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Orphan Drugs: What are the Commercializing Strategies of Marketing Leaders of Orphan Drugs in APAC

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ABSTRACT

The Asia-Pacific (APAC) region presents a unique landscape for orphan drugs, catering to a population affected by rare diseases. This comprehensive article delves into the commercializationstrategies employed by marketing leaders within this domain. Orphan drugs, designed for diseasesimpacting a small fraction of the population, pose distinct challenges in pricing, regulatory compliance, and market access. The article explores the prevalence of rare diseases in APAC, outlining the diverse regulatory environments across countries like Japan, Taiwan, and China. It analyzes the market size, growth projections, and key players in the pharmaceutical industry focusing on orphan medications. The article highlights the regulatory hurdles, emphasizing the complexities arising from varied standards, certification procedures, and intellectual property rights. Additionally, it underscores the need for increased awareness, streamlined regulatory frameworks, and improved access to specialized care for individuals affected by rare diseases. Thearticle concludes by envisioning future prospects, including advancements in gene therapies and personalized medicine, that are poised to revolutionize the landscape of orphan drugs in the APACregion.

KEYWORDS: Orphan drugs APAC, rare diseases, commercializing strategies of orphan drugs, regulatory hurdles for orphan drugs, Market Landscape Rare Diseases APAC

INTRODUCTION

A medicine that has been produced especially to treat a rare medical condition known as an "orphan disease" is referred to as an orphan drug. Eighty percent of uncommon diseases have beenlinked to genetic causes. Other rare diseases are the result of infections (bacterial or viral) and allergies or are due to degenerative and proliferative causes **(Cortial et al., 2022)**. The major businesses have been compelled by the increasing number of rare disease cases to create cutting- edge remedies, which are expected to dominate the market in the coming years **(Tadepalli et al., 2022)**.

Delays in diagnosis and difficult access to care are caused by a lack of specialized health policy for uncommon diseases and a shortage of specialists. Overcoming a number of obstacles pertaining

to research and health technology assessment is necessary for the successful development of newmedicines for rare diseases and their long-term patient access **(Bouwman et al., 2020).**

The Rare Disease and Orphan Drug Act (the Act) was passed into law in Taiwan in 2000 with thegoals of promoting the prevention and early diagnosis of rare diseases, facilitating the research, development, and accessibility of orphan drugs and special nutritional foods, and offering patientswith rare diseases intensive care **(Lanar et al., 2020)**.

To some extent, special payment guidelines have been put in place for medications for rare diseasesand orphans. Orphan medications that are not covered by Australia's Pharmaceutical Benefits Scheme (PBS) may be covered under the Life-Saving Drugs Programme (LSDP), which offers 100% reimbursement **(Lopata et al., 2021)**.

In order to be available, orphan drugs need to be covered by national reimbursement programs. Developing partnerships with local health authorities and advocating for beneficial reimbursementschemes is crucial **(Thakur, 2022a).**

One of the main barriers to the commercialization of orphan drugs in APAC is the region's fragmented healthcare system and lack of awareness regarding rare illnesses among both patientsand doctors. Fewer people know that rare diseases even exist, and even fewer know about possibletreatments **(Pijeira Perez et al., 2023)**.

LITERATURE REVIEW

Orphan Drugs:

A tiny portion of the world's population is afflicted with orphan illnesses, more commonly knownas orphan diseases. Orphan medications are often prescribed for illnesses that impact fewer than 200,000 people in the US or a comparable small percentage of people in other nations **(Gorini etal., 2022)**.

They frequently have high pricing since they are costly to create and promote. Budget increases, more awareness, and standardized legislation are all necessary to enhance pricing and reimbursement. In addition, we may employ risk-sharing arrangements, offer funding, and employvalue-based pricing models more frequently **(Thaker et al., 2019a)**.

Different countries and regions have different definitions of uncommon diseases. A condition mustfulfil certain requirements in order to be designated as an orphan medication in Japan, such as having a prevalence of less than 50,000 patients **(Mao, 2021).**

In South Korea, a condition must normally have a prevalence of less than 20,000 patients in orderto qualify for orphan drug classification. Less than 10,000 patients with the condition must residein Taiwan in order for a medication to be eligible for orphan drug designation **(Patel, n.d.).**

Orphan drug landscape in the Asia Pacific:

Over 60% of the world's population resides in the Asia Pacific area, which is also a hotspot for uncommon illnesses. Thus there is a significant demand for orphan medications in this area. Over45 million individuals in Asia may be afflicted with a rare disease, with 10 million of those caseshappening in China alone **(Lim et al., 2019)**.

Clinical trials are being promoted in some Asian nations, such as South Korea, Taiwan, Singapore,and the Philippines, by the implementation of legislative frameworks like the US Orphan Drug Act **(Novotech)**.

Pharmaceutical firms seeking to address unmet medical needs are finding the area to be an increasingly attractive market due to the emergence of specialised regulatory frameworks in several nations **(Wilson-l-Orphan-Drugs-Ispor-Asia-Pacific-2020-Pdf)**.

