International Journal of Advanced Research and Review

www.ijarr.org

Global Regulatory Operations for Rare Diseases: Overcoming Submission and Approval Barriers

Author Name**: Sharath Reddy Venna**
Role: Senior Manager Regulatory Operations/Informatics
Affiliation: Leadiant Biosciences, USA
Email: vennasharath@gmail.com

Abstract: *The operations of rare diseases have challenges on submission and approval by the regulators because there are many requirements that need to be met, costly and patients affected are few. This paper aims to assess the contribution of global regulatory agencies towards the streamlining of orphan drug approvals. In this paper, with the help of the analysed literature and identified cases, it is examined that includes the aspects of pricing, risk factors, and shifts in regulations. It shows that there is a requirement to increase the number of policies to be adaptive and to have shorter cycling times as well as improving patient access. With these barriers, this study intends to contribute to the understanding of how rare disease drug approval can be made efficient across the world.*

Key Terms: Orphans medicines, rare diseases drugs, approval agencies, gene therapy, patients' treatment, fast-track approval, pricing issues.

I. Introduction

A. Background of the study

Rare diseases, which are characterised by low prevalence, are normally categorised as high-risk diseases in drug development and registration. Some of the challenges include limited patient populations and high research costs that are triggered by the complexity of clinical trials. The various regulatory bodies across the globe have laid down mechanisms that help in fast-tracking the approval systems, however, there are differences in submission procedures and time taken for the review process [1]. It is, important to become acquainted with how regulatory operations occur at the global level to enable the elimination of those barriers, fast-track access to treatment for rare indications and spur innovation of such therapeutics.

B. Overview

This research will look into the global tendency of Orphan drug submission and approval worldwide. It covers pathways such as the regulatory pathways, the expedited programs and the harmonization between different agencies including the FDA (Food and Drug Administration

USA), the EMA (European Medicines Agency) and the PMDA (Pharmaceuticals and Medical Devices Agency, Japan). The challenge areas discussed in the study include the clinical trial data standards, orphan designation, and market access [2]. Drawing from this analysis, this paper avails the knowledge on the inefficiency of the current regulatory environment, the areas of regulatory excellence and the ways by which approval delays can be enhanced by Congress and other related authorities in varied countries across the world.

C. Aim and Objectives

The paper aims to understand the regulatory hurdles of rare diseases drugs across the world and give recommendations for the improvements of rare disease drugs submission and approvals. The objectives of these research are; 1) To analyse the main regulation's focal points in major markets worldwide. 2) To determine barriers to submission and approval of drugs and the extent of their effects on drug access. 3) To recommend the synchronization of regulatory approaches that may enhance the faster development of rare disease therapeutics internationally.

D. Problem statement

The presence of regulatory incentives such as orphan drug status and expedited approval programs, rare disease products undergo long submission and approval processes. Such differences in rules and policies across the globe also exacerbate the challenges to market access and education of therapy availability to patients. Thus, this research seeks to establish the key regulatory gaps and collaborative actions to enhance efficiency and shorten of approval time of rare disease therapies.

E. Scope and Significance

This study specifically examines general regulatory policies prevalent in the major markets of the Global Pharmaceutical industry with a comparison made with the emerging markets. It measures the limit and approval factors of the submission such as data demands, assessment and market entry hurdles. The outcome will be helpful for pharmaceutical companies, regulatory authorities and policymakers where several recommendations have been given that can help in the improvement of efficiency for approval of rare diseases drugs to ensure that there is improvement in the patient-centric access to medicine at the global level.

