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PHARMACOECONOMICS OF ORPHAN DRUGS: A COMPREHENSIVE REVIEW

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ABSTRACT:

The pharmacoeconomics of orphan drugs is a field that evaluates the economic implications of developing and providing treatments for rare diseases. This review article offers a comprehensive overview of key factors affecting orphan drugs' cost-effectiveness and policy landscape. It starts by defining pharmacoeconomics and its role within orphan drugs, highlighting challenges due to limited patient populations. Financial hurdles such as high development costs and market sustainability issues are discussed. The article examines methods for evaluating the cost-effectiveness of orphan drugs, emphasizing the balance between clinical benefits and economic considerations. The role of Health Technology Assessments (HTAs) in the approval process is explored, noting their impact on healthcare decisions. Policies and incentives, including market exclusivity and tax credits, aimed at promoting orphan drug development are reviewed. The budgetary implications for healthcare systems and society are analyzed, along with ethical issues like access and affordability. Case studies of successful orphan drug developments are included to illustrate economic strategies. Finally, potential future developments in orphan drug pharmacoeconomics are discussed, with strategies proposed to improve affordability and access. This review aims to provide a nuanced understanding of the economic dynamics in orphan drug development and their effects on healthcare policy and patient outcomes.

KEYWORDS:

Orphan Drugs, Rare Diseases, Market Exclusivity, Cost-Effectiveness Analysis, Regulatory Assistance, Budget Impact, Ethical Considerations, Global Cooperation, Non-Economic Values, Clinical Benefits, Patient Needs, Innovation, Healthcare Policy, Patient Outcomes.

I. INTRODUCTION

Orphan drugs are medicines or vaccines for rare diseases. Examples include genetic disorders, rare cancers, and tropical or degenerative diseases. What counts as a rare disease can vary, but it usually depends on how common the disease is, how severe it is, and if there are other treatment options. (1,2). The rapid growth in the development of new orphan drugs makes it increasingly challenging for health systems to reimburse them on an exceptional basis. Understanding the value societies place on orphan drugs compared to other health technologies is now a crucial factor in policy discussions. (3).

The Orphan Drug Act of 1983 in the United States was established to promote the development of drugs for rare diseases affecting fewer than 200,000 people. The Act amends the Food, Drug, and Cosmetics Act, acknowledging that pharmaceutical companies may incur financial losses due to small sales volumes for these drugs. It sets criteria for orphan drugs, specifying that they treat conditions affecting fewer than 200,000 patients or where development costs cannot be recovered. The FDA provides support by assisting in the drug approval process and potentially funding clinical testing. Additionally, the Act offers significant incentives, including tax breaks allowing up to 50% of clinical trial costs to be claimed as tax credits, and a market exclusivity period of seven years, even for non-patentable drugs. These measures ensure robust support and incentives for developing treatments for rare conditions, encouraging pharmaceutical companies to invest in this critical area. (4).

Advantages of Orphan Drug:

- **Market Exclusivity**: Orphan drugs often receive market exclusivity for a certain period, typically seven years in the US, which allows the manufacturer to recoup the costs of development without competition from generic versions (5,6).
- **Tax Credits**: Companies developing orphan drugs can benefit from tax credits, such as a 25% credit on research and development costs in the US, which helps reduce the financial burden of drug development (7).
- **Regulatory Assistance**: Regulatory bodies like the FDA and EMA provide protocol assistance and expedited review processes for orphan drugs, which can speed up the approval process and bring treatments to patients more quickly (5).
- **Fee Waivers**: Orphan drug designation often comes with fee waivers for regulatory applications, reducing the financial barriers to drug development (7).
- **Increased Reimbursement Levels**: Orphan drugs typically receive higher reimbursement levels from healthcare payers, reflecting the high cost of development and the limited patient population.
- **Encouragement of Innovation**: The incentives provided for orphan drugs encourage pharmaceutical companies to invest in research and development for rare diseases, leading to medical breakthroughs that might not otherwise occur due to the economics of drug research (5).
- **Global Impact**: Orphan drug designation programs exist in many countries, including the US, EU, Japan, and India, promoting global collaboration and access to treatments for rare diseases (5).