Prevalence of Rare Diseases:

The WHO defines rare diseases as those that are uncommon, frequently crippling, or even fatal, with a prevalence of 0.65 –1. It is estimated that over 60 million individuals in APAC suffer fromone of the approximately 7,000 known rare diseases **(Song et al., 2012).** Factors contributing to this prevalence include the diverse genetic makeup of the population, variable access to healthcare,and improved diagnostics **(Patel, n.d.).**

The burden of rare diseases is substantial, emphasizing the need for increased awareness, improvedresearch efforts, and greater access to specialized care for affected individuals in the APAC region**(Shafie et al., 2016)**.

Regulatory Environment and Incentives:

The pharmaceutical industry is given a set of incentives and requirements under the Orphan Drugs Act to produce pharmaceuticals for the treatment of uncommon diseases. Actually, compared to before the orphan drug legislation, a considerably higher number of orphan medications have beenapproved at the centralized level **(Bouwman et al., 2020)**.

The regulatory environment of every country is different. We have discussed some of them:

Australia:

The Therapeutic Goods Rule, 16 H, defines an orphan drug as follows in Australia:

It has to meet one of two requirements: either it can only be supplied commercially to treat, prevent, or diagnose a rare disease, or it must be intended to treat, prevent, or diagnose a differentdisease or condition **(Neelakandan et al., n.d.).**

Incentives: There are two types of incentives to ensure availability and access to orphan drugs. We summarize these below:

1. **Financial Incentives:** Incentives mainly focus on national strategy, expedited approval(accelerated review and approval, priority review and approval, conditional approval), safety and efficacy requirements (clinical trial exemption, acceptance of overseas clinical trial data), exclusivity (data protection, market exclusivity) **(Zhao et al., 2023)**.

2. **Non-Financial Incentives:** These consist of accelerated clearance; pre-licensing access (off- label or compassionate); and scientific advice, which includes free protocol support and development consulting **(Thaker et al., 2019b).**

Review Process for Orphan Drugs in Australia:

The pre-submission meeting is arranged with TGA 3-6 months prior to the date of registration application submission. Within approx. 3 months designation application is recommended The designation application is assessed against relevant eligibility criteria and the designation decisionis made by the Chief Medical Advisor **(Neelakandan et al., n.d.)**.

Japan:

Orphan Drug Designation System: Japan created the Orphan Drug Designation System, which offers tax breaks, subsidies, and priority reviews as well as other incentives to encourage the development of therapies for rare diseases. The government offers financial assistance for the treatment of some orphan diseases and has instituted a fast-track review procedure **(Shivam Zalke).**

Taiwan:

The Rare Disease and Orphan Drug Act (the Act) was passed in Taiwan in 2000 with the intentionof providing patients with rare diseases with intensive care, encouraging the prevention and earlydiagnosis of rare diseases, and facilitating the research, development, and accessibility of orphan drugs and special nutritional foods **(Hsiang et al., 2021)**.

China:

China has announced plans to lower the Value Added Tax (VAT) on 21 rare illness therapies andfour active pharmaceutical ingredients by 80% in an attempt to grow the domestic rare disease therapy market **(Credevo)**. In recent years, China has also begun to publish a number of positive policies regulating the research and approval of orphan drugs. However, in the 1980s, the FDA introduced the Orphan Drug Act, and in the 1990s, Japan started a government-led assistance campaign **(Mao, 2021)**.

Market Size and Growth:

The market for orphan pharmaceuticals in Asia-Pacific is projected to reach US$35.08 billion in 2021 and grow at a compound annual growth rate of 8.92 percent during the course of the forecastperiod (2021-2030**) (Insights 10*).*** The market for orphan disease drugs in Japan is expected to expand at a compound annual growth rate (CAGR) of 10.80% from $9.623 billion in 2022 to
$21.858 billion by 2030. In Japan, hemophilia, Gaucher disease, and Morquio syndrome are among the most prevalent orphan diseases **(Shivam Zalke et.al.).**

Market Leaders in Orphan Drugs:

The few noteworthy businesses that are involved in the APAC orphan medication industry and arehighlighted in this research are: Novartis, Glaxo Smith Kline, Roche, Alexion, Sanofi, Bristol Myers Squibb, Pfizer, Vertex, Celgene, Merck. **(https://www.marketdataforecast.com/market-reports/asia-pacific-orphan-drugs-market)**

The Top Selling Orphan Drugs are:

The top-selling orphan drugs globally are Revlimid, Darzalex, Rituxan, Tafinlar, Ninlaro, Imbruvica, Myozyme, Soliris, Jakafi, Kyprolis **(Mordor Intelligence).**

Myelodysplastic syndrome and multiple myeloma are conditions that are treated with the medication revlimid, also known as lenalidomide. It is used for multiple myeloma after at least one previous therapy and in combination with dexamethasone **(Insight Partner)**.

