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From Penicillin to Trillions: Strategies, Influence, and Deviations in the Pharmaceutical Sector [1]

Manipulation, fraud, crimes, billions spent on lobbying and electoral financing, undue interference in regulatory bodies, and massive investments in marketing are recurrent strategies employed by the pharmaceutical sector to maximize profits, often at the expense of individual and public health.

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Perspectives:

Since the discovery of penicillin by Alexander Fleming in 1928, the first antibiotic in history, advances in medicine and modern pharmacology have revolutionized the quality of life across various regions of the world. Fleming's discovery not only earned him the Nobel Prize in 1945 but also marked the beginning of an era of expansion and diversification of medicines, driving the exponential growth of the pharmaceutical industry over the past century (Stacciarini, 2023).

Following this milestone, companies in the sector evolved from small, family-owned operations to multinational giants valued at hundreds of billions of dollars (Stacciarini, 2024a), exerting global influence in a market that generates approximately $1.5 trillion annually (Statista, 2024). However, beyond the discovery and diversification of medicines, increased demand, and expanded production capacity, part of this evolution has been driven by questionable - and in some cases, perverse - strategies that prioritize profit maximization over public health, some of which will be discussed below.

Manipulation of research, articles, and drug trials

Pharmaceutical industries have long been accused of manipulating or distorting the results of drug trials (Sismondo, 2008; Lexchin, 2011; Flacco et al., 2015). According to several authors, these practices can start as early as the study design phase, through methodological choices that skew

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outcomes in favor of the drug being tested. Examples include the selection of inferior comparators (Djulbegovic et al., 2000), the use of inadequate doses for competing drugs (Lexchin, 2011), or the use of placebos as controls (Lundh et al., 2018) in trials of new pharmaceutical products, aiming to streamline approval and licensing processes.

These trials are often followed by selective publication of results (Bekelman et al., 2003), a tactic that conceals the true effects of the new drug and its potential side effects compared to competitors, thereby increasing the product's chance of success (Lexchin et al., 2003). Legal documents (Spielmans et al., 2010) revealed that the pharmaceutical conglomerate AstraZeneca, for instance, withheld studies that linked the use of quetiapine (marketed as Seroquel) to weight gain and an increased risk of hyperglycemia and diabetes.

Moreover, these documents suggest that, to protect the drug's substantial revenue - over $5 billion annually (Stacciarini, 2023, p. 51) - the company allegedly manipulated data to show that the drug offered advantages in treating schizophrenia compared to a competitor. In April 2010, after a prolonged investigation by the U.S. Department of Justice, AstraZeneca agreed to a $520 million settlement to resolve claims related to Seroquel (United States, 2010). The drug's labeling was updated, revising its indications and restrictions, which allowed its continued availability in the global market.

Pharmaceutical industries frequently pay scientists, doctors, or academics to publish scientific articles written by company-employed writers, a practice known as "ghostwriting." This strategy is used to provide medications with an appearance of independence and credibility (Sismondo, 2007), promote a new pathology or disorder that the drug is intended to treat (Moffatt & Elliott, 2007), or counter unfavorable research and articles about pharmaceutical companies and their products (Lexchin, 2011).

In the early 2000s, SmithKline Beecham (now GlaxoSmithKline) implemented the CASPPER program, which funded, through ghostwriters, the production of scientific articles that favored its antidepressant Paroxetine (marketed as Paxil) or criticized competing medications (McHenry, 2010). Years later, GlaxoSmithKline faced lawsuits related to the use of Paroxetine in children and adolescents, including cases of suicide. The company was accused of publishing misleading articles about the drug's effectiveness in treating depression in individuals under 18 (United States, 2012). In 2012, GlaxoSmithKline pleaded guilty to charges involving this and two other drugs (Wellbutrin and Avandia) before the United States Department of Justice, agreeing to pay $3 billion in fines (United States, 2012). However, this amount represented only a small fraction of the $27.9 billion the company had earned from sales of the three drugs during the period in question (Thomase & Schmidt, 2012).

Lobby and Electoral Financing

To directly influence politics, legislation, and public health policies, the pharmaceutical sector invests billions in lobbying (OpenSecrets, 2024), employing professionals specialized in persuading legislators to support specific interests. In the United States, where this practice is regulated and publicly

reported, the "pharmaceutical and health products industries" spent $5.45 billion on lobbying activities between 1998 and 2022 (Stacciarini, 2023, p. 41), making it the highest-spending sector in this area (OpenSecrets, 2024).

The number of registered lobbyists representing the sector grew in proportion to the increasing investments, rising from 747 professionals in 1998 to 1,840 in 2022 (OpenSecrets, 2024). Of these, 64.35% are former government employees (OpenSecrets, 2024), highlighting the "revolving door" phenomenon - where former regulators, public officials, and members of Congress transition to lobbying positions in private companies with which they once had oversight relationships (Higham & Bernstein, 2017).

