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A Study on Factors Attributed to Failure of Pharmaceutical Products

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ABSTRACT
The Pharmaceutical Industry plays a pivotal role in healthcare by developing, manufacturing, and marketing drugs to treat a myriad of medical conditions. However, despite rigorous research, development, and testing processes, a significant number of pharmaceutical products fail to meet the expected standards or gain market acceptance. This study aims to explore the multifaceted factors that contribute to the failure of pharmaceutical products, focusing on the product life cycle as a framework for analysis. The product life cycle of a pharmaceutical product encompasses several stages, including research and development, clinical trials, regulatory approval, launch, and post-marketing surveillance. At each stage, various factors can influence the success or failure of a product. These factors range from scientific challenges and regulatory hurdles during the R&D phase to manufacturing issues, competitive pressures, and post-market safety concerns.
Through a comprehensive theoretical reviews and authors understanding of the subject, this study identifies key factors attributed to the failure of pharmaceutical products. These include but are not limited to **Scientific Challenges**: Inherent complexities in drug discovery and development, including target identification, drug design, and optimization, can lead to unforeseen efficacy or safety issues. **Regulatory Hurdles**: Stringent regulatory requirements and evolving guidelines can delay approvals, increase development costs, and limit market access for new drugs. **Manufacturing Issues**: Quality control failures, supply chain disruptions, and manufacturing inconsistencies can compromise the integrity, efficacy, and safety of pharmaceutical products. **Competitive Pressures**: Intense competition from generic drugs, biosimilars, and innovative therapies can erode market share and profitability, especially for products with limited differentiation. **Post-Market Safety Concerns**: Adverse events, drug interactions, and long-term side effects discovered after product launch can result in recalls, litigation, and damage to the brand reputation. By understanding and addressing these factors proactively, pharmaceutical companies can mitigate risks, enhance product quality, and improve the likelihood of success throughout the product life cycle. This study underscores the importance of comprehensive risk management, continuous monitoring, and adaptive strategies to navigate the complexities and challenges inherent in the pharmaceutical industry.

Keywords: pharma marketing, pharma crisis, pharma products, pharmaceutical industry, product withdrawal

I. INTRODUCTION

Pharma Marketing refers to the promotion and advertising of pharmaceutical products, services, or treatments. It involves the use of various channels and tools to reach potential buyers and communicate the benefits of the products or services being offered
Some key aspects of Pharma Marketing include:

- **Effectiveness**: Digital pharma promotional tools are effective in reaching potential buyers and communicating the benefits of the products or services being offered
- **Time-saving**: Digital marketing strategies can save time compared to traditional marketing method
- **Informative and Convenient**: Digital marketing allows for more informative and convenient communication between patients, doctors, and healthcare organizations
- **Reduced Paper Cost**: Digital marketing reduces the need for paper-based promotional materials, making it more environmentally friendly
- **Impact on Pharmaceutical Industry**: The recent development of digital pharma marketing resulted to an ease of interaction between patients, physicians, and healthcare organizations, eventually affecting the pharmaceutical sector.

Pharma-marketing trends have changed in the post-COVID-19 era, with an emphasis on telemedicine revolution, digital marketing, e-detailing, customer relationship management, e-sampling, advanced marketing, and innovative work behavior to highlight product value and streamline prescriptions to the target consumer (1,2).

The withdrawal of pharmaceutical products refers to the removal of these products from the market, often due to safety concerns or other regulatory reasons. The withdrawal period of a pharmaceutical product is the time required after its administration before the animal or its products (e.g., meat, milk) are considered safe for human consumption. This period is an important safety criterion for veterinary medicinal products used in food-producing animals

Several factors can influence the withdrawal period of pharmaceutical products, including the pharmacokinetic parameters of the product, clinical characteristics of the disease being treated, and regulatory policies. Research has shown that many pharmaceutical products, including analgesics, have been withdrawn from the market due to adverse drug reactions. The reasons for withdrawal can include hepatic, hematologic, cardiovascular, dermatologic, and carcinogenic issues. In the context of regulatory policy, pharmaceutical regulatory authorities play a crucial role in monitoring the quality, efficacy, and safety of pharmaceutical products, including the decision to withdraw a product from the market. The withdrawal of pharmaceutical products is a complex and important aspect of public health and safety, and it is governed by stringent regulatory processes to ensure the well-being of both humans and animals (3–6).