Drug	Uses
Keytruda	melanoma, lymphoma, urothelial carcinoma,
Revlimid	Multiple myeloma, Follicular Lymphoma,
Trikafta	Cystic Fibrosis
Imbruvica	Mantle Cell Lymphoma; Chronic Lymphocytic Leukemia;
Darzalex	Multiple Myeloma
Soliris	Paroxysmal Nocturnal Hemoglobinuria, Hemolytic Uremic Syndrome,
Jakafi	Myelofibrosis

Source:Biospace

Profile of Key Market Leaders: The table below lists the top ten global market leaders fororphan drugs. Johnson & Johnson's orphan medicine prescription sales up to 2026 are expected toreach 22 US billion dollars, according to Melanie Senior and Andreas Hadjivasiliou's Orphan DrugReport 2022 **(ORPHAN DRUG, 2022).**

Orphan Prescription Sales($bn) in 2026	Company Name
22	Johnson & Johnson
18.6	AstraZeneca
15.8	Roche
13.2	Novartis
12.2	AbbVie
11.3	Bristol Myers Squibb
10.8	Sanofi
10.1	Vertex Pharmaceuticals
8	Takeda
7.7	Pfizer

Source: (ORPHAN DRUG,2022)

Market Share and Dominance:

Share of Worldwide Orphan Drug Sales by Therapeutic Category:

The segmentation of the orphan drug market is based on the treatment class, which comprises blood, endocrine, cardiovascular, respiratory, oncology, and central nervous systems **(Kinjoli Dey)**. The Evaluate Pharma report 2022 states that the pharmaceuticals in the oncology class holda 48 percent market share, while the drugs in the blood disease class hold a 15 percent market share. The drugs in the respiratory and central nervous systems each have a 9 percent market share.**(Evaluate Pharma)**

Share of some of India's Rare Disease therapies by Molecule Type:

India leads at 19% in Enzymes, 12% in synthetic peptides, 11% in inactivated vaccines, 10% in recombinant proteins, 9% in toxoid vaccines, and 8% in conjugate vaccines (Akosua Mireku and Irena Maragkou, 2023)

Regulatory Hurdles:

Businesses and stakeholders in the Asia-Pacific (APAC) region have expressed serious concerns about regulatory obstacles. Smooth market entrance and operations are hampered by the APAC nations' complex and varied regulatory environment **(Franco, 2013).**

Many other regions, including the European Union (EU), Australia, Japan, and Taiwan, have nowadopted orphan drug-specific legislation, which was first implemented by the USA **(Yu- Jun Huang, 2023).**

The region's differences in standards, certification procedures, and intellectual property rights haveincreased the complexity of the regulations. The absence of coherence in the regulatory landscapeof the area has resulted in heightened expenses associated with compliance and challenges for multinational enterprises seeking entry into the market, underscoring the necessity of a more unified and standardized regulatory framework in APAC **(Khosla & Valdez, 2018).**

For the past 40 years, ODA (Orphan Drug Act, 1983) has successfully encouraged R&D investments to generate innovative pharmaceutical solutions for the treatment of rare diseases in numerous nations. The two most populous nations, China and India, do not have nationalregulations pertaining to orphan pharmaceuticals or uncommon diseases **(Gubyal VarshithKumar, et.al., 2022).**

The patent system in India prohibits pharmaceuticals from being evergreened, and a sizable generic manufacturing sector offers plenty of opportunity to investigate the possibilities of repurposed medications, sometimes known as repurposed orphan therapies, for the treatment of RDs **(Rajueni & Chakraborty Choudhury, 2023**).

Opportunities:

To increase access to readily available and reasonably priced orphan medications, policies that promote market availability as well as research and development should be taken into consideration. Singapore, Japan, Australia, South Korea, and Taiwan are among the several authorities that have enacted orphan drug laws for their respective regions **(Chan et al., 2020)**.

Commercializing orphan drugs in the Asia-Pacific (APAC) region presents a unique set of opportunities. As the region witnesses a rising burden of rare diseases, including lysosomal storagedisorders, rare genetic diseases, and rare cancers, there is a growing need for orphan drugs **(Hughes& Poletti-Hughes, 2016)**.

In order to remove obstacles to healthcare and social welfare services for people affected by rare diseases, the Asia-Pacific Economic Cooperation (APEC), an intergovernmental conference for 21member nations in the Asia-Pacific Region, issued an action plan for rare diseases in 2025 **(Akosua Mireku, 2023)**

Additionally, the APAC market, with its burgeoning middle class and increasing healthcare expenditure, offers a substantial market potential for pharmaceutical companies focusing on orphan drugs **(Harada et al., 2020)**

Collaborations between local and international pharmaceutical companies, as well as advancements in biotechnology, are further facilitating the commercialization of orphan drugs in the region **(Kang et al., 2019).**

Commercialization Strategies for Orphan Drugs in APAC

Market research and access:

The first step towards commercializing orphan medications is market research. It is crucial to comprehend the incidence of uncommon illnesses in the various APAC nations and to pinpoint patient populations **(Adachi et al., 2023).** The APAC region's orphan drug regulatory environments are very different from one another. It is essential to have a thorough understandingof regulatory standards, including orphan drug designation and approval procedures **(Yi et al., 2023).**

Pricing and Reimbursement Strategies:

Because the patient populations for orphan pharmaceuticals are generally limited, it might be difficult to determine a suitable price approach. The nations in the Asia-Pacific area have differingdegrees of economic development. It can be difficult to consistently price a medicine in this broadmarket **(Schmid et al., 2007).**

Asia offers a huge potential for the commercialization of orphan medicines (OD) for uncommon illnesses due to its large population and notably high GDP growth rates **(Sherwin et al., 2014).**

Orphan medications must be included in national reimbursement programmes in order to be accessible. It is essential to form alliances with regional health authorities and promote reimbursement systems that are advantageous **(Lu et al., 2015).**

Pricing Considerations:

Pharmaceutical firms must take into account several considerations when setting the price of orphan pharmaceuticals, such as the development costs, the product's value to patients, the availability of substitute therapies, and the reimbursement rules of the countries where the productwill be marketed **(Hu & Mossialos, 2016).**

Value-based pricing enables pharmaceutical companies to set the price of their goods according tothe benefits they offer to patients and the healthcare system **(Verghese et al., 2019a)**.