SCOPE

The scope of pharmacoeconomics of orphan drugs covers these key areas to ensure that treatments for rare diseases are effective and safe and provide value to patients and healthcare systems.

Cost-Effectiveness Analysis (CEA) is aimed at evaluating the value for money of orphan drugs by comparing their costs with the health outcomes they produce. The method involves using quality-adjusted life years (QALYs) to measure the effectiveness of treatments. This helps determine whether the health benefits provided by the orphan drug justify its costs. For example, CEA may compare the cost per QALY gained from an orphan drug to that of standard treatments for the same condition, providing a framework to assess the economic viability and health impact of the drug. (8).

Budget Impact Analysis (BIA) is designed to assess the financial implications of adopting orphan drugs on healthcare budgets. The method involves estimating the total cost to the healthcare system over a specified period, taking into account factors such as the patient population and drug prices. For example, BIA might calculate the overall expense of introducing a new orphan drug to a national healthcare system, helping policymakers understand the potential financial burden and plan accordingly. (9).

Health Economic Models are used to compare the costs and outcomes of different treatment options by utilizing simulation models. These models employ various techniques, such as decision trees and Markov models, to simulate the progression of a disease and the impact of different treatments. For example, health economic models might be used to assess the lifetime costs and benefits of an orphan drug compared to existing therapies, providing valuable insights for decision-makers on the economic viability and potential health outcomes of the drug. (9).

Incentives and Policies aim to analyze how government incentives support the development and pricing of orphan drugs. This involves reviewing policies such as tax credits, market exclusivity periods, and accelerated approval processes that encourage investment in orphan drug development. For example, evaluating the impact of the Orphan Drug Act on the number of new orphan drugs brought to market provides insights into how these incentives drive innovation and make the development of treatments for rare diseases more attractive to pharmaceutical companies. These policies play a crucial role in promoting the availability of therapies for patients with rare conditions. (8).

Patient Access and Equity aims to ensure that patients with rare diseases have timely access to necessary treatments. This involves examining barriers to access, such as high drug costs and regional disparities, and suggesting policies to improve equity. For example, assessing the effectiveness of patient assistance programs in providing orphan drugs to underserved populations can help identify gaps and implement solutions to ensure that all patients, regardless of their location or financial status, can access the treatments they need. This approach is essential for addressing the unique challenges faced by those with rare diseases and promoting fair and equitable healthcare for all. (10).

Post-marketing surveillance aims to monitor the real-world effectiveness and safety of orphan drugs after they have been approved. This involves collecting and analyzing data on the performance and adverse effects of the drug from clinical practice. For example, post-marketing studies are conducted to gather additional evidence on the long-term safety and efficacy of an orphan drug, ensuring that any potential issues are identified and addressed promptly to protect patient health. This ongoing monitoring is crucial for maintaining the safety and effectiveness of treatments for rare diseases. (8).

By addressing these aspects, we can make significant strides in developing, evaluating, and delivering orphan drugs to those who need them most. These areas collectively contribute to a comprehensive understanding of the economic implications of orphan drugs, ensuring that they provide value to patients and healthcare systems while being financially sustainable.

II. METHODOLOGY

i. ECONOMIC CHALLENGES

The economic challenges in orphan drug development are multifaceted and significant. Developing orphan drugs is often expensive due to the need for specialized research, small patient populations, and complex manufacturing processes (5). The limited market size for these drugs reduces financial incentives for pharmaceutical companies to invest in their development. Additionally, navigating the regulatory landscape for orphan drugs can be complex and time-consuming, requiring additional data and longer approval processes (5). Standard economic evaluations, such as cost-effectiveness analysis (CEA), often struggle to capture the full value of orphan drugs due to uncertainties in clinical data and the high costs involved. Securing funding and reimbursement for orphan drugs can also be challenging, as payers may be hesitant to cover high-cost treatments with limited evidence of cost-effectiveness (9). Despite the availability of orphan drugs, patients may face barriers to access due to high costs, limited insurance coverage, and logistical challenges in obtaining treatment (11).

ii. COST-EFFECTIVENESS ANALYSIS (CEA) OF ORPHAN DRUGS:

