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Original article

Cross-national comparative study of orphan drug policies in Saudi Arabia, the United States, and the European Union

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ABSTRACT

Background: Rare diseases are chronic, serious, and life-threatening conditions that have not received sufficient attention from drug developers due to their rarity. Policies have been implemented to encourage research and incentivize the development of orphan drugs. However, the implementation of these policies has been inconsistent worldwide.
Objective: The primary aim of this study was to compare orphan drug policies in the United States, Europe, and Saudi Arabia (SA) and assess their impact on the number of approved indications.
Method: Lists of all drugs granted orphan designations and authorized for marketing in the United States, European Union, and SA were extracted using orphan drug lists available in regulatory body databases. The availability of these drugs, regarding their approval for orphan indication and designation, was assessed and classified using Anatomical Therapeutic Chemical codes.
Result: A total of 792 orphan drug designations with at least one authorized indication were identified in this study. Of these, 92% were designated by the Food and Drug Administration (FDA), and 27% were designated by the European Medicine Agency (EMA). The FDA, EMA, and Saudi Food and Drug Authority approved 753, 435, and 253 orphan drugs, respectively.
Conclusion: Fewer orphan drug approvals were found in SA than in the United States and Europe. This highlights the need to focus on rare diseases and orphan drugs and for policies to be created in SA to attract pharmaceutical markets and fulfill unmet orphan drug approval needs.

1. Introduction

Rare diseases (RDs) are often debilitating conditions that are typically serious, chronic, and life-threatening. Given their rarity and small market size, they have received insufficient attention from drug developers (Boat and Field 2011). This is primarily because of the limited number of patients who could enroll in clinical trials and the low probability of return on investment caused by low demand. In 1962, following Thalidomide tragedy, many drugs regulatory systems had undergone reforms to ensure safety and efficacy of medications before being available for marketing under the surveillance of the regulatory bodies (ASBURY and STOLLEY 1981). In the United States (US), drug developers are required to provide scientific evidence to the FDA to demonstrate the safety and effectiveness of their products before marketing. They must also submit an Investigational New Drug (IND) request before conducting clinical trials. This requirement applies to both new drugs and those already under investigation during development (ASBURY and STOLLEY 1981). Approximately around 25% of the drugs treating rare diseases that were under investigation during the implementation period were withdrawn by their sponsors because of their low commercial profitability, which was primarily due to the limited patient population (Mikami, 2017). This highlights the fact that rarity of these diseases make them less attractive to pharmaceutical industry due to lower return on investment. The process of developing products to treat RDs is further complicated by multiple factors, including governmental, pharmaceutical, and social considerations (Crompton 2007). As a response to this need, various legislations and policies have been established to encourage research on RDs and promote the development of orphan drugs (ODs). ODs are pharmaceutical products

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designed to treat RDs that affect a small number of individuals; however, their implementation is inconsistent worldwide (Boat and Field 2011). The first legislative framework that supported the development of ODs for RD was passed in the United States in 1983, known as the Orphan Drug Act (ODA) (Orphan Drug Act, 1983).

The aim of ODA is to address public health needs and serve under covered or neglected disease areas. Japan, Australia, and the European Union (EU) developed similar regulations and policies in 1993, 1997, and 2000, respectively (Wong An Qi 2022). These policies were established with several criteria, and drug developers are obligated to demonstrate that these criteria are met before their products can be designated and incentivized (Gibson and von Tigerstrom 2015). These criteria include evidence proving that the drug is intended to treat a RD based on the disease's prevalence threshold set by regulatory bodies in the region and proof that the cost of developing the drug is unlikely to be recovered under the usual market circumstances (Kontoghiorghe et al., 2014, Mikami 2019).

The US Congress has set a disease prevalence threshold of 200,000, leading the Food and Drug Administration (FDA) to modify its requirements. The FDA presently assumes that any drug intended to treat a condition affecting fewer than 200,000 humans in the US is commercially nonviable rather than requiring evidence of commercial nonviability (Herder 2017). Currently, the most commonly adopted definition of RDs is based on their prevalence thresholds; however, the rationale behind this choice is unclear (Torrent-Farnell and Morros 2001). The literature suggests a need to progress beyond the prevalence threshold and focus on diseases that have been neglected by pharmaceutical companies (Thomas and Caplan 2019).