In order to assess prescription medications that were taken off of global pharmaceutical markets for safety apprehensions throughout the past forty years, the study used a descriptive analysis. We looked at the list of medications, their indications, how long they were marketed for, and the causes of withdrawal. Amongst the 121 products found, non-steroidal anti-inflammatory medications (13.2%), non-opioid analgesics (8.3%), antidepressants (7.4%), and vasodilators (5.8%) were the most often recalled medicine categories. Hepatic (26.2%), hematologic (10.5%), cardiovascular (8.7%), dermatologic (6.3%), and carcinogenic (6.3%) problems were the top five safety reasons for withdrawals. Approximately one-third of the 87 items for which the date of marketing was available were removed within the primary two years, with a median tenure on market of 5.4 years (4). Another relevant search result is a study titled "The magnitude of a product recall: offshore outsourcing vs. captive offshoring effects". In the context of global sourcing methods for the pharmaceutical industry, the study investigates the recall's scope and if variations in these decisions affect the ability to decrease the recall's overall cost in addition to raising the probability of a recall. According to the study, captive offshoring and offshore outsourcing have different impacts on how much people recall a product [(7).

II. OBJECTIVES OF THE STUDY

The Researchers have considered the following objectives for the study:

1. To understand the significance & essence of pharmaceutical products.
2. To study the factors attributed to failure of pharmaceutical products.
3. To cite examples of the failure of pharmaceutical products and present relative learning.

III. RESEARCH METHODOLOGY

- **Type of Research:** Descriptive Research
- **Data Collection Sources**: Secondary Data
- **Scope of the study**: The selected Pharma Products and respective failure cases
- **Limitation of the Study:** The Researchers express the extent of data collection & interpretation possible in the limited time frame. The inferences gathered are indicative in nature not exhaustive.