Cost-Effectiveness Analysis (CEA) is a critical tool in evaluating the economic value of pharmaceuticals by assessing the cost per quality-adjusted life year (QALY) gained. However, its application to orphan drugs, which are designed to treat rare diseases, presents unique challenges:

Uncertainty:

- **Efficacy and Safety Concerns**: Orphan drugs often face significant uncertainty regarding their efficacy and safety when first introduced. This is primarily due to the small size of clinical trials, which limits the amount of data available.
- **Lack of Randomization:** Small trial sizes also make it difficult to randomize participants adequately, potentially affecting the reliability of the results.
- **Surrogate Efficacy Measures:** Often, orphan drugs rely on surrogate markers (such as biomarkers) instead of direct clinical outcomes to demonstrate their effectiveness. These surrogate measures may not fully capture the drug's true impact on patients (8).

Health Gains:

- **Population Health Impact:** Reimbursing orphan drugs that are not cost-effective could divert resources from other healthcare needs. This can potentially reduce overall population health if significant funds are allocated to expensive treatments with limited benefits (12).
- **Resource Allocation:** The high cost of orphan drugs can strain healthcare budgets, limiting the availability of funds for other essential health services and treatments.

Patient Access:

- **Access vs. Cost-Effectiveness:** There's an inherent conflict between ensuring patient access to orphan drugs and the economic goal of maximizing overall population health. Every patient has the right to access necessary care, but high-cost drugs can create financial barriers.
- **Ethical Considerations:** Balancing the need to provide life-saving treatments for rare diseases with the need to maintain a sustainable healthcare system poses ethical dilemmas (12).

Financial Risks:

- **Uncertain Disease Population**: Payers (such as insurance companies and government healthcare programs) face financial risks due to the uncertainty in estimating the size of the population affected by rare diseases.
- **Budget Impact:** The unpredictable number of patients requiring treatment and the high costs of orphan drugs can result in significant budgetary challenges (8).

These limitations highlight the need for specialized approaches when applying CEA to orphan drugs. Ensuring the sustainability of healthcare systems while providing access to necessary treatments for rare diseases requires careful consideration of these unique factors. Ongoing research, innovative funding models, and policy adjustments are crucial to address these challenges effectively.

iii. HEALTH TECHNOLOGY ASSESSMENT:

Health Technology Assessment (HTA) is a systematic process that evaluates the safety, effectiveness, economic, and social aspects of medical technologies. HTA for orphan drugs poses unique challenges due to the small patient populations and high costs involved in diagnosis and treatment.

Steps in HTA (13,14)**:**

Steps	Description
1) Defining Assessment Questions	Establishing the key questions to be addressed
2) Data Collection	Gathering relevant data from various sources
3) Data Analysis	Analysing the collected data to draw meaningful conclusions
4) Synthesizing Evidence	Combining the analyzed data to form a cohesive understanding
5) Forming Recommendations	Making informed recommendations based on the evidence
6) Reporting	Documenting the findings and recommendations
7) Dissemination	Sharing the report with relevant stakeholders

Characteristics Triggering aHTA:

1) Urgency: Immediate need for assessment.
2) Certainty: High level of confidence in the data available.

3) Low Budget Impact: Minimal financial implications (15).

Methods Used in HTA:

1) Evidence Appraisal and Synthesis: Evaluating and combining evidence to inform decision-making.
2) Economic Evaluation: Assessing the cost-effectiveness of medical technologies (16).
3) Health Economic Models: Comparing the costs and outcomes of different treatment options (17).
4) Discussion: In-depth discussions to identify and agree on the most suitable methods for HTA (18).

HTA is crucial for making informed decisions about the adoption and use of medical technologies, ensuring they provide value and benefit to patients and healthcare systems.

The common orphan drugs are Sumatriptan, Rifabutin, Digoxin antibody, Liothyronine (T_3), Famipizole, Amphotericin B, and Nitrates Here, are some other Orphan drugs with trade names as well as their manufacturers with their years.