A few nations have put in place certain regulations to assist with the cost of orphan medications, including South Korea and Japan. These regulations might include price surcharges, loosened guidelines for pricing, or accelerated evaluations of reimbursements **(Lee, 2021).**

Reimbursement Considerations:

In the Asia-Pacific area, orphan medication reimbursement is another complicated matter. Every nation in the area has a distinct set of reimbursement laws. The kinds of medications that are covered, the amount of reimbursement, and the conditions that patients must fulfil in order to get payment for their prescription pharmaceuticals might all differ across these policies **(Wilson, 2020)**.

Adopting regulatory frameworks that enhance the licensing, pricing, reimbursement, and researchand development processes of orphan medicines is one practical approach to address the unfulfilledmedical requirements of individuals with rare illnesses **(Chan et al., 2020)**.

Budgets for healthcare are tight in many of the region's nations, and orphan medications are frequently costly. Additionally, orphan drug firms may find it challenging to negotiate acceptablereimbursement rates due to the tiny patient populations for uncommon illnesses **(Lin et al., n.d.)**.

Early access programs:

EAPs give patients with uncommon illnesses access to orphan medications prior to their commercialization approval. For orphan drug firms, this can be a useful tactic since it enables themto gather information on the efficacy and safety of their drugs in a real-world environment **(Rana & Chawla, 2018)**.

Market access partnerships:

For orphan pharmaceuticals in Asia-Pacific, forming market access relationships with regional pharmaceutical corporations is another important commercialization approach. These collaborations can assist orphan medicine firms in navigating the APAC region's complicated andsometimes disjointed healthcare systems **(Attwood et al., 2018)**.

Patient support programs:

In APAC, patient assistance initiatives can be a useful commercialization tactic for orphan medications. Patients may be able to get financial support, information, and other services throughthese programs. Patient support programs can enhance treatment compliance and patient outcomes,which can benefit orphan drug firms financially **(KidStock, n.d.).**

Real-world evidence:

RWE refers to patient data that is gathered from actual settings, such claims data and electronic health records. RWE may be utilised to back up orphan medication price and clinical value claims**(Lin et al., n.d.)**.

Distribution and Supply Chain Management

To guarantee timely medicine availability, effective supply chain management and distribution arecrucial. Research has shown how crucial it is to establish a strong supply chain network that is suited to the particular requirements of orphan medications **(Jin & Chen, 2016).**

Challenges of Commercializing Orphan Drugs in APAC

There are about 4 billion people living in the Asia-Pacific (APAC) area, and over 30 million of them are thought to be affected with uncommon illnesses. However, there are a number of particular difficulties with commercializing orphan pharmaceuticals in APAC **(Drummond et al.,2007).**

The fragmented character of the healthcare systems in APAC is one of the major obstacles to the commercialization of orphan medications in the area. Because of this, it may be challenging for orphan drug manufacturers to negotiate the market and get their goods in front of patients who need them **(Thakur, 2022).**

A further obstacle to the commercialization of orphan medications in Asia-Pacific is the low knowledge of uncommon diseases among patients and medical experts. Fewer individuals are aware that uncommon diseases even exist, and even fewer are aware of the potential therapies. Because of this, it may be challenging for orphan medicine businesses to create demand for their goods **(Introduction and Executive Summary, n.d.).**

For orphan drug businesses, it can be challenging to justify the funds needed to develop and markettheir drugs due to the limited market size. Commercializing orphan pharmaceuticals in APAC is further hampered by the high expenses associated with their development and production **(Griggset al., 2009)**.

It can be difficult to navigate the regulatory obstacles in APAC to commercialize orphan medications. Every APAC nation has its unique set of laws governing orphan medications. Because of this, it may be challenging and time-consuming for manufacturers of orphan drugs to introduce their goods to consumers **(Cheng & Xie, 2017)**.

