epstein, 1934, 2).

The meteoric rise of pharmaceutical industry queries its dynamic (Borisova, 2017, 67). The modern pharmaceutical industry was formed in the 1960s when it went beyond the field of production and fell into the focus of analysts (Ilieva-Tonova, Pencheva, & Serbezova, 2022, 18). In 1963, Kenneth Arrow found the emergence of a new economics – the one of medical-care economics as opposed to health economics (Arrow, 1963, 943). Pharmaceutical industry is entering the public agenda through foundation-sponsored scientific publications for sectors with rising costs (Yuleva, 2019, 25).

The social, demographic and economic context in which the pharmaceutical industry operates is changing dramatically (PricewaterhouseCoopers, 2009, 7). A series of new moments in the 1980s changed the landscape in pharmacy (Madgerova & Kyurova, 2014, 97). Patents and protection of intellectual property, new functions of competent authorities for safety, launch of over-the-counter pharmaceutical products, generics sale without clinical trials determine the basis of modern pharmacy (Gergova, Stoimenova, & Sidjimova, 2019, 53).

Value-added chain in pharmaceutical industry

In our discussion, the concept of "value" is distinct from other economic terms as "quality" and "cost" (Armstrong & Mullins, 2017, 292). The value in pharmaceutical industry is defined as "…quality divided by costs, where quality reflects patient outcomes and costs represent the total costs for providing care, whether these be costs related to an episode, a diagnosis, or per capita" (Lee, Austin, & Pronovost, 2016, 323).

Hence, there are two types of value in pharmacy (Toumi & Rémuzat, 2017, 9):

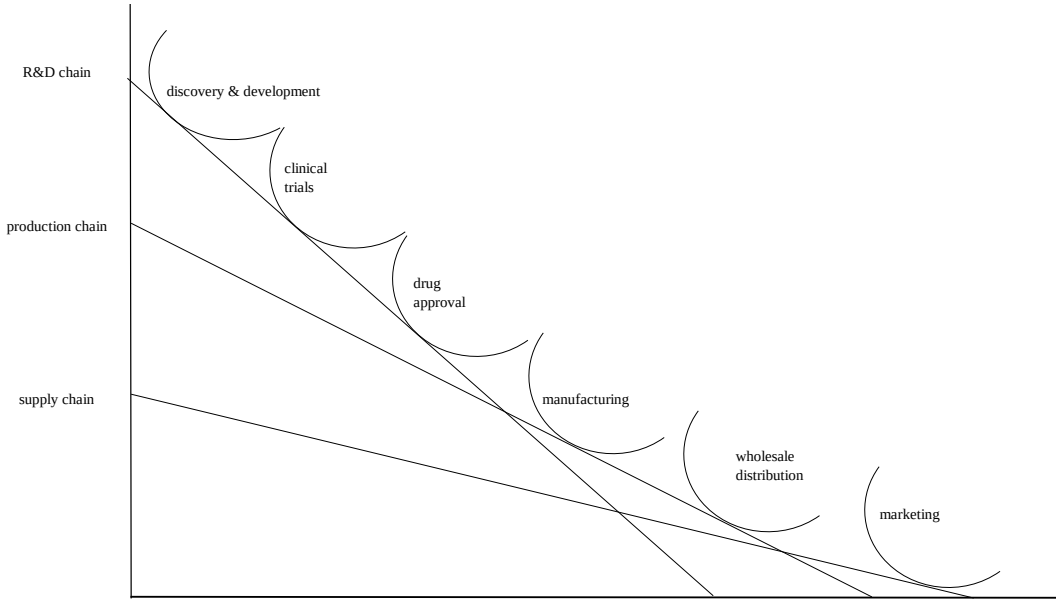
– value for patients (better efficacy, safety and/or tolerability profile; optimised route of administration and/or convenience of use; access to new therapeutic uses of already existing products covering unmet needs);

– value for society (addressing a number of medicine-related healthcare inefficiencies; enhancing healthcare system efficiency by improving healthcare provision and organization; contributing to sustainability of healthcare systems through economic advantages).