In addition to lobbying, pharmaceutical companies have made substantial electoral contributions (OpenSecrets, 2024). In the most recent U.S. electoral cycle in 2020, candidates for federal offices (Congress and Presidency) received approximately $76.7 million in donations (Stacciarini, 2023, p. 42). At the state level, 2,467 legislators - more than one-third of representatives - reported receiving campaign contributions from the pharmaceutical sector (Facher, 2021).

Members of Congress who serve on committees related to the pharmaceutical industry's interests tend to receive larger donations (Knight et al., 2021). Conversely, those who advocate for lowering drug prices have been the targets of smear campaigns orchestrated by industry representatives. These actions included national advertising campaigns with misleading messages - linking price reductions to socialism, drug shortages, and job losses - and the distribution of threatening letters containing false information to voters (Torbati & O'Connell, 2021).

Influence on Regulatory Agencies and Patient Organizations

The pharmaceutical sector has been accused of exerting undue influence on the advisory committees of regulatory agencies (Hayes & Prasad, 2018), which are responsible for decisions regarding the approval and continued availability of drugs on the market. Investigations reveal that it is common for members of these committees to receive substantial financial compensation through partnerships with companies in the sector (Lurie et al., 2006), potentially resulting in decisions that favor the interests of these sponsors (Pham-Kanter, 2014; Nejstgaard et al., 2020).

Notable cases, such as the approval and continued sale of the drugs Bextra (valdecoxib) and Vioxx (rofecoxib) (Berenson, 2007), highlight this strategy. Although studies (Mukherjee et al., 2001) indicated an increased risk of cardiovascular issues associated with these drugs, they remained on the market (Harris & Berenson, 2005), causing significant damage to the global reputation of the Food and Drug Administration (FDA) (NYT, 2005). During the five years it was available, Vioxx was used by over 80 million patients (Topol, 2004), generating approximately $2.5 billion in annual sales (Reuters, 2006). The situation with Bextra was similar: marketed from 2002 until April 2005, the drug generated $2 billion in sales in just 2003 and 2004 alone (Pfizer, 2005).

In 2007, Merck agreed to pay $4.85 billion to settle approximately 27,000 lawsuits filed by users or their families, who alleged injuries or deaths due to Vioxx use (Berenson, 2007). Four years later, the company agreed to pay an additional $950 million to resolve criminal and civil charges brought by the U.S. Department of Justice, which accused it of promoting the drug for conditions for which it had not yet been approved (United States, 2011).

Studies also suggest that the influence of pharmaceutical companies extends to "Clinical Guidelines" - documents providing information and guidance to assist healthcare professionals in making decisions about patient treatment, including recommending specific medications (Choudhry et al., 2002; Neuman et al., 2011; Bindslev et al., 2013). An investigation by Tabatabavakili et al. (2021), which analyzed 14,700 guideline authors published between 1980 and 2019, found that 45% of them had at least one financial conflict of interest. In specialties with high-cost treatments, such as oncology, these percentages are even higher, as are the sums involved (Mitchell et al., 2016).

Pharmaceutical companies also fund Patient Organizations (McCoy et al., 2017; Ozieranski et al., 2019; Mulinari et al., 2020; Lexchin et al., 2022) - non-governmental, non-profit entities that, in theory, should advocate for public health. However, many of these organizations are co-opted (Lexchin et al., 2022), prioritizing corporate interests (McCoy et al., 2017) over the collective good.

A notable example involves the U.S. pharmaceutical company AbbVie, which in 2015 donated $24.6 million (Kopp et al., 2018) to patient associations related to Humira (adalimumab), a high-cost medication that generated $14 billion in revenue that year (Stacciarini, 2023, p. 48). These organizations, funded by AbbVie, remained silent about the high cost of Humira, focusing instead on debates about the safety of biosimilars (Kopp et al., 2018). Furthermore, AbbVie exploited loopholes in U.S. legislation to create a complex protection system for Humira, engaging in lawsuits against competitors, boycotts, lucrative deals, and filing 311 patents for the drug (Robbins, 2023). This made Humira one of the most profitable franchises in pharmaceutical history, with $196.3 billion in global revenue between 2010 and 2022 (Stacciarini, 2023, p. 48).

Funding and Gifts for Prescribers

The pharmaceutical industry also seeks direct contact with healthcare professionals, especially doctors, who play a crucial role in prescribing medications, driving sales, and generating profits for companies and their shareholders. One of the most common strategies is offering "gifts," a historically recurring and widespread practice (Orlowski & Wateska, 1992; Wazana, 2000; Yeh et al., 2016; Fresques, 2019).

