Revista Terceiro Incluído
https://revistas.ufg.br/teri/

| ISSN 2237-079X | V. 14 | n. 1 | 2024 |
DOI: https://doi.org/10.5216/teri.v14i1.79594

| Received: 11 Jan. 2024 | Accepted: 22 Jul. 2024 | Published: 06 Aug. 2024 |

Research and Development (R&D) in the Pharmaceutical Sector: advances, limitations, selectivity, and neglect

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Abstract
In order to contribute to the studies and debates on the Research and Development (R&D) process in the pharmaceutical sector, this paper conducted an extensive collection, organization, and analysis of data on the topic, exploring the advances, limitations, selectivity, and neglect in this area. It was revealed that the pharmaceutical sector is the second largest investor in R&D, with global expenditures of $238 billion in 2021. The pursuit of profits from successful drugs has driven significant growth in the number of pharmaceutical companies focused on R&D, resulting in 5,416 corporations testing over 20,000 drugs in various phases of research and development. However, this study also points to the limitations of products derived from pharmaceutical R&D, noting that many newly approved drugs do not present significant advantages over existing ones and tend to prioritize maintaining profitable franchises or market competition over population well-being. Furthermore, the selectivity and neglect in R&D investments are highlighted, with certain diseases receiving more attention due to a variety of interests, including socioeconomic aspects.

Keywords: Pharmaceutical Sector; Research and Development (R&D); Investments; Growth; Limitations.

Introduction

In the current context, characterized by intensified globalization and increasingly fierce economic competition, rapid innovation is crucial for the growth and profitability of companies. Businesses and government entities, striving for technological leadership in their fields and markets, allocated approximately $2.5 trillion to Research and Development (R&D) in 2021 - a term used to describe the range of activities encompassing research, discovery, testing, introduction, and improvement of new products and services (Statista, 2022a).

The pharmaceutical sector, due to its dynamic nature and continuous need for innovation, has historically remained one of the largest financiers of research and development worldwide. In 2021, investments in R&D by pharmaceutical companies reached $238 billion, a 74% increase compared to 2012 (Statista, 2022b). These figures reaffirm the sector as the second-largest investor in R&D, surpassed only by the software technology segment (Statista, 2023).

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The research and development of new drugs play a crucial role in improving quality of life and life expectancy worldwide, significantly contributing to progress in the treatment and potential cure of various diseases. Since Alexander Fleming's discovery of penicillin in 1928, a pivotal milestone that marked the beginning of an exponential transformation in this industrial sector on a global scale, the pharmaceutical industry has made remarkable strides (Stacciarini, 2024a). The successful creation of a new drug can generate billions of dollars in annual profit for producing companies (Abbvie, 2023), incentivizing substantial investments in this process (Dimasi et al., 2016). Currently, as we will see throughout the text, approximately 20,000 drugs derived from 5,400 companies are at various stages of the pharmaceutical research and development process (Citeline, 2022).

However, despite the importance of this endeavor, analyses (Morgan et al., 2005; Van Luijn et al., 2010; Light; Lexchin, 2012) have raised concerning points, indicating that most newly launched drugs do not offer significant benefits compared to existing ones. Furthermore, pharmaceutical industries have been criticized for allocating most of their R&D resources to areas with high profit potential (Citeline, 2022), while diseases primarily affecting low-income populations in developing countries are often neglected (Trouiller et al., 2002).

Therefore, aiming to further investigate this topic, this article will address the landscape of the pharmaceutical research and development (R&D) process on a global scale. It will highlight the growth in the number of drugs under investigation, the increase in the number of pharmaceutical companies involved in this process, and provide a critical analysis of the limitations of the current pharmaceutical R&D model, including a discussion on the low degree of innovation and the selectivity/neglect in research.

Methodology

To achieve the objectives outlined and contribute to the deepening of studies and discussions on the Research and Development (R&D) process in the pharmaceutical sector, this study adopted a comprehensive methodology involving the collection, tabulation, and analysis of extensive data derived from various international sources.

Data on pharmaceutical R&D investments were extracted from the Statista database (2022a; 2022b; 2023), a German consulting company specializing in the collection and visualization of global information. The evolution of the number of drugs in research and development over the past two decades, as well as the global increase in companies involved in this activity, was tabulated from the "Pharma R&D: Annual Review 2022" report prepared by Pharma Intelligence (Citeline, 2022). Information on "new chemical and biological entities" approved from 2002 to 2021 was consulted in "The Pharmaceutical Industry in Figures," published by the European Federation of Pharmaceutical Industries and Associations (EFPIA, 2022).