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IV. RESEARCH PROCESS

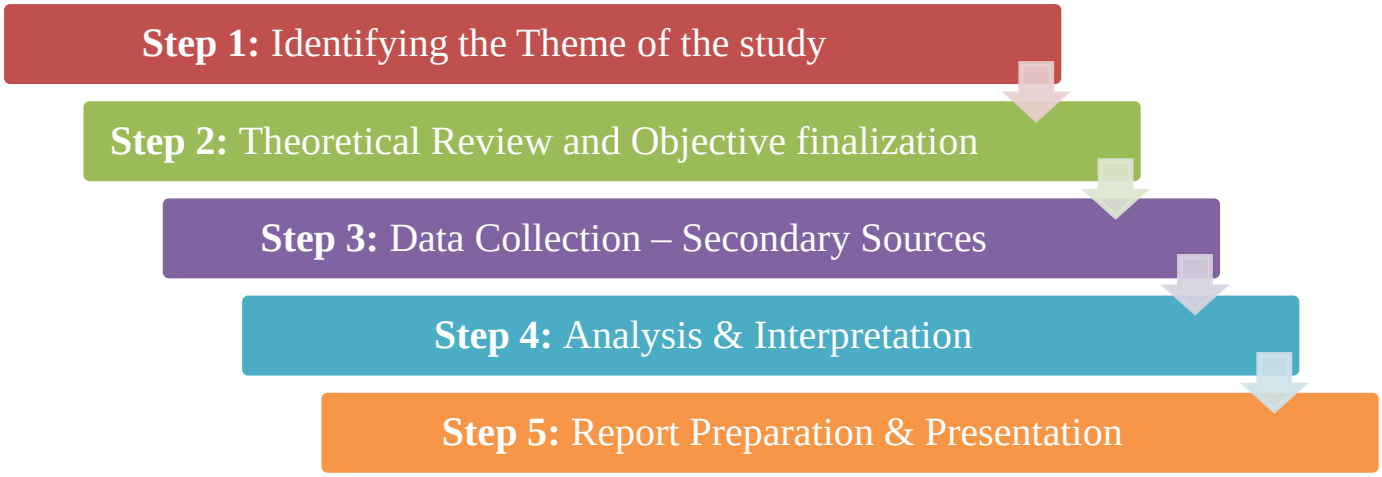

Chart 1: Research Process adopted for the study
Source: Authors' Study

V. PHARMACEUTICAL INDUSTRY

The pharmaceutical industry is involved in the discovery, development, production, and marketing of drugs and medications for medical purposes. It is a global industry that plays a crucial role in the healthcare sector, aiming to cure and prevent diseases, alleviate symptoms, and improve patients' quality of life.(8)
Key aspects of the pharmaceutical industry include:

1. **Drug Discovery and Development**: The industry is constantly seeking new and improved medications. Drug discovery and development help in treating new diseases. (9)
2. **Regulatory Compliance**: Regulatory requirements are a critical aspect of the pharmaceutical industry. They are designed to maintain the quality, safety, and efficacy of medical products. Regulatory compliance is essential for the approval, manufacturing, and commercialization of pharmaceutical products (10)
3. **Validation**: Validation is a crucial procedure in the pharmaceutical industry to ensure that processes, methods, and activities consistently produce products that meet predetermined requirements. Equipment validation, in particular, is an important aspect of this process, involving various components related to processing, cleaning, facilities, equipment, and instrumentation (11)
4. **Scale-up and Manufacturing**: The pharmaceutical industry faces challenges in scaling up production. Regulatory compliances in the development of commercial-scale processes, such as the production of nanoparticles, are a significant focus of research and review articles (10)
5. **Global Market**: The pharmaceutical industry is a global market, with major players in North America, Europe, and other regions. In 2020, approximately 46% of sales came from North America
6. **Marketing and Sales**: Pharmaceutical companies engage in marketing activities to promote their products, often through advertising and other forms of communication. In the United States, pharmacy benefit management companies administer prescription drug programs

These aspects provide a glimpse into the multifaceted nature of the pharmaceutical industry, encompassing scientific research, regulatory oversight, and manufacturing processes. The industry's ongoing efforts are aimed at advancing medical science and improving global health. (8)

VI. PHARMA PRODUCT CLINICAL STAGES

The pharmaceutical product development process involves several stages, from initial research to market withdrawal. These stages are crucial for ensuring the safety, efficacy, and success of a new drug.