Given the limited market size, for pharmaceutical companies to invest in the research and development of ODs is often not economically viable (Torrent-Farnell and Morros 2001). The incentives provided can be categorized into financial and nonfinancial incentives. Financial incentives include market exclusivity, fee waivers, tax credits, and research grants (Rinaldi 2005), whereas nonfinancial incentives include protocol assistance, accelerated approval, and pre-licensing access (Gammie et al., 2015). Both the incentives provided and the prevalence thresholds of diseases are factors that affect the development of ODs (Gammie et al., 2015). For example, without the 50% Orphan Drug Act tax credit on the clinical trial cost, investment in ODs would approximately be smaller by a third, both historically and in the future (Daniel et al., 2016). Furthermore, the scientific guidance and incentives provided by the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) are contributing factors to the higher success rate of market authorization for ODs (Hofer et al., 2018). Even though these incentives have been driving the research and development of drugs for treating RDs, it has been suggested that they are not sufficiently incentivizing for diseases that have no available pharmaceutical treatment options or diseases with low prevalence (Rinaldi 2005, Yin 2008, Miller and Lanthier 2018).

Despite being a major contributor to the development of RDs, the landscape of global OD policies remains unclear. Although similarities may exist between OD policies across countries, the standards and methods of designation are inconsistent. Pharmaceutical policies and legislation regulating ODs were investigated in 194 World Health Organization (WHO) member countries in six areas (Chan et al., 2020). By 2020, 46% of countries worldwide had implemented OD legislation, regulations, and policies (Chan et al., 2020). The US and Europe are considered leaders in this area with well-established policies and procedures for the development and approval of ODs. In contrast, a notable gap exists in the knowledge and policies related to ODs in Saudi Arabia (SA). The Saudi Ministry of Health (MOH) is responsible for the provision of healthcare to the public at all levels, the promotion of general health, and the prevention of disease, in addition to developing laws and legislation regulating both governmental and private health sectors ((MOH) 2012). Although the MOH has established an RD definition based on a disease prevalence threshold, no OD definition was found in our search.

RD have a significant impact on individuals and their families, making it a top public health priority in Saudi Arabia. OD policies can improve healthcare access and treatment options, benefitting local and global populations. These policies reflect the country's dedication to public health and research, attracting potential collaborations and investments. Despite Saudi Arabia's smaller share in the global OD market, prioritizing these policies remains essential to address the unique challenges posed by rare diseases within the country and to enhance overall healthcare outcomes. Currently, insufficient clarity exists regarding RDs and ODs in SA. Furthermore, a notable gap in the literature exists, as no studies have investigated the approval, availability, and official policies or framework of ODs in SA. The insufficient information and policies on ODs in SA have created significant uncertainty for patients, healthcare professionals, and policymakers. As a result, there is a pressing need to assess the current situation and identify potential gaps and challenges. To address this knowledge gap, this study aims to compare OD policies in the US, Europe, and SA. In particular, this study assesses the approval, availability, official policies, and frameworks for ODs in these regions. This study examines the number of approved indications, types of approved drugs, and the market exclusivity granted for approved orphan indications. The findings of this study can provide valuable insights into the policies and practices related to RDs and ODs in these regions and provide policymakers with information that could improve the availability and accessibility of ODs in SA.

2. Materials and methods

2.1. Data sources

OD lists were obtained from the regulatory bodies of the United States (USFDA 2023), EU(EU 2022), and Saudi Food and Drug Authority(SFDA 2022). These lists were used to identify all drugs that had been granted orphan drug designation (ODD) and were authorized for marketing in these regions.

2.2. Measures/data

The collected data included ODDs, regions of designation, active ingredient names, trade names, authorized indications under each ODD, dates of authorization for each orphan indication, and market exclusivity end dates for each authorized orphan indication. In addition, formulations authorized for the use of the authorized orphan indication were collected to ensure the accuracy of the comparison.