In the field of pharmacy, value is not a subjective concept and reflects the opinion of a wide range of stakeholders and competent authorities (Petrova, 2018, 29). Different stakeholders have different perceptions of value in healthcare and different authorities encourage generating different data about value in pharmacy (Antoñanzas, Terkola, & Postma, 2016, 1227). All costs in creating value of a new pharmaceutical product are directed to obtain approval by competent authority to launch instead of pricing and reimbursement decisions (Keremidchiev & Nedelchev, 2020, 63).

The value-added chain is an industry analysis for step-by-step manufacturing in creation of value. For our discussion, we will be focusing on R&D chain (Chart 1).

Chart no. 1 Value-added chains for pharmaceutical products



Source: adapted to Agrawal, 1999, 43.

The value-added chain of a new pharmaceutical product has the following features:

– research, unlike other industries, is at the first step and can be considered as input material for the chain;

– experts, certified by a state entity, are required at each step;
– a competent authority carries out quality control at each step;
– mandatory good practices are applied at each step.

New steps have been inserted between the traditional first and last step due to non-traditional chemical extraction and absence of history of effects of a new pharmaceutical product. Each new pharmaceutical product has complex value-added chain – it includes four steps from pharmaceutical product discovery to it launch:

– Discovery. The discovery is the start step for each new pharmaceutical product. In most cases, the discovery is a result of new insights into the disease process, consequence of a molecular testing, outcome of application of advanced technology, and unpredictable effects of existing treatments. The core scientific approaches in discovery process are synthesis, research and screening. The discovery methods by ingredient extraction from natural products, lucky accidents, unexpected events and observations become history due to requirements for information disclosure by competent authority in approval of a new pharmaceutical product.

– Development. The second step is the development of a new pharmaceutical product. The step constitutes an optimisation process by testing the initial molecules. The aim is to determine whether the lead compounds have the potential to become a pharmaceutical product.

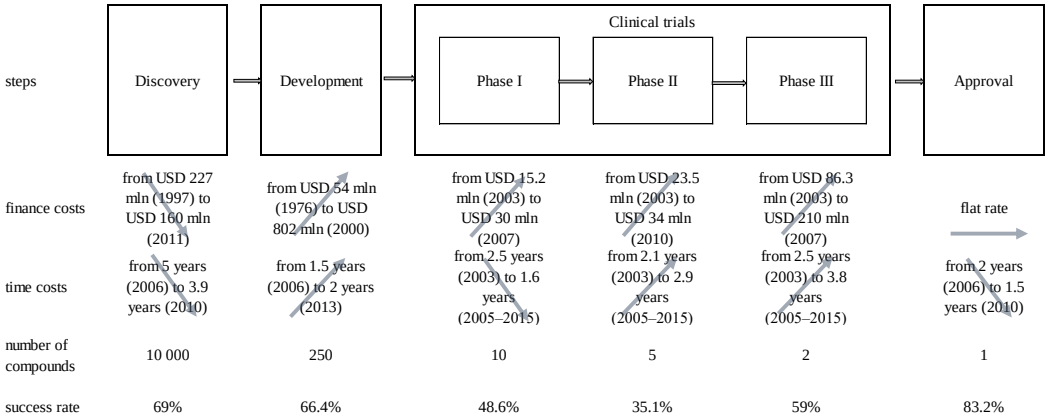
– Clinical trials. The first clinical trials via statistical methods were conducted in the UK, in 1948 (Gittelman, 2016, 1570). Since the 1960s, clinical trials have become mandatory in most national legislations after a number of side effects of one new pharmaceutical product. Estimating the number of clinical trials globally is inexact and the true scope of clinical trials is not known due to their complex global field (Sim & Detmer, 2005, e365).

– Approval. Approval process by a competent authority is an assessment of benefits and potential risks of a new pharmaceutical product. The approval process a balance between benefits and risks of the new pharmaceutical product. At this step, the functions of the competent authority are competitive and contradicting each other.

Dynamics of value-added chain

We will describe the dynamics of a new pharmaceutical product by following the steps of value-added chain (Figure 1).