To contextualize, interpret, and discuss these data, an interdisciplinary set of literature was used, including scientific articles, systematic reviews, and meta-analyses published in a wide range of academic and scientific journals.

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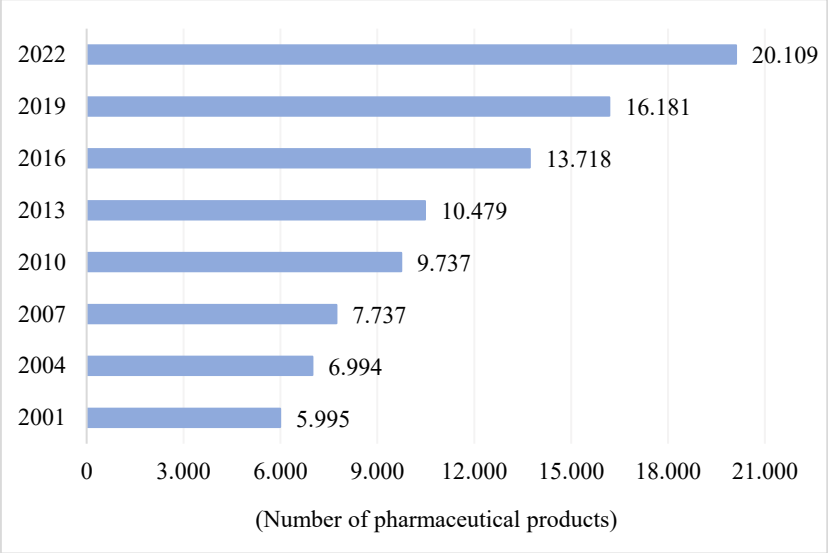
Research and Development (R&D) in the Pharmaceutical Industry

The process of developing a new drug is complex and costly, often requiring several years and investments that can reach millions or even billions of dollars (Dimasi et al., 2016). Before a drug is available to patients, it must go through all the stages of the "research and development pipeline." This term refers to the comprehensive process that encompasses research and discovery, development, clinical trials, and regulatory approval for new drugs by the pharmaceutical industry (FDA, 2018).

The analysis of data extracted from the "Pharma R&D: Annual Review 2022" report, published by Pharma Intelligence (Citeline, 2022), indicates that over the past two decades, the volume of pharmaceutical products in Research and Development (R&D) has grown 3.4 times, increasing from 5,995 in 2001 to 20,109 in 2022, as illustrated in Figure 1.

Figure 1: Growth in the number of pharmaceutical products in Research and Development (R&D) globally.



Source: Citeline (2022). Elaborated by the author.

The process of research and development for a drug begins in the laboratory with the potential discovery of a new compound. After this initial stage, the investigation moves to the preclinical phase, during which laboratory and animal model studies assess the safety and efficacy of the compound. The subsequent clinical phases I, II, and III involve human testing to determine the drug's safety, efficacy, and appropriate dosage. Following successful tests, the pre-registration and registration phase ensues, where the data are evaluated by regulatory authorities. With satisfactory results, approval is granted, allowing the drug to be marketed (FDA, 2018).

Currently, around 20,000 pharmaceutical products are distributed across the various stages of the Research and Development (R&D) process, as shown in Figure 2. Due to the complexity of this progression, most compounds are retained in the preclinical phase. Consequently, it is common to observe a decrease in the number of substances advancing to subsequent stages.

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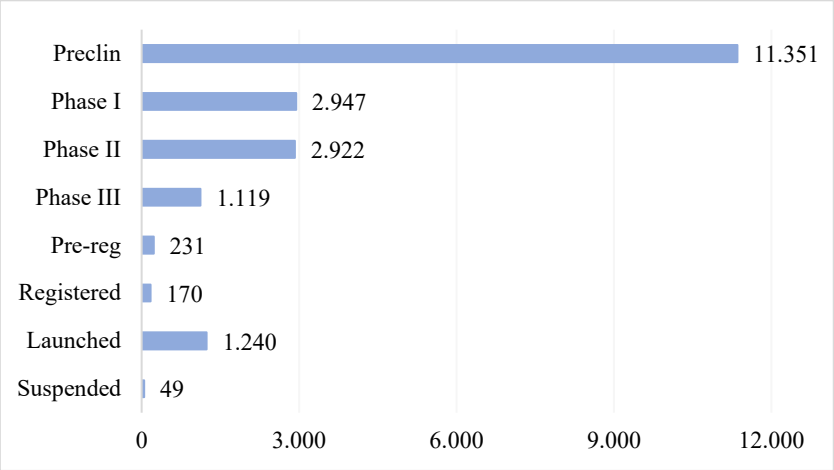
Figure 2: Distribution of pharmaceutical products across the stages of the Research and Development (R&D) process in 2022.