II. Literature Review

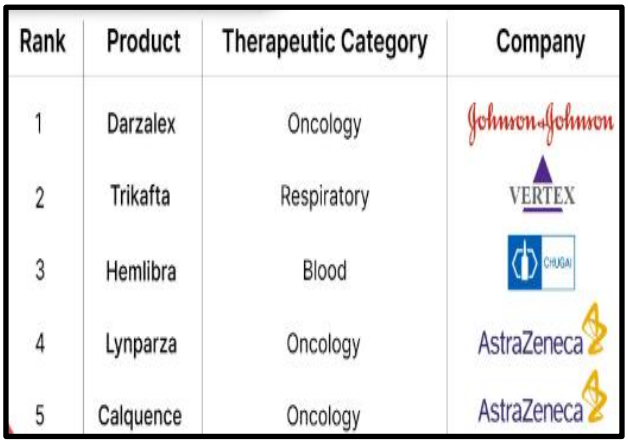
A. Regulatory Frameworks for Rare Disease Drug Approvals

Authorities like FDA, EMA, and PMDA have laid down guidelines to fast-track approval for rare disease treatments. The Orphan Drug Act (1983) in the United States included the tax credit, market exclusivity for devices, and faster approval for therapies for rare diseases [3]. Likewise, the EMA's Orphan Medicinal Product Regulation provides scientific advice and fee concessions concerning incentives for the development of orphan drugs within Europe. Similarly, Japan's PMDA also has a similar mechanism, providing priority review and regulatory support to rare disease treatments [4]. Nevertheless, there are some disparities in regulations of the trials, data, and approval processes. Furthermore, while FDA's Breakthrough Therapy Designation provides expedited approval the EMA's Adaptive Pathway hinges on Real-world evidence, and on the other hand, PMDA goes with expedited conditional approval [5]. Thus, the efforts made to harmonise these guidelines, like the ICH (International Council for Harmonisation) guidelines remain still

filled with certain challenges. Studies showed that realistic harmonisation of the submission requirements and review earlier than before could improve the utilisation of accessible treatments for rare diseases.

B. Barriers in Submission and Approval Processes for Rare Disease Drugs

Despite the motivation applied by the regulations, rare disease drugs have challenges such as a small market, enrolment, design of clinical trials and high costs of development. According to the literature, it is possible to acknowledge the opinion that the requirements for efficacy and safety contribute to increasing time taken for approval. For instance, RCTs (Randomised Controlled Trials) require patient recruitment in large numbers due to the need for sufficient subjects [6]. This is hard as patients diagnosed with rare diseases are few. Real-world evidence and adaptive trial designs have been offered as possible solutions although their adoptions differ between regulatory agencies.



Rank	Product	Therapeutic Category	Company
1	Darzalex	Oncology	Johnson & Johnson
2	Trikafta	Respiratory	VERTEX
3	Hemlibra	Blood	CHUGAI
4	Lynparza	Oncology	AstraZeneca
5	Calquence	Oncology	AstraZeneca

Figure 1: Examples of orphan drugs

Source: [20]

Another challenge is related to regulation disparity, or regional specificities of requirements for data submission, which can slow down submission across the world. The current research reveals the fact that although the FDA allows many surrogate endpoints for approval, in the case of EMA further post-marketing information is normally insisted upon while the PMDA has a different approach when it comes to condition approvals. Also, patient access is affected by pricing and reimbursement policies since pharmaceutical companies experience market access issues through health technology assessments (HTAs) [7]. Another challenge is the expenditure accrued in the course of developing a rare disease drug, thus restricting the amount of funding that can be assigned to research. Small and mid-sized biopharmaceutical manufacturers confront great financial risks, thus working with a venture capitalist or receiving state grants. Furthermore, such measures as post-approval assessment may also act as an inhibitor by prolonging market access and patient availability [8]. Overcoming these obstacles entails certain amendments in regulation, better coordination between the agencies, and the better implementation of digital health data for the simplification of the approval cycle.

