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Review Article

Orphan Drug Pricing and Cost Trends in USA: An Analysis of Impact of Orphan Drug ACT

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ABSTRACT

Objectives: The study analyses the impact of incentives in Orphan Drug Act on Orphan Drug revenue strategies of pharmaceutical and biotechnology companies in USA and proposes policies and steps to address the same. **Results:** There are 389 orphan drugs in circulation as of 2019 with average price of $32,000; prices ranging between $6,000 till more than $500,000. 39% of the marketed drugs costing more than $100,000 treats 23% of patient population. Out of 1.8 million treated patients in 2019, only 0.1% of patients received treatment with drugs having cost greater than $500,000. Orphan drug research and development spending by pharmaceutical and biotechnology companies was 11% of total expenditure of the companies in 2019. The high cost of orphan drugs remains an issue as overall 10% of impacted patient population receiving treatment. **Conclusion:** The Orphan Drug Act of 1983 has introduced various incentives for pharmaceutical companies to invest more in orphan drug research. It has been observed that there is increase in investment as well as orphan drug approvals because of the incentives and grants. Orphan Drug development is not aligning with the provided incentives and overall cost overall remains high, and availability of treatment is not as expected due to the high costs. Incentives to manufacturers needs to be balanced with treatment availability based on affordable pricing to ensure increased research and higher therapeutic coverage.

Keywords: Orphan Drug Act, Orphan drug, Rare Disease, Volume Based Contract, Outcome Based Contract, Value Based Pricing.

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INTRODUCTION

Any disease that affects less than 200,000 people in USA or any disease for which research and development costs are not expected to be recovered are generally regarded as "rare disease." There has been substantial progress in development and approval of drugs required for treating rare diseases in the last 40 years. These drugs are referred to as "Orphan Drugs". But significant unmet medical need still exists not only in USA but around the globe and almost 7000 rare diseases effecting millions of people remain to be treated with proper therapeutics.[1]

As there are unknown risks associated with development of orphan drugs; due to low patient population the economic benefits of cost recovery are difficult due to low revenue potential, as a consequence various incentives are provided by the Federal Government to promote research on rare diseases.[2] As mentioned in the provisions of The Orphan Drug Act (ODA) of 1983, US Government provides incentives for research and marketing of orphan drugs which includes research and clinical trial grants for academic and corporate sponsors of rare disease research, 25% tax credit on clinical trial expenditures, Prescription Drug User Fee Act (1992) marketing application fees waiver, access to FDA fast track approval, access to FDA's Investigational New Drug Program and pre-approval mechanism of drugs under development, and a seven-year market exclusivity provided by FDA for designated orphan drugs. During the seven-year period, FDA will not approve any new or generic drug application for the same disease or same product.[3]

The economic incentives are not sufficient to promote innovation in the long run and are also or unable to address the orphan drug pricing and treatment cost for patients and insurance companies.[4-6] From a value point of view, patients end up paying indirectly for orphan drug development through taxes and directly for purchasing the treatment.[7] Lack of significant development in orphan drug research area despite economic benefits to sponsors and increasing financial burden to all stakeholders,[8] due to rising cost of treatment is a major concern in the society. It is important to address both the treatment affordability of patients to increase therapeutic coverage as well as required incentives to promote research and development of orphan drugs.[9,10]

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MATERIALS AND METHODS

Analysis was performed on Orphan Drug designations and approvals obtained from Orphan Drug Database and Orange Book Database of FDA. Patient population and revenue information were taken from IQVIA reports. The information gave a view of orphan drug approval and pricing landscape in USA.

RESULTS

There has always been a lag between patient needs and available treatment. Along with that, rising cost of treatment, lack of adequate insurance coverage and premium pricing of drugs are contributing to bigger issues.[11] The primary health care cost factors associated with the expense of treating rare indications are inpatient care and cost of prescription medications. A small population of patients who require a lot of treatment resources often cause the average treatment cost to be skewed.[12] In addition, the significant degree of variation in healthcare needs, as well as the kind and cost of therapy, makes it difficult to conclude the incurred cost per patient or as per rare indication.[13]

Orphan Drug Cost Trends

As illustrated in Figure 1, in 2019, treatments ranged in cost from $6,000 to $500,000 per year, with an average yearly cost of $32,000 for each patient who received an orphan drug treatment. 389 drugs were in circulation as in 2019.[2,4,14]

As per insurance or payer data, there has been increase in patient population receiving treatment with annual cost greater than $1 million. 77% of patients with population of about 1.4 million, received treatment with annual cost up to $100,000 out of which 52% of patients with a population of 0.94 million, received treatment with annual costing less than $50,000.[15]

Annual cost of treatment with 39% or 152 of listed orphan drugs cost higher than $100,000 but covers only 23% or 0.4 million of patient population. Hence, treatments with high costs are prescribed to a smaller number of patients. Specialty treatments involving gene and cell therapies are costlier with pricing starting from several thousand dollars. Treatments with annual cost more than $500,000 are extended to less than 0.08% or 0.014 million of treated patient population.