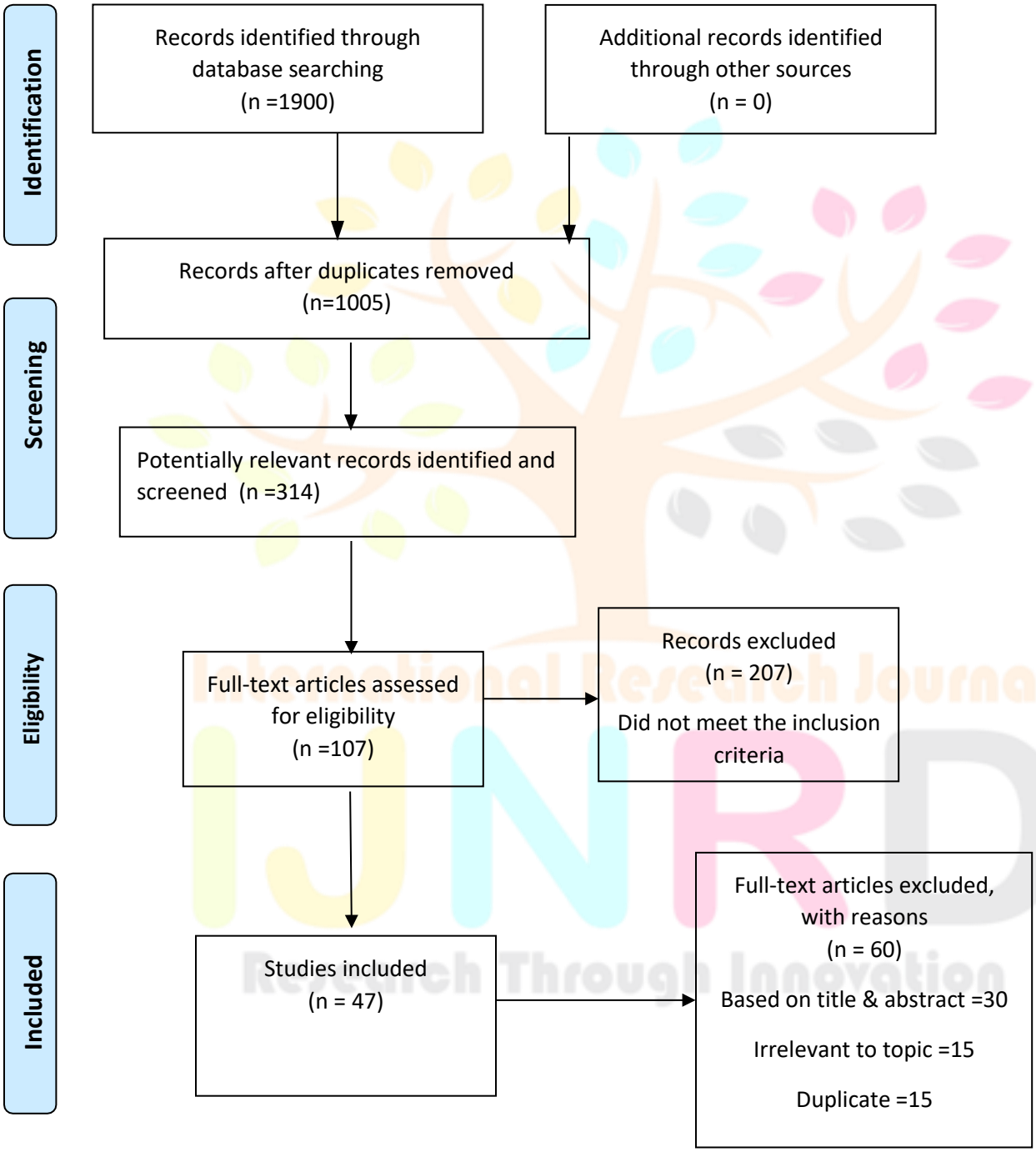
Pharmaceutical businesses can set the price of their medicines according to the value they offer topatients and healthcare systems by using value-based pricing. Pharmaceutical businesses can set the price of their medicines by referencing the costs of comparable products in other nations through reference pricing **(Chen & Schweitzer, 2008).**

Since orphan medications are usually created for tiny patient groups with rare diseases, the development of these drugs is sometimes associated with significant costs. The price of orphan medications must account for this high development cost. Patients suffering from rare disorders may find orphan medications to be highly beneficial **(Verghese et al., 2019b).**

Future Prospects:

There is room for development and innovation in the orphan medicine industry in Asia-Pacific. It is anticipated that developments in gene and cell treatments, personalized medicine, and genomics will influence the future of orphan drug development and availability in the area **(Seoane-Vazquezet al., 2008).**

PRISMA Flow Diagram



Final data set

The research database search resulted in all keywords search results obtained 1900 research articles. After scanning the title, there was the same article in two different databases. The resultsafter deducting the duplicates are 1005 articles. A total of 314 articles were screened. 207 Articles excluded that they not meet the inclusion criteria.

Articles accessed for eligibility are 107 articles. A Total number of 60 articles excluded based ontitle and abstract (30) Irrelevant to topic (15) Duplicate (15).

The final data set consists of 47 articles.

The oldest included study was published in the year 2007 and the most recent study was conductedon 2023. The Entire process is shown in figure

METHODOLOGY

The literature search was limited to articles published from 2007 - 2023. The search for articles was done online by using the search words, "Orphan Drugs Asia-Pacific, Orphan drugs commercializing strategies,Rare Diseases APAC, Regulatory Environment Orphan Drugs Asia Market Landscape Rare Diseases APAC, APAC Orphan Drug Market Growth" in the title and keywords in research databases at Wiley, Elsevier, Taylor & Francis, ERIC, Springer, SAGE, Frontiers.

Analysis

The method used is the Preferred Reporting Item for Systemic Reviews and Meta analytic (PRISMA) method. All articles that have passed the selection process were then reviewed and summarised based on the objectives, year of publication, number of citations and suggestions for further research.

Inclusion & Exclusion criteria

The studies included have to meet some criteria

(a) Studies have included some kind of selection criteria (orphan drugs in APAC and commercializing strategy). These criteria limited the number of studies. (b) Accordingly excludedthe studies in which it is based on irrelevant information, there is no proper Title, Abstract & Review.