C. Harmonization Strategies for Accelerating Global Approvals of Rare Disease Treatments

Calls for regulatory harmonisation have been considered in the most recent literature approaches that hold the potential for enhancing rare disease drug approvals globally. Despite this, some agencies have yet to achieve compatibility in their requirements with the help of ICH guidelines for standardizing regulatory expectations. One such approach is the Mutual Recognition Procedure (MRP) available in the European context, whereby approval in several states occurs after one evaluation [9]. In the same manner, the simultaneous scientific advice process of the FDA and EMA permits pharmaceutical industries to obtain feedback from both agencies in a single instance, thereby clearing common submission issues.

Another source is the collaboration of the FDA with Project Orbis which focuses on the pivotal idea of the simultaneous regulatory review being performed in different countries. For instance, changes in daily submissions by adopting eCTD (Electronic Common Technical Document) systems and artificial regulatory intelligence analytics for submissions across the world have been recommended [10]. The experts believe that an improved framework for sharing data and developmental information, experimental or real-life evidence as well as harmonized orphan designation criteria could have a great impact on the approval periods. These harmonization measures would help to drive faster market access for life-saving treatments of rare diseases hence benefiting patients worldwide.

III. Methodology

A. Research Design

This research uses ***explanatory research design*** to examine the regulatory issue and harmonisation of rare disease drugs approval. Exploratory research assists in establishing the relationship between the existing regulation standards, submission hurdles and approval delays [11]. Thus, the research will use several cases, policies, and drug approval statistics to enable the identification of effective measures to reform the global regulatory systems.

B. Data collection

This research adopted secondary data and included both qualitative and quantitative data sources. The sources of qualitative data are case studies, publications and research papers. Quantitative data includes existing data from the industry including graphs and charts. A summary of the comparisons made and any certain regulatory disparities is presented in the form of graphs, bar charts and trends. This mixed-methods approach allows a more comprehensive picture of the regulatory issues and possible solutions for rare disease drug approvals around the globe.

C. Case studies and example

Case 1: Zolgensma (Onasemnogene Abeparvovec) for Spinal Muscular Atrophy (SMA):

In May 2019, the FDA approved the name Zolgensma, it is a gene therapy product of Novartis and is used for the treatment of SMA in any patients who are below the age of 2 years. This was based on a pivotal clinical trial that established an improvement in the motor function of the study participants [12]. This in part calls out flexibility regarding the FDA in terms of the approval of innovative therapy for rare diseases especially from the accelerated approvals. Despite this, issues such as long-term safety concerns, and issues of pricing of the therapy, are seen to have attributed to some of the challenges of developing gene therapies.

Case 2: Vyondys 53 (Golodirsen) for Duchenne Muscular Dystrophy (DMD):

Vyondys 53 was approved in December 2019 by the FDA and directed to DMD patients candidate to exon 53 skipping. The approval process from the start was rejected and only after appealing a reason of safety was considered valid [13]. This case also factors in how regulatory assessments are constantly evolving and how safety data have to be tackled holistically to gain approval for compounds to treat such neglected diseases.

Case 3: Palynziq (Pegvaliase) for Phenylketonuria (PKU):

In May 2018, BioMarin Pharmaceutical got the FDA's approval to market Palynziq for adults with PKU, an inherited metabolic disorder. This was given based on clinical studies demonstrating the general lowered phenylalanine blood levels [14]. This case also shows how the FDA's Microscopic approach to approving, to rare disease therapies takes patient-reported outcomes, and real-world evidence into account.

The cases described in this article depict the complex aspect and issues surrounding global regulatory evaluation for the treatment of rare diseases, reveal the necessity and importance of adaptive approach on constructing and implementing new regulatory framework which also exhibit international cooperation for patients to gain better access to these novel therapies.

D. Evaluation metrics

This research employs some of the specific measures for evaluating the functioning of the rare disease regulation strategies. The number of days each reference took to approve drugs will be compared to determine efficiency, using the FDA, EMA and PMDA approvals as the main benchmark [5]. It will also determine the success rate of the orphan drugs as compared to other normal drugs which got approval. Concerning the measures of patient access, the price and location of service will be examined. Market safety data and regulatory compliance issues will be monitored on the long-term treatment concerning overall patient treatment safety and cure.