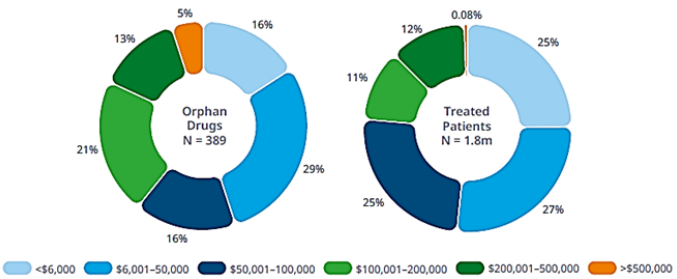

Figure 1: Orphan Drugs and Patients Treated by drugs with an orphan indication in 2019 by Annual Drug Cost Bands. Adapted from Orphan Drugs in the United States: Rare Disease Innovation and Cost Trends through 2019: IQVIA Institute for Human Data Science. Dec 2020.

An orphan drug becomes a blockbuster if it costs $100,000 annually covering 10,000 patients and has the capability of generating $1 billion revenue annually. Few examples are Neurontin (Gabapentin) from Pfizer, Gleevec (Imatinib) from Novartis, Alimta (Pemetrexed) from Eli Lilly and Spiriva (Tiotropium) from Boehringer Ingelheim.[13,15]

Orphan Drug Price Growth Trend (1993-2017)

When comparing orphan drug price trend of 25 years, as illustrated in Figure 2, it is observed that increase in orphan drug price increases have been slower than non-orphan drug price for much of the decade of 2010, while being higher than the market in the 1990s.[2,15] The higher price growth is noteworthy considering that many orphan medications licenced in the 1990s were older generic drugs that were repurposed, and their pricing were adjusted to the new targeted patient demographics.[16] Drug prices have fluctuated across the market, but those that gain an orphan designation (whether novel or repurposed) have continuously increased at a slower rate than the market.[17]

DISCUSSION

Factors contributing to high price of Orphan Drugs

Concentration of research on specific therapeutic class

Oncology contributed to 32% of orphan designations while other individual therapeutic classes hardly crossed 10%. As a result, only oncology has shown growth in orphan drug designation which caused overall growth in orphan drug market.[18] The concentration of research in the field of oncology makes it the rapidly growing and highly lucrative therapeutic class. As a result of this, other areas of rare diseases are not given much attention. This results in low availability of treatment for certain disorders thereby raising the overall cost due to demand of drugs.[19]

Less Payer coverage and increasing pressure on insurance companies for increasing cover

Due to recent scientific advances and regulatory flexibility, there are significant number of orphan drugs awaiting approval and more are in the budgetary pipeline of pharmaceutical companies.[20] Orphan Drugs being good revenue generator segment, there is increased focus of manufacturers and sponsors to invest more. Previously, rare disease treatment coverage by payers was not significant and there was no clear roadmap for the payer companies for addressing rare disease treatment coverage.[21] Payers are now confronted with additional issues in the management of orphan pharmaceuticals as a result of demand from patient advocacy organizations, clinicians, and plan sponsors to increase access and reduce healthcare spending.[22] There has been no new policy brought in by the payer companies

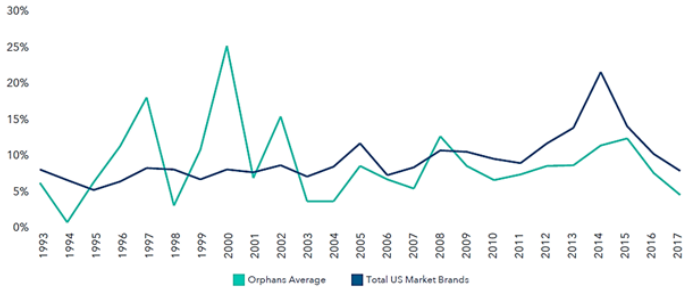

Figure 2: Average price growth trend, orphan versus branded drug market, 1993-2017. Adapted from Orphan Drugs in the United States: Exclusivity, Pricing and Treated Populations. IQVIA Institute for Human Data Science. Dec 2018.