Sr. No	Generic name (trade name)	Manufacturers	Year
1.	Ibrutinib (Imbruvica)	Janssen	2017
2.	Everolimus (Afinitor)	Novartis Pharmaceuticals	2017
3.	Daratumumab (Darzalex)	Janssen	2017
4.	Pegylated liposomal irinotecan (Onivyde)	Shire	2017
5.	Afatinib (Giotrif)	Boehringer Ingelheim Pty Ltd	2017
6.	Vandetanib (Caprelsa)	Sanofi	2018
7.	Romiplostim (Nplate)	Amgen	2018
8.	Eltrombopag (Revolade)	GlaxoSmithKline	2018
9.	Cabozantinib (Cabometyx)	Ipsen	2018
10.	Cenegermin (Oxervate)	Dompe	2018
11.	Cabozantinib (Cometriq)	–	2018
12.	Obinutuzumab (Gazyvaro)	Roche	2018
13.	Ixazomib with lenalidomide and dexamethasone (Ninlaro)	Takeda	2018
14.	Pirfenidone (Esbriet)	Roche	2018
15.	Lenvatinib with everolimus (Kisplyx)	Eisai	2018
16.	Kebilidi	PTC Therapeutics, Inc	2024
17.	Aucatzyl	Autolus Inc	2024
18.	Tecelra	Adaptimmune LLC	2024
19.	Beqvez	Pfizer, Inc	2024

20.	Lenmeldy	Orchard Therapeutics Limited	2024
21.	Amtagvi	Iovance Biotherapeutics, Inc	2024

(9)

iv. POLICY AND INCENTIVES:

Orphan drugs often receive market exclusivity for a period, typically seven years in the US, which allows the manufacturer to recoup development costs without competition from generic versions. Companies developing orphan drugs can benefit from tax credits, such as a 25% credit on research and development costs in the US, which helps reduce the financial burden of drug development. Regulatory bodies like the FDA and EMA provide protocol assistance and expedited review processes for orphan drugs, speeding up the approval process and bringing treatments to patients more quickly. Orphan drug designation often comes with fee waivers for regulatory applications, reducing the financial barriers to drug development. Orphan drugs typically receive higher reimbursement levels from healthcare payers, reflecting the high cost of development and the limited patient population. The incentives provided for orphan drugs encourage pharmaceutical companies to invest in research and development for rare diseases, leading to medical breakthroughs that might not otherwise occur due to the economics of drug research. Orphan drug designation programs exist in many countries, including the US, EU, Japan, and India, promoting global collaboration and access to treatments for rare diseases (5,6).

v. BUDGET IMPACT:

The budget impact on the Pharmacoeconomics of orphan drugs is a critical aspect to consider, given the high costs associated with developing and providing treatments for rare diseases. Orphan drugs often require significant investment in research and development due to the small patient populations and complex nature of rare diseases (19). This leads to higher prices for these drugs, which can strain healthcare budgets. Regulatory incentives such as extended market exclusivity can delay the entry of generic or biosimilar competitors, resulting in prolonged high prices and increased budget impact (9). For example, the Orphan Drug Act in the US provides seven years of market exclusivity, which can be extended with additional approvals for different rare disease indications.

Studies have shown that the budget impact of orphan drugs can vary significantly depending on factors such as the number of patients, drug prices, and reimbursement policies (19). A budget impact analysis in Chengdu, China, estimated that the budget required for high-priced orphan drugs could range from CNY 32 million to CNY 156 million under different policy scenarios. Policymakers need to balance the need for innovation with the financial sustainability of healthcare systems (19).Conducting robust economic evaluations, including cost-effectiveness and budget impact analyses, is essential to inform decision-making and ensure that resources are allocated efficiently. However, there is often a scarcity of evidence for these evaluations, making it challenging to assess the true value of orphan drugs.