IV. Results

A. Data Presentation

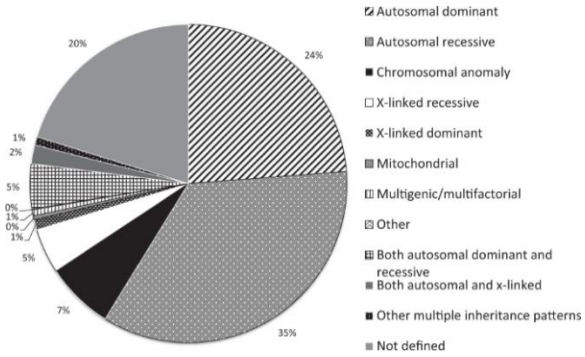


Figure 2: Estimating cumulative point prevalence of rare diseases

Source: [15]

It is revealed in the chart that 35% of rare genetic diseases occur through an autosomal recessive mode of inheritance, and the remaining 24% through an autosomal dominant pattern [15]. Together, these are the dominant patterns of inheritance implying that rare disease prevalence should be predominantly attributable to a monogenic causation. Importantly, 20% of it is defined that leaves significant diagnostic gaps and calls for more research and classification of genetics [15].

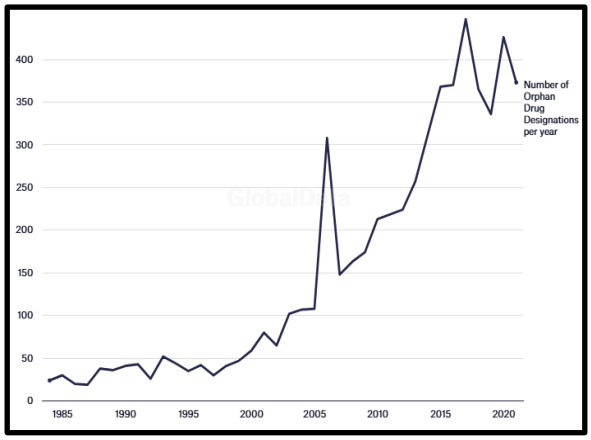


Figure 3: The number of orphan drug designation from 1983 to 2020

Source: [16]

The special graph shows total orphan drug designations by three time periods, 1983–2000, 2001–2010 and 2010–2021 [16]. It shows the constant trend where it designated only 568 in the first phase and increased to 1,527 in the second phase and again increased more than doubled in the third phase [16]. This can be attributed to a rise in regulatory measures aimed at encouraging ODs, the development of new therapies for rare diseases and the more and more attention of pharmaceutical companies to this area.

B. Findings

Graphical analysis shows an upward increase in progressive trend in the number of orphan drug designation which signifies the enhanced concern on the treatment of rare diseases. The image shows most rare genetic diseases caused from autosomal mechanism. The diagnostic uncertainty is manifested by the existence of undefined and complex categories that depict the developing profile of genetic classification. Thus, it highlights the need of more in depth genomic research to aid in the resolution of ambiguity toward application of targeted therapeutic development in rare conditions [15]. While between 1983 to 2000, 568 drugs got orphan status, the numbers transferred to the next one-and-a-half decades were 1,527 [16]. The total designations have increased from 2010 to 2021, and the rise was steep starting from 2015, implying a rise in regulatory approvals and investment in the industry. They include higher funding; progression in the technology in the field of biology, and patients' advocacy which have equally been instrumental in the discovery of these Scientific breakthroughs. The result also highlighted that further enhancement of regulatory support and effective procedures are highly crucial to maintain these changes in rare disease drug discovery.