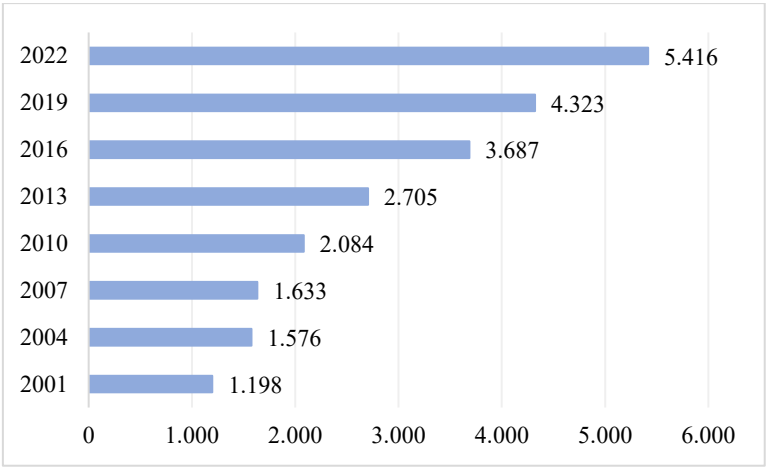


Source: Citeline (2022). Elaborated by the author.

Although the development of a new drug involves significant costs, the potential financial return motivates companies to invest in the discovery of new drugs. The commercial success of a medication can translate into billions of dollars in revenue for the developing company. For example, Humira (adalimumab), a high-cost drug from the American pharmaceutical company AbbVie, amassed $196.3 billion in global revenues between 2010 and 2022 (Abbvie, 2023).

Motivated by the prospect of developing "blockbuster drugs" - which can generate significant profits for the company and its shareholders - a growing number of companies worldwide have been investing and entering the competition for new drug development (Figure 3). This trend is evidenced by the 4.5-fold increase in the number of pharmaceutical companies dedicated to research and development (R&D) from 2001 to 2022, reaching a total of 5,416 organizations.

Figure 3: Growth in the number of companies involved in pharmaceutical Research and Development (R&D) from 2001 to 2022.



Source: Citeline (2022). Elaborated by the author.

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The analysis of the data also highlights that four entities - the United States (44%), Europe (23%), China (12%), and Japan (3%) - comprise 82% of the companies participating in the pharmaceutical research and development process. In a previous study (Stacciarini, 2023, p. 45), I discuss the geopolitical aspects of this concentration, examining how various companies and nations compete for economic indicators, influence, and prestige in the global pharmaceutical arena.

Approximately half (2,642) of the 5,416 companies active in pharmaceutical Research and Development (R&D) have only one or two drugs in the testing phase (Citeline, 2022), establishing themselves as smaller participants on the global stage. Conversely, a select group of 25 leading R&D companies, detailed in Table 1, concentrates more than 3,000 drugs currently under investigation.

Table 1: List of the 25 leading companies with the highest number of substances in development, totaling more than 3,000 drugs in testing.

Position	Name	Number of Drugs in the Pipeline		Position	Name	Number of Drugs in the Pipeline
1	Novartis	213		14	Bayer	105
2	Roche	200		15	Otsuka Holdings	93
3	Takeda	184		16	Jiangsu Hengrui Pharma	89
4	Bristol Myers Squibb	168		17	Amgen	83
5	Pfizer	168		18	Eisai	80
6	AstraZeneca	161		19	Astellas Pharma	75
7	Merck & Co	158		20	Daiichi Sankyo	75
8	Johnson & Johnson	157		21	Gilead Sciences	72
9	Sanofi	151		22	Regeneron	68
10	Eli Lilly	142		23	Shanghai Fosun Pharma	68
11	GlaxoSmithKline	131		24	Biogen	66
12	AbbVie	121		25	Sumitomo Dainippon	66
13	Boehringer Ingelheim	108		Total		3.002

Source: Citeline (2022). Elaborated by the author.

Among the companies highlighted in Table 1, ten are from the United States, covering a total of 1,203 pharmaceutical products in Research and Development (R&D). Following, European companies, with seven representatives, total 1,069 products. Japan, with six companies, contributes 573 products, positioning itself in third place. Finally, China, with two companies, sums up to 157 products in the R&D stage.