to address rare disease coverage and it is expected to follow pathways similar to that of non-orphan and specialty drugs. The covered benefits may not be able to address needs as per specific orphan conditions which may not reflect as an efficient price control or treatment benefit outcome.[23]

Lack of competition due to Orphan Drug Exclusivity

The FDA is not permitted to approve a new brand name or generic medicine application for the same product and for the same rare disease indication once a product has been granted orphan drug exclusivity of seven years.[24] However, a medicine can be approved for use in more than one indication, and no restriction is there on drugs that can be authorized for a given disease. Patients may profit from the availability of more therapy alternatives and price reductions brought about by increased competition if more medicines are allowed for certain rare diseases.[24] But non availability of branded alternatives still causes monopoly of specific brands thereby reducing the perceived benefit of therapy alternatives. But removing the exclusivity clause may remove a key incentive for investment in orphan drug research.[24]

Higher cost of perceived value of treatment

Individual cost of treatment is highly dynamic since many biologic agents, and expensive orphan drugs, fall under the category of "tier 4" drugs,[25] for which patients are required to cover between 20 and 33 percent of total costs under the increasingly prevalent private coinsurance-like plans in the United States.[26] Although more orphan pharmaceuticals enhance patients' health and quality of life, the expense of newer drugs restricts access of patients to quality healthcare.[27]

Non-alignment of incentives with perceived societal benefits

With new diagnostic techniques and understanding of specific causes of disease there have been rise in the number of orphan drug patients.[28,29] Whereas supply of effective treatment is still not as expected. The high cost of available treatments causes significant financial burden on patients, government aided healthcare programs and private insurers.[30] Lack of alignment of research grants and incentives with societal demographic and economic aspect has caused benefits to be skewed in favor of companies and neglected patient priorities. It is important to address every aspect of regulatory, clinical, and economic landscape to ensure rare disease patients get access to quality, affordable and effective treatments.[31]

Lack of clinical data to assess cost benefit effectiveness

There is lack of information about overall health status of a patient and pre-market cost strategy of a company related to Orphan Drugs. Due to this proper cost-benefit effectiveness assessment is not of proper quality.[32] Thus, it is still crucial to weigh the costs of economic incentives on orphan development initiatives against their overall advantages and enhancements in treatment outcomes. If not, there is a chance of exacerbating market imperfections and maintaining inefficiencies. Given the diversity of the medications authorized for orphan indications, study results should be evaluated with caution.[32]

Freedom of pricing and minimal competition

Drug manufacturers in the US negotiate with patient organizations and insurance companies but can set own initial prices as US market allows "free pricing". Additionally, competition between manufacturers has little impact on regulatory standards compared to price caps.[32] Due to the challenges in proving therapeutic equivalence and the rarity of large-scale trials by generic manufacturers, many orphan medications, particularly biotechnology products, have minimal competition even when exclusivity restrictions expire.[33] Hence these generics are still expensive with prices being only 20-25% less expensive than branded biologics.[34]

Proposals to address pricing issue

Adopt best practices from other regulated markets

Initiatives from Japan could be taken into consideration to solve the issue of commercial pharmaceuticals that have benefited from various incentives for orphan drug development (such as research and development support funds, fee waivers, and tax credits). Pharmaceutical companies in Japan are required to charge a 1% sales tax on orphan drugs with yearly gains of more than 100 million yen until the obtained government subsidies have been returned.[35] This provision has not caused any roadblock in orphan drug development and there has been approval of almost 100 orphan pharmaceuticals in the twelve years since the policy's enactment in 1993. Incentives given to one R&D company is returned by marketing company. This tax clause might potentially be transferrable. Profitable orphan pharmaceuticals would no longer receive government funding in this fashion, but less successful orphan drugs would continue to receive incentives.

Redefine Rare Disease and Orphan Drugs

Senators Metzenbaum and Kassebaum planned to introduce legislation that would clarify the definition of an orphan drug at the start of the 1990s.[36] The terms "orphan medication" and "rare disease" need to be redefined given the current state of medical technology, which heralds the advent of customized therapy, and the ageing of the population, which causes the emergence of new rare diseases By pursuing this goal, it would be possible to limit the therapeutic market for orphan pharmaceuticals, generate more uniform investment distribution among different therapeutic areas of rare diseases, and manage the number of indications for each condition.