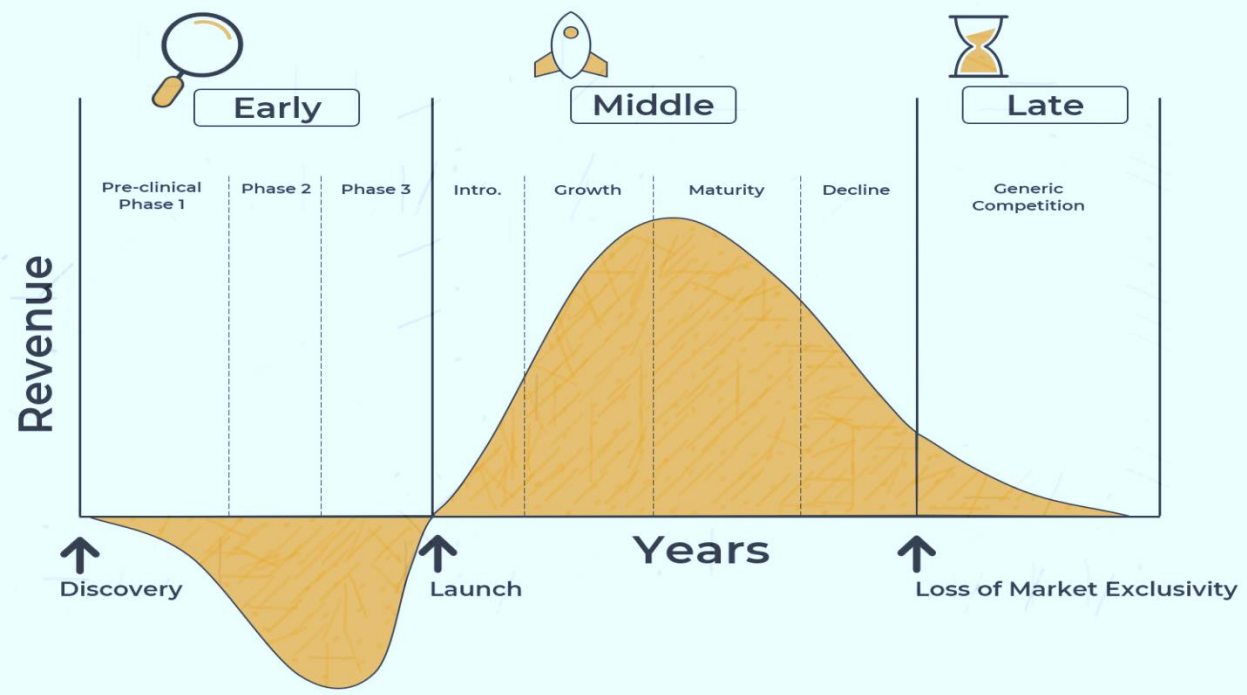

Chart 2: PLC Pharma Products
Image Source: www.pharmamarketer.com

The Early stages can be summarized as follows:

1. **Preclinical Studies**: Before testing a new drug on humans, it undergoes preclinical studies in the laboratory, typically using animals to assess its safety and efficacy.
2. **Phase 1 Clinical Trials**: The medicine is tested on a small group of healthy volunteers to assess safety, dosage, and adverse effects.
3. **Phase 2 Clinical Trials**: During this stage, the medicine is tested on a wider number of patients with the targeted ailment to evaluate its efficacy and safety in real-world settings.
4. **Phase 3 Clinical Trials**: These trials involve a large number of patients and aim to establish therapeutic efficacy, monitor side effects, and gather more information on risks and benefits.
5. **Phase 4 Clinical studies**: also known as post-marketing surveillance, are done after a medicine is approved to assess its long-term safety and efficacy in a broader population.

The pharmaceutical industry also emphasizes product lifecycle management (PLM) to make drug development and production more effective and lower risk. PLM involves creating and managing a company's product-related intellectual capital from the idea stage to final development, benefiting the industry through enhanced patient outcomes and pricing strategies. Additionally, the industry utilizes various technologies, such as osmotic tablet technology, in the early stages of pharmaceutical development to ensure reproducible release rates and suitability for delivering active pharmaceutical ingredients (APIs). Furthermore, validation is a critical procedure in the pharmaceutical industry to ensure that processes, methods, and activities consistently produce products that meet predetermined requirements. Equipment validation, in particular, is an important aspect of this process, involving various components related to processing, cleaning, facilities, equipment, or instrumentation. In summary, the clinical stages of a pharmaceutical product, along with product lifecycle management, technological advancements, and validation procedures, are integral parts of the comprehensive process of pharmaceutical product development. These aspects are essential for ensuring the quality, safety, and efficacy of pharmaceutical products. (11–14)

VII. FACTORS ATTRIBUTED TO FAILURE & WITHDRAWAL OF PHARMACEUTICAL PRODUCTS

The failure and withdrawal of pharmaceutical products can be attributed to various factors, including clinical trial issues, supply and demand challenges, and product life cycle management.