DISCUSSION

In order to successfully commercialize orphan pharmaceuticals in the varied Asia Pacific (APAC)region, marketing executives must adopt a multifaceted strategy that includes careful market research, negotiating intricate regulatory environments, and cultivating strategic relationships. Crucial tasks include creating strong supply chains, adjusting pricing and reimbursement policies,and comprehending the various regulatory frameworks that each APAC nation has. Patient supportprograms, the use of real-world evidence, and creative partnerships are required to address issuessuch as disjointed healthcare systems, low illness awareness, and expensive development costs. However, with the advent of gene therapies and personalized medicine, the future is bright for the development of orphan drugs; it will only need careful balancing act to overcome obstacles and seize possibilities in this niche market.

CONCLUSION

In conclusion, the Asia-Pacific (APAC) region presents a complex yet promising landscape for orphan drugs, where the prevalence of rare diseases underscores the need for heightened awarenessand specialized care. Unique regulatory environments across APAC nations, coupled with variedhealthcare systems, pose challenges for pharmaceutical companies aiming to commercialize orphan medications. Efforts to incentivize research and development, observed in countries like Japan, Taiwan, and China, reflect a growing recognition of addressing unmet medical needs. Despite these strides, navigating diverse regulatory landscapes remains a hurdle. The region's potential for market growth is evident, attracting key players aiming to address rare diseases; however, high development costs and limited patient populations pose pricing a

nd reimbursement challenges. Collaborations between local and international pharmaceutical companies, coupled with advancements in biotechnology and ongoing initiatives like those by the Asia-PacificEconomic Cooperation (APEC), signal a positive trajectory. The future holds promise with anticipated advancements in gene therapies, personalized medicine, and innovative treatments poised to revolutionize the orphan drug landscape in the APAC region.

REFERENCES

1. Adachi, T., El-Hattab, A. W., Jain, R., Nogales Crespo, K. A., Quirland Lazo, C. I., Scarpa, M., Summar, M., & Wattanasirichaigoon, D. (2023). Enhancing Equitable Access to Rare Disease Diagnosis and Treatment around the World: A Review of Evidence, Policies, and Challenges. In *International Journal ofEnvironmental Research and Public Health* (Vol. 20, Issue 6). MDPI. https://doi.org/10.3390/ijerph20064732

2. Attwood, M. M., Rask-Andersen, M., & Schiöth, H. B. (2018). Orphan Drugs and Their Impact on Pharmaceutical Development. In *Trends in Pharmacological Sciences* (Vol. 39, Issue 6, pp. 525–535). Elsevier Ltd. https://doi.org/10.1016/j.tips.2018.03.003

3. Bouwman, M. L., Sousa, J. J. S., & Pina, M. E. T. (2020). Regulatory issues for orphan medicines: A review. In *Health Policy and Technology* (Vol. 9, Issue 1, pp. 115–121). Elsevier B.V. https://doi.org/10.1016/j.hlpt.2019.11.008

4. Chan, A. Y. L., Chan, V. K. Y., Olsson, S., Fan, M., Jit, M., Gong, M., Zhang, S., Ge, M., Pathadka, S.,
5. Chung, C. C. Y., Chung, B. H. Y., Chui, C. S. L., Chan, E. W., Wong, G. H. Y., Lum, T. Y., Wong, I. C.
6. K., Ip, P., & Li, X. (2020a). Access and Unmet Needs of Orphan Drugs in 194 Countries and 6 Areas: A Global Policy Review With Content Analysis. *Value in Health*, *23*(12), 1580–1591. https://doi.org/10.1016/j.jval.2020.06.020

7. Cheng, A., & Xie, Z. (2017). Challenges in orphan drug development and regulatory policy in China.*Orphanet Journal of Rare Diseases*, *12*(1), 1–8. https://doi.org/10.1186/s13023-017-0568-6
8. Chen, Y., & Schweitzer, S. O. (2008). Issues in drug pricing, reimbursement, and access in China with references to other Asia-Pacific region. *Value in Health*, *11*(SUPPL. 1). https://doi.org/10.1111/j.1524- 4733.2008.00376.x

9. Cortial, L., Nguyen, C., Julkowska, D., Cocqueel-Tiran, F., Moliner, A. M., Blin, O., & Trentesaux, V. (2022). Managing rare diseases: examples of national approaches in Europe, North America and East Asia.*Rare Disease and Orphan Drugs Journal*, *1*(2), 10. https://doi.org/10.20517/rdodj.2022.02

10. Drummond, M. F., Wilson, D. A., Kanavos, P., Ubel, P., & Rovira, J. (2007). Assessing the economic challenges posed by orphan drugs. In *International Journal of Technology Assessment in Health Care* (Vol.23).

11. Franco, P. (2013). Orphan drugs: The regulatory environment. In *Drug Discovery Today* (Vol. 18, Issues 3–4, pp. 163–172). https://doi.org/10.1016/j.drudis.2012.08.009

12. Gorini, F., Santoro, M., Pierini, A., Mezzasalma, L., Baldacci, S., Bargagli, E., Boncristiano, A., Brunetto,
13. M. R., Cameli, P., Cappelli, F., Castaman, G., Coco, B., Donati, M. A., Guerrini, R., Linari, S., Murro, V.,Olivotto, I., Parronchi, P., Pochiero, F., … Coi, A. (2022). Orphan Drug Use in Patients With Rare Diseases: A Population-Based Cohort Study. *Frontiers in Pharmacology*, *13*.