Development of patient registry funded by Federal Government

In order to address the needs of patients, doctors, and payers and to effectively analyze the cost effectiveness of therapies, more sophisticated systems for collecting and analyzing observational data are required These data systems ought to be created to be able to record patient-reported outcomes that represent therapeutic effects on the patient and their families. By supporting rare condition registries, the federal government may speed up efforts to improve evidence generation with the aid of illness and patient groups.[24,36]

Orphan Drug price reduction through price control

Spending on orphan medications has risen with the expansion of orphan drug development. Increases in orphan medication volume and their greater cost are clearly visible in available data published by companies and market research agencies. The average annual orphan medication cost in 2017 was 25 times higher than that of non-orphan drugs.[37] An analysis by Institute for Clinical and Economic Review (ICER) revealed that there was huge gap in pricing of top 100 medicines by sales based on treated indications (Cost of therapy for orphan drugs was $150,854 which was 4.5 times that of nonorphan drugs which was $33,654 per patient). This gap needs to be addressed to effective price control measures.[37]

Prevalence and adoption of contracts based on supplied drug volume

Through guaranteed coverage, by encouraging participation and education of patient and payer, by ensuring fair market access and cost utilization, and by simplifying contractual clauses, contracts based on drug volume can be another strategy that could help the commercialization of rare drug products. While the government has historically utilised this type of contract to buy huge quantities of pharmaceuticals (such as vaccines), a similar strategy might be used in the orphan drug market. The government or a consortium of private payers might actively bargain to buy adequate orphan drugs to cover most or all of qualified patients with a specific rare ailment under this scenario. This will provide a clear picture of effected population and data around treatment coverage. A price specific to the concerned orphan indication could be established by the government or a private body consortium under the contract. A simple and understandable contract, better patient accessibility, and utilisation that can be predicted would be advantageous to manufacturers as this will help in better price forecast and cost planning.[36] The adaptability of this policy by manufacturers needs to be seen as it is indirectly taking out price fixing authority.[37]

Patient Assistance Programs (PAP's)

Many patients find great value in patient assistance programmes, which are often the cornerstone of orphan medication company marketing campaigns. The level of financial aid varies depending on the patient's specific income and could involve other organizations. These initiatives provide eligible patients with a limited supply of free medications. Initiatives provided and managed by National Organization of Rare Diseases (NORD), help covered patients with their insurance premiums and co-payments. 34 patient support initiatives that NORD manages on behalf of orphan medicine producers are listed on its website.

CONCLUSION AND SUMMARY

Although multiple factors like scientific advances, regulatory flexibility, lack of competition and accelerated FDA approval pathways are facilitating orphan drug development and increasing the orphan drug market attractiveness to sponsors, still high pricing remains an issue. An analysis of orphan drug landscape throws conflicting results about lack of treatment availability for majority of rare diseases despite increasing innovation and market approvals. Additionally, attention is being redirected away from economic incentives that were implemented to encourage innovation and toward other elements that will encourage long-term and economically viable investments. By lowering treatment and insurance affordability and accessibility, increasing financial strain threatens to undermine the anticipated benefits of orphan drug innovation and exacerbate the already existing problem with premium pricing. Despite these difficulties, patients and their families frequently have no other option but to rely on orphan medications. As a result, it is crucial to continue developing and promoting safe and efficient medicines to meet the health demands of rare disease patients. Adoption of proposed policies may be able to address the high price concern. Price restriction would not impede the research and development of orphan treatments because it would affect all pharmaceuticals,

not just those that target orphan diseases. Additionally, concerns over profitable and exorbitantly priced orphan medications would be addressed. The fundamental inducement for the development of orphan pharmaceuticals, the seven-year exclusivity period for orphan drugs, would be unaffected. Finally, producers would continue to have the opportunity to generate significant profits, enabling returns on investment and economic expansion.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

JSSCP: JSS College of Pharmacy; **JSS AHER:** JSS Academy of Higher Education and Research.