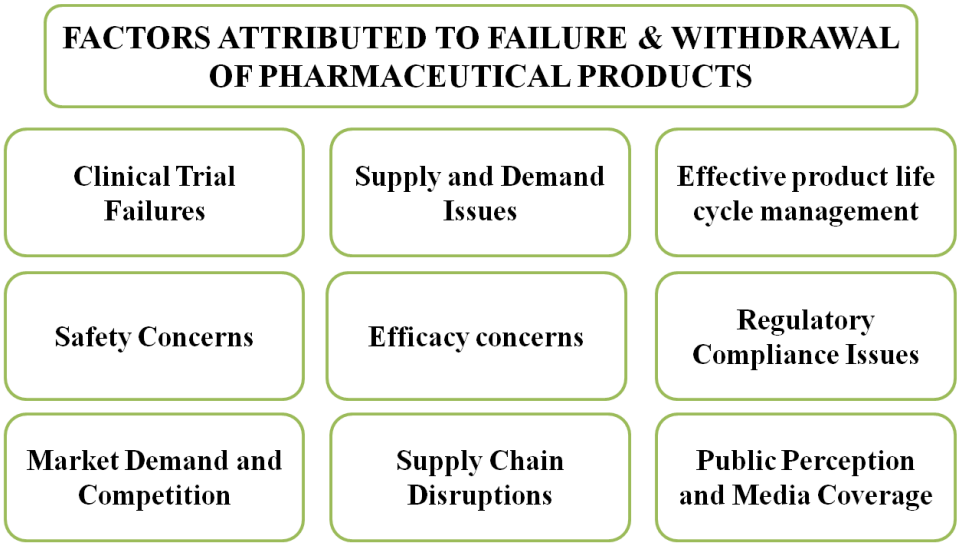

Chart 3: Factors Attributed to Failure & Withdrawal of Pharmaceutical Products
Source: Authors' Understanding based on study

1. **Clinical Trial Failures**: Many novel medication ideas fail to reach the market owing to toxicity, ineffectiveness, or economic issues. Furthermore, difficulties such as chaotic and sluggish patient recruiting, lack of competence in choosing and monitoring partners, lack of practicality of the research design, and inadequate quality of registration data have been cited as key management issues contributing to clinical trial failures (12)
2. **Supply and Demand Issues**: Pharmaceutical drug availability is influenced by supply and demand issues, which are in turn influenced by factors such as health insurance financing schemes, pharmaceutical product registration regulations, pharmacist knowledge levels, changes in disease patterns, disasters, and war. (15)
3. **Effective product life cycle management**: drives pharmaceutical innovation and market success. It entails overseeing the many stages of a pharmaceutical product's lifecycle, including development, approval, launch, commercialization, and decline. Effective product life cycle management may assist avoid a product's deterioration and enhance its lifespan. (16)
4. **Safety Concerns**: The withdrawal of pharmaceutical products can be attributed to various safety concerns, including unexpected adverse reactions or side effects that were not initially observed during clinical trials. Safety issues, such as those seen with thalidomide, can lead to severe consequences, like birth defects and other health complications. In the case of thalidomide, its initial marketing as a safe sedative led to a global epidemic of severe birth differences in children born to mothers who used the drug during pregnancy, highlighting the critical importance of monitoring and reassessment of safety concerns.(17)
5. **Efficacy concerns**: Efficacy concerns may arise when pharmaceutical products fail to demonstrate the expected level of effectiveness in real-world settings compared to what was observed in controlled clinical trials. This discrepancy between trial results and real-world outcomes can impact patient health and treatment outcomes, necessitating a reevaluation of the product's efficacy in practical use.
6. **Regulatory Compliance Issues**: Regulatory compliance issues can encompass a range of problems related to manufacturing processes, quality control standards, labeling inaccuracies, or inadequate documentation of safety and efficacy data. For instance, safety concerns in pharmaceutical manufacturing processes, like the use of certain solvents, can pose significant risks if not properly managed(18)
7. **Market Demand and Competition**: Changes in market dynamics, like the emergence of competing products that offer superior efficacy, safety, or cost-effectiveness, can contribute to the failure of pharmaceutical products. This shift in market demand and competition underscores the importance of pharmaceutical companies staying abreast of evolving market trends and consumer preferences to maintain their competitive edge.
8. **Supply Chain Disruptions**: Disruptions in the pharmaceutical supply chain, such as shortages of raw materials, manufacturing issues, or distribution problems, can significantly affect the availability of pharmaceutical products in the market. These disruptions can lead to delays in production, shortages of essential medications, and impact patient access to necessary treatments. Ensuring a robust and resilient supply chain is crucial for the pharmaceutical industry to mitigate risks associated with such disruptions(19).