14. https://doi.org/10.3389/fphar.2022.869842

15. Griggs, R. C., Batshaw, M., Dunkle, M., Gopal-Srivastava, R., Kaye, E., Krischer, J., Nguyen, T., Paulus,K., & Merkel, P. A. (2009). Clinical research for rare disease: Opportunities, challenges, and solutions. *Molecular Genetics and Metabolism*, *96*(1), 20–26. https://doi.org/10.1016/j.ymgme.2008.10.003

16. Harada, K., Toriyabe, K., & Ono, S. (2020). Survey of Japanese Orphan Drug Program: Factors Related toSuccessful Marketing Approval. *Journal of Clinical Pharmacology*, *60*(1), 117–124. https://doi.org/10.1002/jcph.1501

17. Hsiang, N. C., Huang, W. F., Gau, C. S., Tsai, T. W., & Chang, L. C. (2021). The impact of the rare diseaseand Orphan Drug Act in Taiwan. *Journal of Food and Drug Analysis*, *29*(4), 717–725. https://doi.org/10.38212/2224-6614.3383

18. Hughes, D. A., & Poletti-Hughes, J. (2016). Profitability and market value of orphan drug companies: A retrospective, propensity-matched case-control study. *PLoS ONE*, *11*(10). https://doi.org/10.1371/journal.pone.0164681

19. Hu, J., & Mossialos, E. (2016). Pharmaceutical pricing and reimbursement in China: When the whole is less than the sum of its parts. In *Health Policy* (Vol. 120, Issue 5, pp. 519–534). Elsevier Ireland Ltd. https://doi.org/10.1016/j.healthpol.2016.03.014

20. *Introduction and Executive Summary*. (n.d.). https://doi.org/10.1186/s13023-016

21. Jin, X., & Chen, L. (2016). Orphan drug development in china . turning challenges into opportunities.
22. *Intractable and Rare Diseases Research*, *5*(4), 308–313. https://doi.org/10.5582/irdr.2016.01025Kang, Q., Hu, J., Yang, N., He, J., Yang, Y., Tang, M., & Jin, C. (2019). Marketing of drugs for rare diseases is speeding up in China: Looking at the example of drugs for mucopolysaccharidosis. In *Intractable and Rare Diseases Research* (Vol. 8, Issue 3, pp. 165–171). International Advancement Centerfor Medicine and Health Research. https://doi.org/10.5582/irdr.2019.01090

23. Khosla, N., & Valdez, R. (2018). A compilation of national plans, policies and government actions for rarediseases in 23 countries. In *Intractable and Rare Diseases Research* (Vol. 7, Issue 4, pp. 213–222). International Advancement Center for Medicine and Health Research. https://doi.org/10.5582/irdr.2018.01085

24. KidStock. (n.d.). *White Paper Funding Environment for Rare Diseases in Low and Middle Income Countries A global study of the health financing context, challenges and opportunities for rare diseases inLMICs*.

25. Lanar, S., Acquadro, C., Seaton, J., Savre, I., & Arnould, B. (2020). To what degree are orphan drugs patient-centered? A review of the current state of clinical research in rare diseases. In *Orphanet Journal ofRare Diseases* (Vol. 15, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s13023-020-01400-0

26. *landscape of rare diseases in asia pacific (1)*. (n.d.).

27. Lee, J. H. (2021). Pricing and reimbursement pathways of new orphan drugs in South Korea: A longitudinalcomparison. *Healthcare (Switzerland)*, *9*(3). https://doi.org/10.3390/healthcare9030296

28. Lim, S. S., Lee, W., Kim, Y. K., Kim, J., Park, J. H., Park, B. R., & Yoon, J. H. (2019). The cumulative incidence and trends of rare diseases in South Korea: A nationwide study of the administrative data from the National Health Insurance Service database from 2011-2015. In *Orphanet Journal of Rare Diseases* (Vol. 14, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s13023-019-1032-6

29. Lin, L. W., Ahn, J., Beatriz, D., Bayani, S., Chan, K., Kearney, B., Tunis, S., & Wu, H.-M. (n.d.). *GUIDANCE DOCUMENT, FULL VERSION FOR HTA AGENCIES AND RESEARCHERS USE OF REAL-WORLD DATA AND REAL-WORLD EVIDENCE TO SUPPORT DRUG REIMBURSEMENT DECISION-MAKING IN ASIA CONTRIBUTING AUTHORS*.

30. Lopata, E., Terrone, C., Gopalan, A., Ladikos, N., & Richardson, T. (2021). *Meeting the affordability challenges posed by orphan drugs: a survey of payers, providers, and employers* (Vol. 27, Issue 6).

31. Lu, C. Y., Lupton, C., Rakowsky, S., Babar, Z. U. D., Ross-Degnan, D., & Wagner, A. K. (2015). Patient access schemes in Asia-pacific markets:Current experience and future potential. *Journal of PharmaceuticalPolicy and Practice*, *8*(1), 1–12. https://doi.org/10.1186/s40545-014-0019-x

32. Mao, W. (2021). *Determinants For Approval And Reimbursement Of Orphan Products In China*. https://elischolar.library.yale.edu/ysphtdl/2075

33. Neelakandan, N., Nagasamy Venkatesh, D., & Gomez, A. L. (n.d.). *Orphan Drug Designation in Australia*.*ORPHAN DRUG*. (2022).