Additionally, the high cost of orphan drugs can lead to disparities in access to treatment, particularly in countries with limited healthcare resources. Ensuring equitable access requires careful consideration of pricing and reimbursement policies. Collaborative approaches, such as public-private partnerships and international cooperation, can help mitigate the budget impact and improve access to orphan drugs globally. Furthermore, the development of more efficient manufacturing processes and innovative funding models, like outcome-based pricing, can help reduce costs and make orphan medicines more affordable (20).

vi. ETHICAL CONSIDERATION:

The ethical considerations surrounding orphan drugs are complex and multifaceted, emphasizing the need for a balanced approach that promotes innovation while ensuring patient access. One significant ethical imperative is ensuring timely access for patients with rare diseases, as delays in drug approval and availability can severely impact patients who often have limited treatment options. Balancing economic incentives for pharmaceutical companies with patient needs presents a critical ethical challenge. While incentives like market exclusivity and tax credits are essential to encourage drug development, they can also lead to high drug prices, making treatments unaffordable for many patients. Compassion and beneficence must play a crucial role in decision-making related to orphan drugs, ensuring that the moral obligation to provide care and support to individuals with rare diseases is considered beyond purely economic calculations.

Global cooperation is another vital ethical principle, emphasizing the importance of collaboration among countries to share knowledge, resources, and best practices, thereby ensuring patients worldwide have access to necessary treatments. Differences in regulatory requirements for orphan drug designation and approval can lead to unmet health needs and exacerbate health inequities, making the harmonization of regulatory standards essential to ensure equal access across regions. Establishing decision-making panels that include diverse stakeholders, such as patients, healthcare providers, and ethicists, can help ensure that ethical considerations are adequately addressed in the drug development and approval process. These panels can provide valuable insights into the needs and perspectives of patients, guiding decisions that balance innovation, access, and affordability (21,22).

vii. CASE STUDIES:

Case studies and reviews provide valuable insights into the economic impact and challenges of orphan drug development and evaluation. They highlight the need for continued research, innovative funding models, and policy adjustments to support the development and accessibility of treatments for rare diseases.

Orphan Drug Development: Challenges, Regulation, and Success Stories

This review article, published in the Journal of Biosciences in February 2024, provides a detailed analysis of the challenges and successes associated with orphan drug development. It highlights various economic evaluations and the impact of regulatory policies on the development process. The article emphasizes the importance of collaboration between governments, regulatory bodies, industries, and patient advocacy groups to boost the development of orphan drugs. By working together, these stakeholders can overcome the financial and logistical challenges that often hinder the development of treatments for rare diseases. This comprehensive review also showcases successful case studies of orphan drugs that have made significant impacts on patient care and disease management (5).

Persisting Challenges for Orphan Drugs: Analyzing Three Case Studies on the Effects of NICE Methodology Changes and Innovative Approaches to Valuing Orphan Products

Published in PharmacoEconomics - Open in October 2022, this study explores the impact of the National Institute for Health and Care Excellence (NICE) methods on the assessment and approval of orphan drugs. The article presents three case studies - caplacizumab, teduglutide, and pirfenidone - to illustrate how changes in NICE methods and processes affect the valuation of these drugs. It discusses alternative mechanisms, such as quality-adjusted life-year (QALY) weights and fair rate of return methods, that could improve access to orphan drugs. The study provides valuable insights into the economic and regulatory challenges faced by orphan drugs, emphasizing the need for more flexible and innovative assessment methods to ensure patient access to essential treatments (23).

Regulatory requirements: Orphan drugs in various countries

Published in the International Journal of Pharmaceutical and Clinical Research in January 2024, provides a comprehensive analysis of the distinct regulatory requirements for orphan drugs across various countries. It investigates the regulatory frameworks set by organizations such as India's Central Drugs Standard Control Organisation (CDSCO), the US Food and Drug Administration (USFDA), the European Medicines Agency (EMA), Brazil's National Health Surveillance Agency (ANVISA), and the Saudi Food and Drug Authority (SFDA). Each regulatory body has developed specific criteria and processes for orphan drug designation and approval to address the unique challenges of treating rare diseases. The article highlights how these frameworks impact the economic aspects of orphan drug development, including the high costs and limited market potential. By comparing the regulatory approaches, the review underscores the importance of tailored incentives and support mechanisms that encourage the development of orphan drugs. These measures help offset financial challenges and promote innovation in the treatment of rare diseases, ultimately improving patient access to these vital medications. The article emphasizes the need for continued collaboration among governments, regulatory bodies, pharmaceutical companies, and patient advocacy groups to enhance the development and accessibility of orphan drugs globally (24).