REFERENCES

1. Miller KL, Fermaglich LJ, Maynard J. Using four decades of FDA orphan drug designations to describe trends in rare disease drug development: substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases. Orphanet J Rare Dis. 2021;16(1):265. doi: 10.1186/s13023-021-01901-6, PMID 34107994.
2. Aitkin M, Kleinrock M. Orphan drugs in the United States: Exclusivity, pricing and treated populations. IQVIA institute for human data science. 2018. Available from : https://www.iqvia.com/insights/the-iqvia-institute/reports/orphan-drugs-in-the-united-states-exclusivity-pricing-and-treated-populations [cited 5-1-2023].
3. Orphan drugs in the United States: An examination of patents and orphan drug exclusivity. National Organization for Rare Disorders. 2021. Available from: https://rarediseases.org/wp-content/uploads/2021/03/NORD-Avalere-Report-2021_FNL-1.pdf [cited 5-1-2023].
4. Aitkin M, Kleinrock M, Munoz E, Porwal U. Orphan drugs in the United States: Rare disease innovation and cost trends through 2019. IQVIA institute for human data science. 2020. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states-rare-disease-innovation-and-cost-trends-through-2019/orphan-drugs-in-the-united-states.pdf [cited 5-1-2023].
5. Bagley N, Berger B, Chandra A, Garthwaite C, Stern AD. The Orphan Drug Act at 35: Observations and an outlook for the twenty-first century. Innov Policy Econ. 2019;19(1):97-137. doi: 10.1086/699934.
6. Gericke CA, Riesberg A, Busse R. Ethical issues in funding Orphan Drug Research and Development. J Med Ethics. 2005;31(3):164-8. doi: 10.1136/jme.2003.007138, PMID 15738438.
7. Bouwman ML, Sousa JJS, Pina MET. Regulatory issues for Orphan Medicines: A review. Health Policy Technol. 2020;9(1):115-21. doi: 10.1016/j.hlpt.2019.11.008.
8. Hyde R, Dobrovolny D. Orphan Drug Pricing and payer management in the United States: are we approaching the tipping point? Am Health Drug Benefits. 2010;3(1):15-23. PMID 25126305.
9. Kaltenboeck A, Pearson SD, Mehlman A. Strengthening the accelerated approval pathway: An analysis of potential policy reforms and their impact on uncertainty, access, innovation, and costs. Institute for Clinical and Economic Review. 2022. Available from: https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway--ICER-WhitePaper--April-2021.pdf [cited 5-1-2023].
10. Rodriguez-Monguio R, Spargo T, Seoane-Vazquez E. Ethical imperatives of timely access to orphan drugs: Is possible to reconcile economic incentives and patients' health needs? Orphanet J Rare Dis. 2017;12(1):1. doi: 10.1186/s13023-016-0551-7, PMID 28057032.
11. Wellman-Labadie O, Zhou Y. The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity? Health Pol. 2010;95(2-3):216-28. doi: 10.1016/j.healthpol.2009.12.001, PMID 20036435.
12. Maas A. Better cost-sharing approaches can help patients on orphan drugs. AIS Health. 2008. Available from: http://www.aishealth.com/DrugCosts/specialty/SPN_Orphan_Drugs.html [cited 5-1-2023].
13. Chandra A, Garthwaite C. The economics of indication-based drug pricing. N Engl J Med. 2017;377(2):103-6. doi: 10.1056/NEJMp1705035, PMID 28700848.
14. Emerging market solutions for financing and reimbursement of durable cell and gene therapies. Massachusetts Institute of Technology new drug development paradigm initiative. 2021. Available from: https://newdigs.mit.edu/sites/default/files/FoCUS-WP-CGT-Market-Solutions.pdf [cited 5-1-2023].
15. Resources for applicants and grantees. U.S. Food and Drug Administration. FDA. 2022. Available from: https://www.fda.gov/industry/developing-products-rare-diseases-conditions/resources-applicants-and-grantees [cited 5-1-2023].
16. Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL, Visaria J. Incentives for Orphan Drug Research and development in the United States. Orphanet J Rare Dis. 2008;3(1):33. doi: 10.1186/1750-1172-3-33, PMID 19087348.
17. Hyry HI, Roos JCP, Manuel J, Cox TM. The legal imperative for treating rare disorders. Orphanet J Rare Dis. 2013;8(1):135. doi: 10.1186/1750-1172-8-135, PMID 24010951.
18. Handfield RB, Feldstein J. Insurance companies' perspectives on the Orphan Drug Pipeline. Am Health Drug Benefits. 2013;6(9):589-98. PMID 24991385.