Figure no. 1 Value-added chain dynamics of a new pharmaceutical product



Source: prepared by the authors

Discovery

The modern discovery of a new pharmaceutical product is a multidisciplinary science including chemistry, biology, biophysics, computer sciences, mathematics, and engineering (Herrling, 2005, 7). The research capacity is of particular importance for discovery of a pharmaceutical product. A major share in discovering new pharmaceutical products belongs to pharmaceutical companies (76%), universities and biotechnology companies (Kneller, 2010, 867).

Discovery of a pharmaceutical product reflects industrial and academic collaboration (Nedeltchev, 2004, 11). In contrast to pharmaceutical products discovered in the 19th century by a randomized trial or a happy chance, the modern pharmaceutical industry is research-based. To link the laboratory knowledge and unmet clinical needs is necessary not only to increase the investment, but also to align the interests of state institutions, corporations and investors (Nedelchev, 2019, 115).

The academic-industrial collaboration in discovery process of a new pharmaceutical product leads to the increase of:

– the success rate in Phase III of clinical trials (Takebe, Imai, & Ono, 2018, 597);

– the number of approvals by a competent authority (Kneller, 2010, 868);

– the number of patents awarded to academic entities (Cohen, 2005, 78).

The discovery of new pharmaceutical products marked a cost decline over time[*]. For example, the discovery of a product in 2006 took 5 years and in 2010 – it decreased to 3.9 years (Mestre-Ferrandiz, Sussex, & Towse, 2012, 7). If the costs of discovering a new pharmaceutical product in 1997 are USD 227 million (Myers & Howe, 1997, 20), then in 2011 the costs decreased to USD 160 million[**]. The greatest impact on decreasing time and costs is the growth of the bio similar industry.

The success rate of discovery step is 69% (2020) (Hardaker, 2020, 2). This step begins with 10,000 compounds of which only one will be approved (Figure 1).

The artificial intelligence is used to increase the success rate in discovering a new pharmaceutical product. This tool is up to 250 times more effective than the traditional method of pharmaceutical product discovery (Bajpai, 2020, 2). Artificial intelligence focus is mainly on screening (40%) and finding new targets (28%) (Deloitte Centre for Health Solutions, 2019, 11). Artificial intelligence increases the accuracy of forecasts for efficiency and safety, and as a result – reduces the cost of time and money. The cost of artificial intelligence in pharmaceutical industry is expected to reach USD 8 billion (Aboshiha, Gallagher, & Gargan, 2019, 11).

Development

The developing of a new pharmaceutical product remains the biggest expense in modern economy. Even with the annual inflation adjustment, the increase in the costs of a new mass-produced pharmaceutical product has made pharmaceutical industry unparalleled in the economy, incl. the costs in banking, aerospace, IT, oil and gas production industries[***].

The financial costs for developing a new pharmaceutical product in 1976 were USD 54 million (Hansen, 1979, 151) and in 2000 the costs rose to USD 802 million (DiMasi, Hansen, & Grabowski, 2003, 151). The time spent for preclinical testing rose from 1.5 years (2006) to 2 years (2013) (Fargen et al., 2013, 269).

The end result of development step are 250 compounds that will be clinically tested and the success rate is 66.4% (2019) (Wong, Siah, & Lo, 2019, 273).

[*] Each study is based on a specific therapy and company, which explains the differences in the published data (Adams & Brantner, 2006, 420). Our discussion presents the dynamics in the value-added chain of each new pharmaceutical product, not to compare data from individual studies.

[**] Most of the evidence focuses on clinical costs (i.e. on the "D" of R&D), rather than on discovery and development (i.e. on the "R" of R&D). This is because little, if any, project-specific evidence for the early research stages is available (Mestre-Ferrandiz, Sussex, & Towse, 2012, 2).

[***] Return on equity for pharmaceutical industry decreased from 21% (1996) to 12.8 % (2004) (Saltzman, 2005, 9).