9. **Public Perception and Media Coverage**: The media plays a significant role in shaping public perception and awareness of pharmaceutical products. For instance, celebrities like American football player Ricky Williams have used their platform to promote disease awareness and specific drugs, such as Paxil (Seroxat/paroxetine), leading to increased public attention and discussions about mental health conditions and treatments. Similarly, promotional videos developed by organizations like the Pharmaceutical Society of New Zealand have been effective in educating the public about pharmacy services, influencing people's perceptions and increasing their likelihood of visiting a pharmacy in the future. Moreover, negative media coverage or controversies surrounding pharmaceutical products can have adverse effects on their success. Public perception influenced by media reports can impact consumer trust and confidence in medications. Additionally, controversies related to safety issues, efficacy concerns, or regulatory compliance can lead to product withdrawals or failures in the market(20,21)

The failure and withdrawal of pharmaceutical products can be influenced by a range of factors, including issues related to clinical trials, supply and demand dynamics, and the management of a product throughout its life cycle. Addressing these factors is essential for the successful development, approval, and commercialization of pharmaceutical products.

Some of the products are discussed below with respect to failure and withdrawal of pharmaceutical product: -

(1) Beovu, Novartis

Drug name: Beovu
Company: Novartis
First approval: October 2019, U.S. FDA
Indication: Wet age-related macular degeneration (AMD)
Past sales estimate: $4.38 billion by 2021
2020 sales: $190 million

Novartis' drug Beovu has faced significant challenges in the market due to safety concerns and a lack of therapeutic effect. The drug, approved for the treatment of wet age-related macular degeneration, encountered safety issues, including potential vision-threatening side effects such as retinal vasculitis and retinal artery occlusion. As a result, Novartis terminated three clinical trials testing the drug at different dosages and dosing frequencies. The safety issues have led to a decline in Beovu's sales and raised the potential for significant financial impact on Novartis, with analysts suggesting that a "worst case scenario" involving the drug's withdrawal from the market could result in a substantial loss for the company. Additionally, a number of lawsuits have been filed against Novartis by individuals who claim to have experienced vision impairment and other adverse reactions after receiving Beovu injections. These lawsuits allege that Novartis failed to adequately warn.The safety issues have led to a decline in Beovu's sales and raised the potential for significant financial impact on Novartis, with analysts suggesting that a "worst case scenario" involving the drug's withdrawal from the market could result in a substantial loss for the company. about the potential risks associated with the drug. As of now, there have been no trials or court-approved settlements in the Beovu lawsuits (22–26)

(2) Dengvaxia, Sanofi

Drug name: Dengvaxia
Company: Sanofi
First approval: December 2015, Mexico’s Federal Commission for the Protection against Sanitary Risk
Indication: Dengue fever
Past sales estimate: $1 billion by 2020
2020 sales: Not reported

The failure of Sanofi's Dengvaxia in the market can be attributed to several factors, including safety concerns, regulatory issues, and a lack of compliance with post-marketing commitments. The vaccine, which was developed to protect against all four serotypes of dengue, faced a significant setback when safety concerns emerged after its approval. Sanofi failed to comply with its post-marketing commitments, and the vaccine's use was restricted to only those who had prior dengue infection due to reanalysed trial results suggesting limited efficacy in dengue-naïve individuals. This led to a decline in the overall number of individuals eligible for the vaccine. The controversy surrounding Dengvaxia has had a significant impact on vaccine hesitancy, with parents refusing to vaccinate their children not only against dengue but also against other diseases, leading to a phenomenon known as Vaccine Hesitancy. The failure of Dengvaxia has also resulted in the suspension of its sale and distribution in the Philippines. The vaccine's introduction and subsequent issues have led to a high-profile and complex situation, including legal and criminal implications for those involved in its introduction and administration. The failure of Dengvaxia serves as a cautionary tale in the pharmaceutical industry, highlighting the importance of thorough post-marketing surveillance, compliance with regulatory commitments, and transparent communication of safety and efficacy data. (27–30)