Orphan drugs were classified according to their specific therapeutic areas using the WHO Anatomical Therapeutic Chemical (ATC) Classification System. This ATC code was identified for orphan drugs marketed in the US, EU, and SA. If the WHO did not define the ATC code for an OD, it was considered non-coded.

2.3. Inclusion and exclusion criteria

Drugs granted ODD and authorized for marketing were included. Drugs authorized for an orphan indication with a revoked ODD status were excluded. Japan and Australia were excluded from the comparison because of language barriers and unavailability of data.

2.4. Assessment

A collective list that included all the above mentioned information was created. To examine whether these drugs were approved for the same orphan indications, regardless of whether they were granted ODD in the US, EU, or SA, the approved drug databases available on the official websites of the regulatory bodies of these regions were examined against a collective list.

The search was conducted between February 2020 and July 2020 using the generic name of the active ingredient, International Non-proprietary Name, or trade name. If the drug was the same and was approved for the same indication, the trade name and year of approval were collected. If the search yielded a similar active ingredient that was approved for the same orphan indication with different trade names, the dosing and sponsor of the drug were confirmed to ensure that the products were the same. The resources used to confirm approved indications were the product label, summary of product characteristics, Saudi Drug Information System (SDI) on the Food and Drug Administration website, European Commission Union Register of medicinal products, and SFDA websites. Other resources were used to investigate sponsor status in each country. If not labeled in a certain country, it was removed from the list of approved medications in that country.

2.5. Statistical analysis

Descriptive statistics were calculated for all variables included in this study. The number of approvals and trends in the approval of ODs over time were analyzed by counting the number of approvals each year. For market exclusivity, the mean duration and standard deviation were calculated. All analyses were performed using Microsoft Excel 2019 MSO (Version 2110, Build 16.0.14527.20270).

3. Results

This study found that the US and EU have implemented regulations to encourage the development of drugs for RDs, whereas SA has yet to establish a clear policy. A summary of RD policies across the three regions is shown in Table 1. One of the significant differences observed among the regions is the definition of RDs. In the US, a disease is considered rare if it affects fewer than 200,000 individuals, whereas in the EU, a disease is classified as rare if it affects less than 5 in 10,000 people. However, no specific criteria for ODD have been established in SA.

Table 2 compares the number of ODDs and approvals in the US, EU, and SA. The study found that the total number of ODDs with at least one authorized indication, as referred to by Miller et al. (2021) "*Unique designations*" was 792 designations from the year of the enactment of the policy of each jurisdiction to July 2020. Of the collective approvals, the FDA approved 753, EMA approved 435, and SFDA registered 253. A total of 619 products covered these indications, of which 99 covered multiple designations. Of the approved products, 171, 329, and 594 were registered in SA, Europe, and the US, respectively. Among the ODs approved for marketing in the US and EU, the availability of the products in SA accounted for 31% of the total approvals.

From 1983 to 2018, the overall trend of approvals has been increasing, with the highest number of approvals witnessed in the US and EU in 2018 (Fig. 1). In addition, when comparing the mean number of approvals per year, the mean number of approvals per year in the EU and SA was significantly lower than the number of marketed products per year in the US.

Furthermore, upon examining the product types covering approved indications based on the first level of the ATC code, which represents the anatomical group where the identified agents are located, it was discovered that the most common OD type in these regions were antineoplastic and immunomodulating agents, followed by blood and blood-forming organs, and alimentary tract and metabolism in the US and EU (Table 3).

The average market exclusivity for the identified approved indications under each ODD in the US was 7.34 y with a maximum duration of 17 y and a minimum of 5 y. The average duration of market exclusivity in the EU was 9.25 y, with a minimum duration of six months and a maximum of 12 y. Market exclusivity could not be investigated in SA because there was no available information.