Clinical trials

The competent authorities limit both the false data and bias business interests in pharmaceutical industry through control over procedures and data of clinical trials (Marks, 1997, 11). Increasing the requirements by the competent authorities for effective and safety pharmaceutical products tends to extend the trialing of a new pharmaceutical product. The problem lies in the number and variety of the requirements, not in the requirements themselves (Zerhouni & Hamburg, 2016, 338ed6).

The clinical trials are research studies for evaluation of safety and effectiveness of new medical treatments, pharmaceutical products, diagnostic tests, and screenings. They include three phases:

Phase I

In Phase I, the new pharmaceutical product shall be tested for evaluation of safety, tolerability, dose selection of the tested pharmaceutical product and identification of the side effects. The results of Phase I respond to whether or not to proceed with further development of the product.

The average costs per pharmaceutical product in Phase I have grown from USD 15.2 million (2003) (DiMasi, Hansen, & Grabowski, 2003, 151) to USD 30 million (2007) (Damodaran, 2007, 14). The necessary time for trials has been reduced from 2.5 years (2003) (DiMasi, Hansen, & Grabowski, 2003, 152) to 1.6 years (2005-2015) (Wong, Siah, & Lo, 2019, 275).

The core of Phase I are 10 compounds (2020) (Kim, 2020, 3). The success rates has decreased from 80.7% (2004) (Abrantes-Metz, Adams, & Metz, 2004, 17) to 66.4% (2019) (Wong, Siah, & Lo, 2019, 275).

Phase II

The clinical trials in Phase II are aimed to verify if the pharmaceutical product is effective and is within the financial framework (Tamimi & Ellis, 2009, c125).

Unlike Phase I, Phase II is particularly vulnerable to volunteer recruitment for trials. There are conflicts of interest by the supply side (manufacturers and distributors) both due to costs and for the protection of intellectual property. Several measures have been introduced for reduction of volunteer recruitment and some research functions related to the clinical trials.

For clinical trials on Phase II, the average costs per investigational pharmaceutical product are USD 23.5 million (2003) (DiMasi, Hansen, & Grabowski, 2003, 151) and have

been raised to USD 34 million (2010) (Adams & Brantner, 2010, 130). The time for completing the trials rose from 2.1 years (2003) (DiMasi, Hansen, & Grabowski, 2003, 153) to 2.9 years (2005-2015) (Wong, Siah, & Lo, 2019, 274).

The success rate in Phase II declines from 57.7% (2004) (Abrantes-Metz, Adams, & Metz, 2004, 8) to 48.6% (2019) (Wong, Siah, & Lo, 2019, 276). Five compounds remain in the pipeline.

The increased costs are due to additional control by the demand side (health insurance system, patient organizations and government authorities). For example, since 2000 the procedure number on each study volunteer has increased annually more than 10% (Mathieu, 2007, 22).

Phase III

The aim of Phase III is effectiveness confirmation and information collection for product safety. The clinical trials are characterized by increasing the number of volunteers in different countries.

The complexity and expense of trials in Phase III determine a strategy for inorganic growth through outsourcing to companies with research experience and capacity to carry out the trials in compliance with the requirements of competent authorities (Gooneratne, 2019, 16). A necessity for harmonization of good clinical practices worldwide arises.

Over the years, the time for clinical trials in Phase III has increased from 2.5 years (2003) (DiMasi, Hansen, & Grabowski, 2003, 152) to 3.8 years (2005-2015) (Wong, Siah, & Lo, 2019, 278). The higher time and extended requirements in turn lead to rising of costs from USD 86.3 million (2003) (DiMasi, Hansen, & Grabowski, 2003, 154) to USD 210 million (2007) (Damodaran, 2007, 15).

The success rate for Phase III increases from 56.7% (2004) (Abrantes-Metz, Adams, & Metz, 2004, 17) to 59.0% (2019) (Wong, Siah, & Lo, 2019, 276). Two compounds continue the race toward launch step. Strategic issues in ~~the~~ Phase III have less impact on failure (14%) than in ~~the~~ Phase II (21%) (Kimmitt & Vieira, 2020, 17).