Between 2015 and 2021, drug and device companies in the United States allocated approximately $15.5 billion to doctors (Open Payments, 2024), covering gifts, meals, travel, lodging, education, entertainment, consulting fees, compensation for lectures, and research. During the same period, university hospitals in the country received around $14.6 billion from these companies (Open

Payments, 2024), illustrating that efforts to establish relationships can begin as early as the academic phase (Brennan, 2006; Austad et al., 2011) through events, free lunches, book donations, and educational materials, among other means (Moynihan, 2003; Dejong et al., 2016).

However, studies indicate that this interaction, even when involving low-value gifts, can pose risks to patients and public health (Dana & Loewenstein, 2003; Katz et al., 2003). Investigations by ProPublica (Fresques, 2019) and Yeh et al. (2016) revealed that doctors who received payments prescribed more brand-name drugs and in higher quantities.

By analyzing over 56 million payments made by these companies to healthcare professionals between 2014 and 2018, Ornstein et al. (2019) identified more than 2,500 doctors who each received at least half a million dollars, with 700 surpassing the $1 million mark. The anticoagulant Xarelto (rivaroxaban) led the investments related to a specific drug, with approximately $123.2 million paid to professionals during this period (Ornstein et al., 2019). However, the following year, Bayer and Johnson & Johnson, the companies responsible for producing Xarelto, faced accusations concerning health problems associated with its use. In March 2019, both companies agreed to pay $775 million to settle over 25,000 lawsuits that alleged failure to warn patients about the risk of fatal bleeding caused by the drug (Thomas, 2019).

Selectivity, Limitations, and Negligence in Pharmaceutical Research and Development (R&D)

Although there are currently 5,400 companies investigating approximately 20,100 drugs (Stacciarini, 2024b), research shows that most newly approved medications offer little to no significant advantages over existing ones (Morgan et al., 2005; Motola et al., 2006; Van Luijn et al., 2010; Light & Lexchin, 2012; Naci et al., 2015; Cohen et al., 2017; Wieseler et al., 2019; Gloy et al., 2023).

Often, the focus is on creating variants that extend the commercial success of established drugs (Angell, 2005; Light & Lexchin, 2012) or on entering lucrative markets already explored by competitors, rather than on developing truly innovative medicines (Fojo et al., 2014; Rajkumar, 2020). Additionally, studies suggest that research tends to concentrate on areas with greater financial return potential (Camargo Jr., 2016; Citeline, 2022; Stacciarini, 2024b; Somo, 2024), while other conditions, particularly those affecting low-income populations in developing countries, remain neglected (Trouiller et al., 2002; Hotez et al., 2009; Pedrique et al., 2013).

Pharmaceutical Marketing Aimed at Consumers

Although medications are not ordinary consumer goods, pharmaceutical companies invest heavily in consumer-directed marketing (Lee et al., 2015; Applequist & Ball, 2018). In Brazil, the country of origin of this text, a brief history of pharmaceutical marketing reveals the presence of numerous advertisements, many of them misleading, since the early 20th century. Extreme examples

include the promotion of highly harmful substances, such as cocaine, as remedies for various ailments, and advertisements for ineffective medications with unfounded promises of cures (Stacciarini, 2023, p. 69).

Today, the pharmaceutical sector is one of the largest investors in marketing in Brazil (Stacciarini, 2024c). In recent years, three to four pharmaceutical companies have consistently ranked among the top ten advertisers in the country, with some surpassing R$1 billion in investments in a single year (Stacciarini, 2024c). Additionally, marketing strategies have become increasingly complex and sophisticated. Multi-million-dollar studies and sponsorships secure advertisements across various platforms, especially television and the internet. The rise of digital marketing, fueled by advanced algorithms, social media, and influencers, along with advertising campaigns that may pose risks to public health, presents a particularly challenging scenario.

Remarks

The contents presented reveal numerous controversial practices adopted by pharmaceutical companies in their relentless pursuit of profit maximization, often at the expense of public and individual health. The manipulation of research and clinical trials compromises the efficacy and safety of medications, distorting the scientific method and undermining trust in healthcare systems. Furthermore, massive investments in lobbying and electoral funding grant these companies disproportionate influence over legislative and regulatory processes, favoring corporate interests. The provision of gifts and incentives to healthcare professionals compromises medical ethics, influencing decisions that should be based on the best available scientific evidence. Additionally, the prioritization of medications with higher financial returns leaves healthcare needs in less developed regions neglected, while aggressive consumer-directed marketing encourages irrational drug use.

In light of this scenario, it is imperative to rethink control and transparency mechanisms within the pharmaceutical industry. Strengthening the independence of scientific research, ensuring the integrity of regulatory processes, and promoting policies that prioritize public health over commercial interests are essential. Only through an ethical and responsible approach can pharmaceutical advances be aligned with the real needs of society, ensuring that the pursuit of profit does not overshadow the fundamental commitment to human life and well-being.

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