Overview of FDA-Approved Orphan Drugs in 2022: A Pharmacological Perspective

This review article, published in Current Pharmacology Reports in January 2024, offers a scientific analysis of recently FDA-approved orphan drugs for various rare diseases. It covers a wide range of topics, including therapeutic applications, mechanisms of action, pharmacokinetics, adverse effects, doses, and special cases for these drugs. The article provides a detailed pharmacological profile of each drug, helping healthcare professionals understand their potential benefits and risks. By examining the latest orphan drugs, this review highlights the ongoing efforts to develop effective treatments for rare diseases and the complex challenges involved in bringing these drugs to market (25).

These case studies and reviews provide valuable insights into the economic impact and challenges of orphan drug development and evaluation. They highlight the need for continued research, innovative funding models, and policy adjustments to support the development and accessibility of treatments for rare diseases.

viii. FUTURE DIRECTIONS:

Collaboration:

Increased collaboration between biotech firms, pharmaceutical companies, and international health organizations can pool resources, knowledge, and expertise. This synergy boosts research and development efforts, accelerates the discovery of new treatments, and makes it easier to address the unique challenges posed by rare diseases. By working together, these entities can make significant strides in developing more effective and accessible treatments for those who need them most.

New Technology:

Advances in technology and medicines, such as personalized medicines and gene therapy, will improve the availability and efficacy of treatments, making it easier to address rare diseases (26).

Incentives:

Governments, the FDA, and the EU Commission provide incentives to support orphan drug development, including tax credits, market exclusivity, and funding for clinical trials (27).

New business models:

Orphan drugs could help pharmaceutical companies develop new areas of treatment, diagnosis, and patient support, expanding their market and improving patient outcomes (27).

Pooling investments:

Pooling investments into a single portfolio could lower the cost of developing drugs for rare diseases, making it more financially viable for companies to invest in orphan drug research (28).

New payment models:

New payment models and cross-payer collaboration could reduce technical inefficiencies in orphan drug reimbursement, ensuring that patients have access to necessary treatments without undue financial burden (29).

Multiple criteria decision analysis:

MCDA is an emerging value framework for orphan drugs, helping to evaluate their value based on various criteria, including clinical effectiveness, cost-effectiveness, and patient preferences drugs (9).

Profitability:

Orphan drugs can be more profitable than expected when considering developmental drivers like government incentives, smaller clinical trials, and higher regulatory success rates (30).

Patient access:

Drug authorities should develop or refine policies to optimize patient access to orphan drugs, ensuring that those who need these treatments can receive them promptly (31).

Post-approval monitoring:

Monitoring the post-approval use of orphan drugs to evaluate potential safety concerns is important for ensuring ongoing patient safety and drug efficacy (32).

III. CONCLUSION

The pharmacoeconomics of orphan drugs presents a complex and multifaceted landscape that balances the economic, ethical, and practical challenges of developing treatments for rare diseases. High development costs and limited patient populations necessitate innovative financial strategies and robust policy incentives to ensure the viability of orphan drug development. Cost-effectiveness analyses and Health Technology Assessments (HTAs) are critical tools in evaluating the economic value and clinical impact of these drugs, guiding decision-makers in healthcare policy and practice.

Policies such as market exclusivity, tax credits, and regulatory assistance play a vital role in encouraging pharmaceutical companies to invest in orphan drug development. However, the significant budget impact of these high-cost treatments requires careful management to maintain the sustainability of healthcare systems. Ethical considerations emphasize the need for timely access, affordability, and global cooperation to ensure that patients with rare diseases receive the treatments they need without exacerbating health inequities.

Case studies of successful orphan drug developments provide valuable insights into effective economic strategies and highlight the importance of tailored approaches in addressing the unique challenges of rare diseases. Future directions in the field include refining cost-effectiveness models, enhancing global regulatory harmonization, and exploring new funding mechanisms to improve access and sustainability.

Overall, a balanced approach that integrates economic, ethical, and practical considerations is essential for advancing the development and distribution of orphan drugs. By fostering innovation and ensuring patient access, pharmacoeconomics can significantly improve the quality of life for individuals with rare diseases and contribute to the sustainability of healthcare systems worldwide.

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