D. Comparative Analysis

Authors	Focus	Findings	Gaps
[3]	Market expansion of eculizumab in rare diseases	Identifies patent dynamics, orphan drug designation, and licensing effects on revenues	Lacks broader comparison with other orphan drugs
[4]	Optimization of European orphan medicinal product landscape	Proposes guiding principles for improving orphan drug incentives [4]	Limited focus on regulatory challenges outside Europe
[5]	Regenerative medicine regulatory policies	Compares international regulatory frameworks for regenerative medicine [5]	Lacks detailed impact analysis on rare disease treatments
[6]	Guide to randomized controlled trials	Explains methodologies for conducting RCTs	Does not specifically address orphan drug trials
[7]	FDA's accelerated approval using surrogate endpoints	Suggests study designs balancing accelerated approval and post-market safety	Limited global applicability outside the FDA [7]
[8]	Innovation in U.S. biopharma industry	Examines financialization impact on	Lacks focus on rare disease treatments

		innovation	
[9]	Mutual recognition in European medicine regulations	Proposes a framework for increasing medicine access	Does not explore implementation challenges
[10]	Ethics committees for clinical trials	Highlights ethical considerations in global trials [10]	Focuses on Italy, limiting international scope

Table 1: Comparative analysis table

(Source: Self-developed)

C. Case study outcomes

Case	Outcomes	Relevance to Research
Zolgensma (Onasemnogene Abeparvovec) for SMA	FDA approval in May 2019 for patients under two years old. Demonstrated improved motor function in clinical trials. Highlighted regulatory flexibility for innovative gene therapies. Faced challenges related to pricing and long-term safety concerns [12].	Illustrates how accelerated approvals facilitate innovative treatments for rare diseases while also highlighting challenges in affordability and long-term monitoring.

Vyondys 53 (Golodirsen) for DMD	FDA initially rejected approval due to safety concerns but later approved it in December 2019 after an appeal. Demonstrates evolving regulatory assessment and the importance of comprehensive safety data [13].	Highlights the rigorous approval process and the necessity of strong safety evidence for orphan drugs, emphasizing regulatory barriers in rare disease treatments.
Palynziq (Pegvaliase) for PKU	FDA approved in May 2018 based on clinical trials showing reduced phenylalanine blood levels. Incorporated patient-reported outcomes and real-world evidence in approval decisions [14].	Demonstrates the role of real-world evidence and patient-centric approaches in regulatory decisions, which is crucial for rare disease drug approvals.

Table 2: Case study outcomes

(Source: Self-developed)

V. Discussion

A. Interpretation of Results

The evaluation of the literature and cases of studies showed the growing importance of flexibility to regulations in the approval of rare disease drugs. Organizations such as the FDA, EMA, and PMDA have come up with fast-track processes which have been evident in the approval of Zolgensma and Vyondys 53. These cases increase the accessibility of life-saving products, nevertheless, many have raised concerns about post-market safety and pricing issues. Also from the literature it is established that patient advocacy and cooperation with industry are some of the key aspects that dictate the outcome of the decision by the regulatory authorities.

B. Practical Implications

The study emphasises the need for the improvement of regulatory procedures to make approval of drugs for rare diseases more time-sensitive. The experiences implied in the success of accelerated approval pathways indicate that opening up more of such frameworks would be helpful to patients with unmet care demands. Also, cooperation between pharmaceutical companies, agencies, and patients' advocacy brings about the development of more effective drugs [17]. Nevertheless, orphan drugs remain expensive, thus the need for price reforms and improved insurance plans.

C. Challenges and Limitations

Some issues are still found in the process of regulation for rare disease fields. Specifically, the absence of a unified system of approval across the countries reduces the availability of drugs across different regions. The current pricing of the drugs remains high because their development costs are relatively high and the patient population for any specific orphan disease is generally small. Besides, the fast-track assessment may lead to poor long-term safety research, exposing patients to certain dangers [18]. Concerns are expressed concerning efficacy validation increased with the utilization of surrogate endpoints in clinical trials. Another challenge that slows down approval in small regulatory agencies is the limited funds and resources available for the task. These need to be addressed by coordinated action on the global level, sustainable pricing, and better follow-up after the products have reached the markets.