34. Patel, S. (n.d.). *Rare Diseases in India: "Orphan" No More?*

35. Pijeira Perez, Y., Wood, E., & Hughes, D. A. (2023). Costs of orphan medicinal products: longitudinal analysis of expenditure in Wales. *Orphanet Journal of Rare Diseases*, *18*(1). https://doi.org/10.1186/s13023-023-02956-3

36. Rajueni, K., & Chakraborty Choudhury, M. (2023). Assessment of the availability of repurposed orphan drugs in India. *PLOS Global Public Health*, *3*(9), e0001498. https://doi.org/10.1371/journal.pgph.0001498

37. Rana, P., & Chawla, S. (2018). Orphan drugs: Trends and issues in drug development. In *Journal of Basicand Clinical Physiology and Pharmacology* (Vol. 29, Issue 5, pp. 437–446). De Gruyter. https://doi.org/10.1515/jbcpp-2017-0206

38. Schmid, E. F., Smith, D. A., & Ryder, S. W. (2007). Communicating the risks and benefits of medicines. In *Drug Discovery Today* (Vol. 12, Issues 9–10, pp. 355–364). https://doi.org/10.1016/j.drudis.2007.03.003

39. Seoane-Vazquez, E., Rodriguez-Monguio, R., Szeinbach, S. L., & Visaria, J. (2008). Incentives for orphandrug research and development in the United States. *Orphanet Journal of Rare Diseases*, *3*(1). https://doi.org/10.1186/1750-1172-3-33

40. Shafie, A. A., Chaiyakunapruk, N., Supian, A., Lim, J., Zafra, M., & Hassali, M. A. A. (2016). State of raredisease management in Southeast Asia. *Orphanet Journal of Rare Diseases*, *11*(1). https://doi.org/10.1186/s13023-016-0460-9

41. Sherwin, G., Akpinar, P., Saraf, S., & Li, X. (2014). Pricing and Market Access of Orphan Drugs in Asia:a Comparative Study Across Growth Markets. *Value in Health*, *17*(7), A785. https://doi.org/10.1016/j.jval.2014.08.399

42. Song, P., Gao, J., Inagaki, Y., Kokudo, N., & Tang, W. (2012). Rare diseases, orphan drugs, and their regulation in Asia: Current status and future perspectives. *Intractable and Rare Diseases Research*, *1*(1), 3–9. https://doi.org/10.5582/irdr.2012.v1.1.3

43. Tadepalli, M., Veeravalli, S., Kumar, R., & Juturi, R. (2022). COMPREHENSIVE REVIEW ON ORPHAN DRUG

REGULATIONS IN THE USA, EU, JAPAN, AND AUSTRALIA: POSSIBLE

44. RECOMMENDATIONS TO SPECIFIC CHALLENGES. *International Journal of Pharmaceutical Sciences and Research*, *13*(2), 688. https://doi.org/10.13040/IJPSR.0975-8232.13(2).688-06

45. Thaker, Z., Jethva, K., Bhatt, D., Zaveri, M., & Deshpande, S. (2019a). ORPHAN DRUGS: OVERVIEW AND REGULATORY REVIEW PROCESS. *International Journal of Pharmaceutical Sciences andResearch*, *10*(2), 505. https://doi.org/10.13040/IJPSR.0975-8232.10(2).505-18

46. Thakur, S. (2022b). Advances in orphan drug development: Time to change the status and stereotype. In *Perspectives in Clinical Research* (Vol. 13, Issue 3, pp. 123–128). Wolters Kluwer Medknow Publications. https://doi.org/10.4103/picr.picr_193_21

47. Verghese, N. R., Barrenetxea, J., Bhargava, Y., Agrawal, S., & Finkelstein, E. A. (2019a). Government pharmaceutical pricing strategies in the Asia-Pacific region: an overview. *Journal of Market Access & Health Policy*, *7*(1), 1601060. https://doi.org/10.1080/20016689.2019.1601060

48. Wilson, L. (2020). PRO1 The Market Access Landscape for Orphan Drugs in APAC: A Comparison of Policies in FIVE Major Markets. *Value in Health Regional Issues*, *22*, S94–S95. https://doi.org/10.1016/j.vhri.2020.07.496

49. *wilson-l-orphan-drugs-ispor-asia-pacific-2020-pdf (1)*. (n.d.).

50. Yi, H., Shi, F., Wang, Z., Kuai, L., Xu, D., Xie, Y., & Xing, H. (2023). Impacts of adjustment of NationalReimbursement Drug List on orphan drugs volume and spending in China: an interrupted time series analysis. *BMJ Open*, *13*(10), e064811. https://doi.org/10.1136/bmjopen-2022-064811

51. Zhao, Z., Pei, Z., Hu, A., Zhang, Y., & Chen, J. (2023). Analysis of Incentive Policies and Initiatives on Orphan Drug Development in China: Challenges, Reforms and Implications. *Orphanet Journal of Rare Diseases*, *18*(1). https://doi.org/10.1186/s13023-023-02684-8