(3) Eucrisa, Pfizer

Drug name: Eucrisa
Company: Pfizer
First approval: December 2016, U.S. FDA

Indication: Atopic dermatitis
Past sales estimate: $2 billion at peak
2020 sales: Not disclosed ($138 million in 2019)
Pfizer's Eucrisa has faced challenges in the market due to several factors, including:
Lack of efficacy in psoriasis: Eucrisa, which is only approved for eczema, has never been effective for psoriasis. Early safety testing on a higher concentration of the drug failed for psoriasis, leading to a lower dosage and a switch to Eucrisa's current form.Burning or stinging sensation: Even in its current form, Eucrisa causes a burning or stinging sensation, which has significantly limited its uptake.
Unfavourable formulary positioning and higher rebates: Eucrisa faced unfavourable formulary positioning and higher rebates in the face of inexpensive steroids, which contributed to its commercial failure.
Market access issues: Eucrisa's market access was affected by its unfavourable formulary positioning and higher rebates, which made it less accessible to patient.
Inadequate understanding of customer needs: Pfizer may not have adequately understood the needs and preferences of its target customers, leading to poor product differentiation and difficulty in communicating the drug's benefits .
Poor product differentiation: Eucrisa's poor product differentiation may have contributed to its lack of success in the market (31–33).
(4) Lartruvo, Eli Lilly
Drug name: Lartruvo
Company: Eli Lilly
First approval: October 2016, U.S. FDA
Indication: Soft tissue sarcoma (withdrawn)
Past sales estimate: $374 million by 2021
2020 sales: None
Eli Lilly's Lartruvo has faced challenges in the market due to several factors, including:
Lack of efficacy: Lartruvo, which is used in combination with doxorubicin for the treatment of soft tissue sarcoma, has faced challenges due to its limited efficacy
Safety concerns: Although Lartruvo has a unique mechanism of action and an acceptable toxicity profile, it has faced safety concerns, which may have contributed to its market failure
Market access issues: Lartruvo's market access may have been affected by its unfavourable formulary positioning and higher rebates, which made it less accessible to patients
Inadequate understanding of customer needs: Eli Lilly may not have adequately understood the needs and preferences of its target customers, leading to poor product differentiation and difficulty in communicating the drug's benefits
Poor product differentiation: Lartruvo's poor product differentiation may have contributed to its lack of success in the market. (31,34)
(5) Nuplazid, Acadia Pharmaceuticals
Drug Name: Nuplazid
Company: Acadia Pharmaceuticals
First approval: April 2016, U.S. FDA
Indication: Parkinson’s disease psychosis
Past sales estimate: $841 million in 2020
2020 sales: $441.8 million
Nuplazid, developed by Acadia Pharmaceuticals, has faced challenges in the market due to several factors, including:
Lack of efficacy: Nuplazid, which is used to treat Parkinson's disease psychosis, schizophrenia, and depression, has faced challenges due to its limited efficacy
Safety concerns: Nuplazid has faced safety concerns, including potential side effects such as retinal vasculitis and retinal artery occlusion, which have led to a decline in its sales and raised the potential for significant financial impact on Acadia
Market access issues: Nuplazid's market access may have been affected by its unfavourable formulary positioning and higher rebates, which made it less accessible to patients
Inadequate understanding of customer needs: Acadia may not have adequately understood the needs and preferences of its target customers, leading to poor product differentiation and difficulty in communicating the drug's benefits
Poor product differentiation: Nuplazid's poor product differentiation may have contributed to its lack of success in the market. (35–38)
(6) Ocaliva, Intercept Pharmaceuticals
Drug name: Ocaliva
Company: Intercept Pharmaceuticals
First approval: May 2016, U.S. FDA