Part of this concentration in the sector can be explained by analyzing its historically oligopolistic structure, where a small number of companies hold considerable control (Malerba; Orsenigo, 2015). This dominance is reinforced by various factors, such as the high costs associated with the research, development, production, and commercialization of new drugs (DiMasi et al., 2016), which constitute significant barriers to the entry of new, less capitalized companies. Patents provide the holders with a

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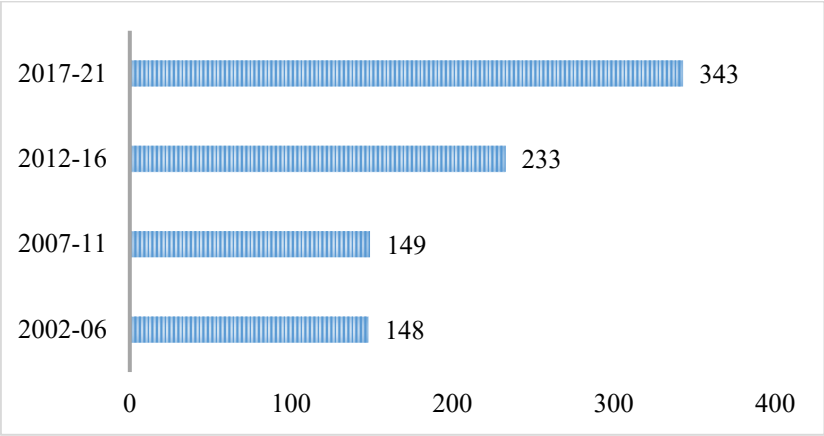
period of market exclusivity, allowing for the maintenance of high prices without the risk of competition from newcomers (Kesselheim et al., 2017). Additionally, some pioneering pharmaceutical companies benefited from an initially less stringent regulatory environment, which facilitated the accumulation of significant profits and their expansion on a global scale (Malerba; Orsenigo, 2015).

Limitations of Pharmaceutical Research and Development (R&D) Outcomes

Although there has been an increase in the approval of new drugs and the predominant discourse emphasizes innovation, several analyses (Morgan et al., 2005; Van Luijn et al., 2010; Light; Lexchin, 2012) highlight that the majority of newly approved drugs do not offer significant advantages compared to existing ones. This reality stems, in part, from the lack of regulatory requirements that mandate new products to demonstrate superiority over those already available on the market (Van Luijn et al., 2010). Additionally, many so-called 'new drugs' are, in fact, (re)formulations or combinations of pharmaceutical agents already on the market.

This discrepancy is partially illustrated by the significant difference between the number of approvals originating from the R&D pipeline (Figure 2) and the number of 'new chemical and biological entities' (Figure 4). The latter are defined as pharmaceutical substances that exhibit novel characteristics compared to previously marketed molecules (Branch; Agranat, 2014).

Figure 4: Number of 'new chemical and biological entities' approved between 2002 and 2021.



Source: EFPIA (2022). Elaborated by the author.

Most of these so-called "non-innovative" drugs are commonly referred to as "me-too drugs," characterized by their similarity in active agents and chemical structures to already known compounds, intended for similar applications (Aronson; Green, 2020). The pharmaceutical industry shows a preference for these drugs due to the lower costs and risks associated with their development, as well as the presence of already established markets for them (Angell, 2005).

This strategy generally aims to generate variants that prolong the commercial success of a particular drug, especially when the original products are about to lose their patent protection (Light; Lexchin, 2012), or to penetrate lucrative markets already explored by competitors. Once on the market, these drugs are driven by aggressive marketing strategies and a biased promotional system, elevating the role of marketing and sales departments to the same level of importance as Research and Development sectors in the commercialization and profitability of products (Stacciarini, 2024b).

However, this approach contrasts with the basic notion that innovation should offer additional clinical benefits to patients, such as greater efficacy and safety compared to existing alternatives. Moreover, these drugs can represent a high economic cost for both public health systems and patients, as they are often marketed as innovative and typically have a significantly higher price than their existing market equivalents (Morgan et al., 2005).

Selectivity and Neglect in Pharmaceutical Research and Development (R&D) Investments

From the perspective of "economic rationality," considered the cornerstone of large capitalist corporations, it is reasonable to think that pharmaceutical companies tend to prioritize actions focused on financial returns, often placing public and collective health initiatives second (SOMO, 2024). In their pursuit of maximizing profits, these companies concentrate most of their resources and efforts on Research and Development (R&D) in high-profit areas (Camargo Jr., 2016). This focus includes highly prevalent diseases, such as chronic and infectious diseases, as well as rare or complex conditions like cancer (Citeline, 2022). Although the latter group affects fewer individuals, the severity of these conditions and the scarcity of therapeutic alternatives allow companies to set high prices.