D. Recommendation

In order to enhance the operations of regulatory approval of drugs and products for use in rare diseases, there is a need to encourage international comparison so that there is fairness in provision across countries. It is therefore possible to have accelerated approval programs more frequently than now but at the same time, naming ways of seriously improving post-marketing surveillance so that the risks are controlled [19]. Close cooperation between the bodies and pharmaceutical firms as well as patient organizations will improve the speed and effectiveness of new developments and guidelines.

Governments should intervene and set some ceilings on the price to be paid for the drugs as well as provide subsidies for these drugs. Promoting real-world utilisation in the regulatory decision-making process would enhance the development of long-term safety analyses.

VI. Conclusion and Future Work

The study explored the issues concerning global regulations in operating concerning rare diseases where the policies involve flexibility of the approval process, the relationship between the industry

and patients and the advocacy of the patients. There has been some improvement in the global efforts to fast-track the drug approvals in the market, there are some issues like high costs of the drug, lack of consistent policy, and safety concerns.

Further research should be devoted to new approaches like Artificial Intelligence for drug discovery, flexible clinical trials and the use of real-life data in decision-making. More research on the regulatory agencies could also help reduce regulating time. These problems can be solved to ensure rare disease treatment research and approval processes are gradually made more fair across the World.

VII. References

[1] Groft, S.C., Posada, M. and Taruscio, D., 2021. Progress, challenges and global approaches to rare diseases. *Acta paediatrica*, *110*(10), pp.2711-2716.

[2] Mulberg, A.E., Bucci-Rechtweg, C., Giuliano, J., Jacoby, D., Johnson, F.K., Liu, Q., Marsden, D., McGoohan, S., Nelson, R., Patel, N. and Romero, K., 2019. Regulatory strategies for rare diseases under current global regulatory statutes: a discussion with stakeholders. *Orphanet Journal of Rare Diseases*, *14*, pp.1-10.

[3] Caetano, R., Cordeiro Dias Villela Correa, M., Villardi, P., Almeida Rodrigues, P.H. and Garcia Serpa Osorio-de-Castro, C., 2021. Dynamics of patents, orphan drug designation, licensing, and revenues from drugs for rare diseases: The market expansion of eculizumab. *Plos one*, *16*(3), p.e0247853.

[4] Aartsma-Rus, A., Dooms, M. and Le Cam, Y., 2021. Orphan medicine incentives: how to address the unmet needs of rare disease patients by optimizing the European orphan medicinal product landscape guiding principles and policy proposals by the European expert group for orphan drug incentives (OD expert group). *Frontiers in pharmacology*, *12*, p.744532.

[5] Qiu, T., Hanna, E., Dabbous, M., Borislav, B. and Toumi, M., 2020. Regenerative medicine regulatory policies: a systematic review and international comparison. *Health Policy*, *124*(7), pp.701-713.

[6] Bhide, A., Shah, P.S. and Acharya, G., 2018. A simplified guide to randomized controlled trials. *Acta obstetricia et gynecologica Scandinavica*, *97*(4), pp.380-387.

[7] Kraus, V.B., Simon, L.S., Katz, J.N., Neogi, T., Hunter, D., Guermazi, A. and Karsdal, M.A., 2019. Proposed study designs for approval based on a surrogate endpoint and a post-marketing confirmatory study under FDA's accelerated approval regulations for disease modifying osteoarthritis drugs. *Osteoarthritis and cartilage*, *27*(4), pp.571-579.

[8] Tulum, Ö., 2018. Innovation and financialization in the us biopharmaceutical industry. *Unpublished doctoral dissertation, Faculty of Economics, University of Ljubljana*, p.241.