Indication: Primary biliary cholangitis
Past sales estimate: Up to $8.6 billion
2020 sales: $313 million

Intercept Pharmaceuticals' Ocaliva has faced challenges in the market, particularly in its bid for approval in the treatment of non-alcoholic steatohepatitis (NASH). The drug's struggles in the NASH market began in 2020 when the FDA rejected its approval bid for the treatment of the liver disease. The rejection was based on concerns related to the drug's efficacy and safety, particularly its potential to cause drug-induced liver injury. In 2023, the FDA's Gastrointestinal Drugs Advisory Committee voted 12 to 2 against the benefits of Ocaliva outweighing the risks in NASH patients with stage 2 or 3 fibrosis. Additionally, the drug failed to demonstrate superiority over a placebo in improving liver scarring among patients with compensated NASH-related liver fibrosis. These setbacks have led Intercept Pharmaceuticals to abandon its NASH research and pivot to a lower-dose version of Ocaliva for the treatment of primary biliary cholangitis. The drug's challenges in the NASH market have been attributed to its limited efficacy, safety concerns, and the use of surrogate endpoints in its clinical trials. (39–41)

VIII. CONCLUSION

The failure rate of clinical drug development is high, with around 90% of drug candidates failing to reach approval. The reasons for failure as per the respective study includes ***lack of clinical efficacy, unmanageable toxicity, poor drug-like properties, lack of commercial needs, and poor strategic planning***.

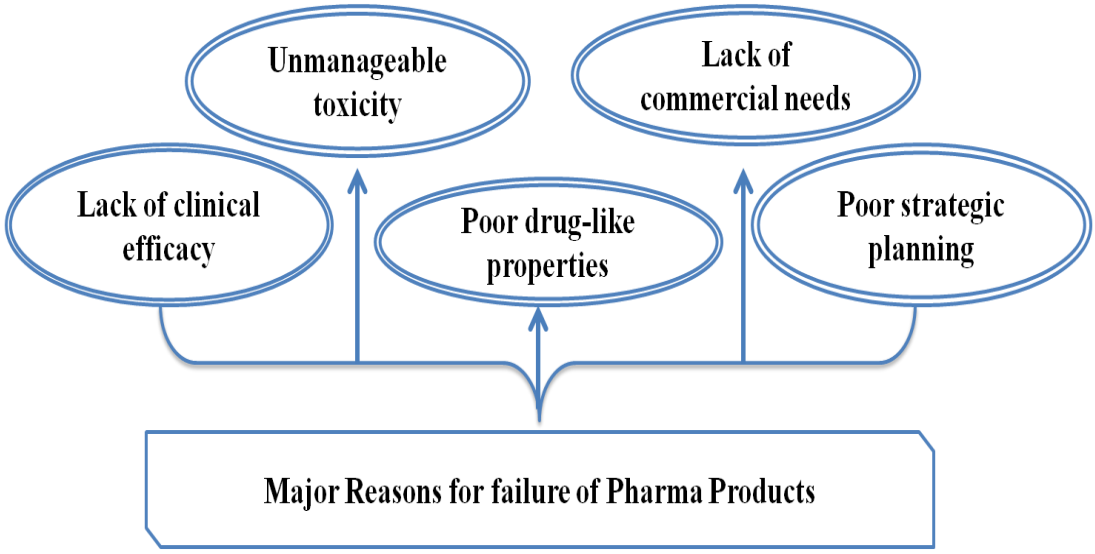

Chart 4: Reasons for Failure of Pharmaceutical Products
Source: Authors' Understanding based on study

In addition, potentially efficacious drugs can still fail to demonstrate efficacy due to flawed study design, inappropriate statistical endpoint, or underpowered clinical trial. Safety is also a major concern, with some drugs failing due to safety issues. Other factors contributing to the failure of new products include failure to understand consumer needs and wants, poor marketing, and inadequate funding. To improve the likelihood of success, it is recommended to address these factors strategically and conduct thorough research and development towards Product innovation.

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