Additionally, considering that the primary funders of these high-cost medications are often governments, public health systems, and private insurers, pharmaceutical companies have even less concern about setting excessively high prices (Prasad et al., 2017). As a result, the cost of treatment for a single patient can reach tens of thousands of dollars per year.

A detailed analysis of the current landscape in drug development (Citeline, 2022) reveals that approximately 39% of research is focused on cancer therapies, followed by investigations into neurological and infectious diseases, which occupy the second and third places, respectively. There is also a recent increase in research related to rare diseases.

Although drugs for cancer treatment dominate the global research and development landscape, with several approvals in recent decades and often being touted as innovative, various studies (Kim; Prasad, 2015; Cohen, 2017; Davis et al., 2017; Gloy et al., 2023) have warned of a potential scarcity, marginalization, or restriction of the clinical benefits and impacts of these new therapies.

These issues raise discussions about the supremacy of commercial interests over real clinical benefits (Cohen, 2017). Moreover, the practice of approving and marketing expensive drugs with limited

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benefits may encourage pharmaceutical companies to reduce significant investments and shy away from risks in the pursuit of truly transformative therapies (Rajkumar, 2020).

Reviewing the approvals of new cancer treatments by the European Medicines Agency (EMA) from 2009 to 2013, Davis et al. (2017) found that most of these drugs were launched without conclusive evidence of survival benefit or improvement in the quality of life for patients. A similar observation was made in the United States (Kim; Prasad, 2015), where two-thirds of the 187 studies that underpinned the approval of new anticancer drugs by the Food and Drug Administration (FDA) between 2014 and 2019 presented limitations (Hilal et al., 2020). This context is exacerbated by the accelerated approval procedure (Gyawali et al., 2019), often supported by single or non-randomized studies (Gloy et al., 2023), increasing the risk of systematic bias (Naci et al., 2019).

As patients eager for curative treatments, physicians influenced by the pharmaceutical sector, health systems, and governments under the sway of lobbyists and legislators with questionable interests (Stacciarini, 2023, p. 56) become more inclined to approve, fund, and use expensive drugs with uncertain clinical benefits, a broad spectrum of other conditions, especially those affecting less privileged populations in developing countries, remain neglected. These conditions, often described as "neglected diseases" (Hotez et al., 2009) or "non-profitable diseases," historically attract limited investment in research and development, contributing to continued high mortality rates in various regions.

A detailed study undertaken by Trouiller et al. (2002) revealed that the likelihood of a drug being available for central nervous system conditions or cancer is 13 times greater than for neglected diseases. Additionally, of the 1,393 new chemical compounds introduced to the market between 1975 and 1999, only 16 were targeted at treating tropical diseases and tuberculosis. Subsequent studies, such as that by Pedrique et al. (2013), confirmed this disparity. According to the authors, of the 336 new chemical entities approved between 2000 and 2011, only four were for neglected diseases - three for malaria and one for diarrheal diseases. The research also highlighted that only 1.4% of the 148,400 clinical trials registered between September 1999 and December 2011 focused on neglected diseases (Pedrique et al., 2013).

Conclusions

Aiming to contribute to studies and discussions in the field of health, this work evaluated how the pharmaceutical sector conducts the Research and Development (R&D) process of its products. It was revealed that, historically, the sector is among the main investors in R&D worldwide. In 2021, pharmaceutical companies allocated approximately $238 billion for this purpose, marking a 74% increase compared to 2012.

The investigation also showed that from 2001 to 2022, the total number of drugs in R&D grew 3.4 times, totaling approximately 20,000 drugs in various stages of development. The number of companies participating in these activities expanded significantly, growing 4.5 times and reaching 5,416

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corporations. Of this number, about half have only one or two drugs in R&D, while a select group of 25 industry leaders concentrates more than 3,000 products. Around 80% of these companies are located in the United States (44%), China (12%), and Europe (23%).

Despite the increase in the number of approved drugs and the frequent references to innovation, it was observed that most new approvals do not bring significant benefits compared to preexisting products. Many of the so-called "new drugs" are, in reality, reformulations or combinations of already known substances. In strategies to maintain commercial success, especially in light of the expiration of patent protection or to enter competitive markets, several companies resort to "me-too drugs." These drugs, due to their similarity to preexisting compounds, require lower investments and development risks, as well as already having established markets.

It was also presented that, although some of these drugs, especially those with high financial return potential, are intensely promoted - raising concerns about the predominance of commercial motivations over clinical benefits - other conditions, especially those affecting low-income populations in developing countries, remain unattended. Various studies indicate that so-called "neglected diseases" historically do not receive the necessary investments in R&D, perpetuating a high mortality rate in several underdeveloped regions of the planet.

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