[9] Škrnjug, I., Uzeirbegović, S., Romčević, M.L., Tomić, S., Meyer, H. and Conrad, C., 2019. Mutual recognition in the European system: A blueprint for increasing access to medicines?. *Regulatory toxicology and pharmacology*, *106*, pp.270-277.

[10] Naureen, Z., Beccari, T., Marks, R.S., Brown, R., Lorusso, L., Pheby, D., Miertus, S., Herbst, K.L., Stuppia, L., Henehan, G. and Falsini, B., 2020. Ethics committees for clinical experimentation at international level with a focus on Italy. *Acta Bio Medica: Atenei Parmensis*, *91*(Suppl 13), p.e2020016.

[11] Rahi, S., 2017. Research design and methods: A systematic review of research paradigms, sampling issues and instruments development. *International Journal of Economics & Management Sciences*, *6*(2), pp.1-5.

[12] Fda.gov, 2019. *FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality*. U.S. Food and Drug Administration. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease [Accessed 21 July 2022]

[13] FDA, 2019. *FDA grants accelerated approval to first targeted treatment for rare Duchenne muscular dystrophy mutation*. U.S. Food and Drug Administration. Available at: https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation.[Accessed 15 April 2022]

[14] FDA, 2019. FDA approves a new treatment for PKU, a rare and serious genetic disease. FDA. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pku-rare-and-serious-genetic-disease.[Accessed 25 May 2022]

[15] Nguengang Wakap, S., Lambert, D.M., Olry, A., Rodwell, C., Gueydan, C., Lanneau, V., Murphy, D., Le Cam, Y. and Rath, A., 2019. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. European Journal of Human Genetics, 28(28).

[16] Pharmaceutical-technology.com, 2021. Rare Disease Spotlight – Tracing the rise of orphan drug designations over almost 40 years. Pharmaceutical Technology. Available at: https://www.pharmaceutical-technology.com/features/rare-disease-spotlight-tracing-the-rise-of-orphan-drug-designations-over-almost-40-years/?cf-view&cf-closed [Accessed 25 June 2022]

[17] Stein, S., Bogard, E., Boice, N., Fernandez, V., Field, T., Gilstrap, A., Kahn, S.R., Larkindale, J. and Mathieson, T., 2018. Principles for interactions with biopharmaceutical companies: the development of guidelines for patient advocacy organizations in the field of rare diseases. Orphanet Journal of Rare Diseases, 13, pp.1-10.

[18] Berdud, M., Drummond, M. and Towse, A., 2020. Establishing a reasonable price for an orphan drug. Cost Effectiveness and Resource Allocation, 18, pp.1-18.

[19] Ahuja, V., A. Alvarez, C., Birge, J.R. and Syverson, C., 2021. Enhancing regulatory decision making for postmarket drug safety. Management Science, 67(12), pp.7493-7510.

[20] Wissenresearch, 2021. Orphan Drugs for Rare Diseases. Wissen Research. Available at: https://www.wissenresearch.com/orphan-drugs-for-rare-diseases/ [Accessed 5th March 2022]

[21] Chintale, P. (2020). Designing a secure self-onboarding system for internet customers using Google cloud SaaS framework. IJAR, 6(5), 482-487.

[22] INNOVATIONS IN AZURE MICROSERVICES FOR DEVELOPING SCALABLE", int. J. Eng. Res. Sci. Tech., vol. 17, no. 2, pp. 76–85, May 2021, doi: 10.62643/

[23] "The Role of Artificial Intelligence in Enhancing Data Security and Compliance in Cloud-Based Ecommerce Logistics Integration", int. J. Eng. Res. Sci. Tech., vol. 18, no. 3, pp. 176–185, Aug. 2022, doi: 10.62643/.

[24] "Intelligent Process Automation in S/4 HANA FICO: A Machine Learning Approach ", IJIEE, vol. 10, no. 2, pp. 57–70, Feb. 2020, doi: 10.48047/aqtbk646.