Approval

The competent authorities have a flat rate for approval costs with the aim of ensuring a fair decision. The time costs for approval of a new pharmaceutical product are reduced from 2 years (2006) to 1.5 years (2010) (Paul et al., 2010, 203). The average time for approval new pharmaceutical product by the European Medicines Agency is 417 days (2015) while by the Food and Drug Administration – 351 days (Bujar & McAuslane, 2014, 5). The authorities' approval increases from 11.8 months to 13 months for companies that

are not in the top 50 (Getz, 2020, 4). The success rate for approval is the highest for entire value-added chain – 83.2% (Wong, Siah, & Lo, 2019, 277).

Discussions

The value-added chain of each new pharmaceutical product has high costs:

– total costs of USD 2.8 billion (Wouters, McKee, & Luyten, 2020, 844);

– time to launch is 15 years (English, Lebovitz, & Giffin, 2010, 47);

– success rate to launch is discouraging – less than 12%;

– return of equity equals to 13% (Saltzman, 2005, 9);

– high degree of artificial intelligence application and other scientific tools;

– volume of approval application is 100,000 pages (Van Norman, 2016, 170).

The dynamics reflects the focus on safe and effective pharmaceutical products. The disproportion of costs and approvals is a "conundrum" (Munos, 2009, 959) that can be resolved by revision of the entire value-added chain and practices used.

The costs have the following dynamics:

– money costs increased from USD 231 million (1987) (Tamimi & Ellis, 2009, c127) to USD 2.8 billion (2014) (Wouters, McKee, & Luyten, 2020, 845);

– time costs increased from 12.8 years (1990) (Dickson, 2009, 172) to 15 years (2010) (English, Lebovitz, & Giffin, 2010, 5);

– approvals decreased from 52 (1996) to 15 (2016) (Ernst&Young, 2017, 14);

– registered clinical trials increased from 2,119 (2000) (Mikulic, 2021, 4) to 89,647 (2018) in 175 countries (Drain, Parker, Robine, Holmes, & Bassett, 2018, e0192413);

– granted patents increased from 2,106 (2007) to 3,089 (2016) (Copenhagen Economics, 2018, 8);

– the staff involved in introduction of a new pharmaceutical product has increased from family level to 1,000 people (Scalable Health, 2017, 8);

– the number of terminated projects due to economic and safety reasons is increasing (Wong, Siah, & Lo, 2019, 18).

Approval fees and patent life are without any dynamics.

Despite the increased costs, the economic effects should be taken into account – a new pharmaceutical product may prevent USD 19 billion in lost wages (Garthwaite, 2012, 116). In case that a new pharmaceutical product has USD 15 billion R&D expenditures, this pharmaceutical product saves 1.6 million life-years per year, whose annual value is about USD 27 billion (Lichtenberg, 1998, 3).

Conclusions

Our analysis outlines a significant increase in financial costs of a new pharmaceutical product. The greatest dynamics were reported in the steps that can be outsourced. While the dynamics of the development step is the result of collaboration between science and laboratories, the dynamics in Phase III of clinical trials is due to increased requirements and expectations for safe and effective pharmaceutical products in more than one country.

While the time for a new pharmaceutical product is dynamic, the patent term remains constant (20 years). As a consequence, the time for reimbursement the costs of a new pharmaceutical product is reduced, which in turn leads to an increase in the product price. The patent life is 20 years and after deducting 12-15 years for research and approval, there are 5-8 years left to sell the pharmaceutical product and recoup the costs.

The data reveal a disproportionate increase in financial costs compared to time costs. Benefactors such as the use of smart solutions, inter-sector collaboration and strategies for inorganic growth have significantly increased the likelihood of approval of new pharmaceutical products, but have also increased the investments. Practice recognizes the achievement of the goal of safe and effective pharmaceutical products, while the achievement of innovative and affordable pharmaceutical products remain questionable.

Our results paved the way for a new type of research to simultaneous consideration of costs and results at all steps according to the shifts in external environment. Data should not be viewed from the perspective of pharmaceutical industry solely. At present time pharmaceutical products that have been started in difficult times – the global financial crisis (2007-2008) are approved. We can expect a similar situation in the next ten years, i.e. after the time it takes to launch a pharmaceutical product from the pipeline.

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