19. Pearson SD, Dreitlein WB, Henshall C, Towse A. Indication-specific pricing of pharmaceuticals in the US Healthcare System. J Comp Eff Res. 2017;6(5):397-404. doi: 10.2217/cer-2017-0018, PMID 28699779.
20. Rare diseases. National Institutes of Health. United States Department of Health and Human Services. 2022. Available from: https://www.nih.gov/about-nih/what-we-do/nih-turning-discoveryinto-health/rare-diseases [cited 5-1-2023].
21. Chambers JD, Silver MC, Berklein FC, Cohen JT, Neumann PJ. Orphan drugs offer larger health gains but less favorable cost-effectiveness than non-orphan drugs. J Gen Intern Med. 2020;35(9):2629-36. doi: 10.1007/s11606-020-05805-2, PMID 32291711.
22. Ollendorf DA, Chapman R, Pearson SD. Assessing the effectiveness and value of drugs for rare conditions. Industry council for electronic equipment recycling. 2017. Available from: https://icer.org/wp-content/uploads/2020/10/ICER_Assessing-the-Value-of-Drugs-for-Rare-Conditions_051017.pdf [cited 5-1-2023].
23. Modifications to the ICER value assessment framework for treatments for ultra-rare diseases [review]. 2017.
24. Pearson C, Schapiro L, Pearson SD. The next generation of Rare disease drug policy: Ensuring both innovation and affordability. J Comp Eff Res. 2022;11(14):999-1010. doi: 10.2217/cer-2022-0120, PMID 35946484.
25. Patient assistance programs, medication specific assistance programs. NORD (National Organizationfor Rare Disorders). 2022. Available from: https://rarediseases.org/for-patients-and-families/help-access-medications/patient-assistance-programs-2/ [cited 5-1-2023].
26. Livingston S. CIGNA aims to expand affordable access to gene therapies. Mod Healthc. 2019.
27. Search orphan drug designations and approvals. US Food and Drug Administration. 2022. Available from: accessdata.fda.gov. Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/ [cited 5-1-2023].
28. Murrin S. High-expenditure Medicare drugs of ten qualified for Orphan Drug Act incentives designed to encourage the development of treatments for rare diseases. OEI-BL-20-00080 09-28-2021. Department of Health and Human Services. 2021. Available from: https://oig.hhs.gov/oei/reports/OEI-BL-20-00080.asp [cited 5-1-2023].
29. Kaufmann P, Pariser AR, Austin C. From scientific discovery to treatments for rare diseases – the view from the National Center for Advancing Translational Sciences – Office of Rare Diseases Research. Orphanet J Rare Dis. 2018;13(1):196. doi: 10.1186/s13023-018-0936-x, PMID 30400963.
30. Glover GJ. The enduring role of orphan drug exclusivity for biologics. Pharmaceutical law group. 2021. Available from: https://www.pharmalawgrp.com/blog/13/the-enduring-role-of-orphan-drug-exclusivity-for-biologics/ [cited 5-1-2023].
31. Padula WV, Parasrampuria S, Socal MP, Conti RM, Anderson GF. Market exclusivity for drugs with multiple orphan approvals (1983-2017) and associated budget impact in the US. Pharmacoeconomics. 2020;38(10):1115-21. doi: 10.1007/s40273-020-00934-2, PMID 32533523.
32. Braun MM, Farag-El-Massah S, Xu K, Coté TR. Emergence of orphan drugs in the United States: A quantitative assessment of the first 25 years. Nat Rev Drug Discov. 2010;9(7):519-22. doi: 10.1038/nrd3160, PMID 20531273.
33. Clinical trial and natural history study grants. U.S. Food and Drug Administration. FDA; 2020. Available from: https://www.fda.gov/industry/about-orphan-products-grants [cited 5-1-2023].
34. Developing products for Rare Diseases and Conditions. U.S. Food and Drug Administration. FDA. 2022. Available from: https://www.fda.gov/industry/developing-products-rare-diseases-conditions [cited 5-1-2023].
35. Berdud M, Drummond M, Towse A. Establishing a reasonable price for an orphan drug-Cost effectiveness and Resource Allocation. Office of Health Economics. 2020;18(1):1-8.

36. Fagnan DE, Gromatzky AA, Stein RM, Fernandez JM, Lo AW. Financing drug discovery for Orphan Diseases. Drug Discov Today. 2014;19(5):533-8. doi: 10.1016/j.drudis.2013.11.009, PMID 24269746.

37. Hemphill TA. Extraordinary pricing of Orphan Drugs: Is it a socially responsible strategy for the U.S. pharmaceutical industry? J Bus Ethics. 2010;94(2):225-42. doi: 10.1007/s10551-009-0259-x.

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