4. Discussion

This study conducted an international comparison of OD policies and availability in the US, EU, and SA, focusing on the impact of these policies on the development and availability of these drugs. The study found that both the US and EU have implemented policies based on the definition of ODs, which are either based on RD prevalence thresholds or the financial viability of the product. These policies aim to incentivize drug sponsors to develop new products for the treatment of RDs by offering financial and non-financial incentives. The results of this study show that the overall trend of approving ODs increased across all countries from 1983 to 2018, primarily because of the policies and regulations established to encourage the development of ODs. This study identified 792 unique ODDs, of which 736 were designated by the FDA and 216 by the EMA. This trend suggests an increased focus on addressing RDs globally and a growing interest in developing ODs to address the unmet medical needs of patients. The results of this study are consistent with previous observations that the US has the most designations and approvals of ODs compared to other countries (Giannuzzi et al., 2017).

While policies in the US and the EU share some similarities, they are not identical. For example, a product can be incentivized each time its sponsor proves that it can treat a condition that falls below the prevalence threshold or when the product is financially nonviable under usual market circumstances. These incentives and policies were set to stimulate drug sponsors to develop new products to treat RDs, consequently satisfying unmet needs, accelerating drug availability in the market, and facilitating access to these products (Giannuzzi et al., 2017). The impact of these policies was measured based on the number of medications approved after implementation. For example, the ODA have approved approximately 503 ODs for marketing in 2018 (Lichtenberg 2013, Aitken and Kleinrock 2018). Regarding the impact on treatment outcomes, the premature mortality rate from RDs was analyzed over 6–7 y in the US and France, and the reduction in the premature mortality rate from RDs was inversely related to the number of newly approved ODs (Lichtenberg, 2013). In contrast, this study reveals that the approval of ODs in SA is low. Only one-third of the drugs approved in the USA and EU are registered in SA. This may indicate that the approval process for ODs in SA is slow or more stringent, which may delay access to treatment for RDs. Thus, SA has potential opportunities to increase the number of approved ODs to meet the increasing demand for RD treatments. The differences in the number of registered orphan drugs can be attributed to several factors, including variations in the definition of rare diseases, the specific policies and incentives for orphan drug development in each country, and differences in the regulatory approval process.

Our study highlights the importance of policies and incentives for promoting OD development. The market for ODs is limited in the absence of such policies, and pharmaceutical companies may not invest in the development of these drugs because of financial constraints (Adachi et al., 2023). This is confirmed in our study,

Table 1
Summary of RDs policies in the US, EU, and SA.

Regions	US	EU	SA
Total prevalence of RDs	25–30 million (20)	27–36 million	Data unavailable
RDs prevalence threshold	Affects < 200,000	1 in 2000	5 in 10,000
RDs advocacy organizations	National Organization for Rare Diseases	European Organization for Rare Diseases	None
OD definition	A drug intended to treat a condition affecting fewer than 200,000 humans in the United States or which will not be profitable within seven years following approval by the FDA.	A medicine for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 humans in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs.	Unofficial
ODs policy	Yes	Yes	Unofficial
Year of policy implementation	1983	1997	None
ODDs	Yes	Yes	Unofficial
Incentives: Market exclusivity	7 years	Ten years that can be reduced to six years if it can be shown that a drug is "sufficiently profitable" after five years on the market	None
Incentives: others	50% tax credit for research and development expenses Protocol assistance Research grants Accelerated marketing procedure	1. Centralized authorization procedure Protocol assistance Regulatory fees reduction Research grants Accelerated marketing procedure.	None

Table 2
Number of approvals among all regions.

Region	US	EU	SA*
Number of ODDs in each region	736 (92%)	216 (27%)	–
Total number of approvals/registrations	753 (95%)	435 (54%)	253 (31%)
Number of products	592 (95%)	327 (52%)	171 (27%)
Number of ODDs covered by products that cover multiple indications	237 (87%)	75 (27%)	–
Number of products covering multiple Designations¥	88 (88%)	27 (27%)	–
Number of ODDs per product	1–5	1–6	–

*no ODD were registered during the study period.
¥Multiple designations, in the context of ODD, refer to a situation where one drug receives different regulatory designations as an orphan drug.

where SA, which lacked publicly official policies for ODD, presented the lowest number of marketed ODs among the three countries. The lack of official public policy for ODD in SA is a factor contributing to the lower number of OD approvals in the country. In addition, the SFDA's recent implementation of a pricing policy and fast-track process for drugs in SA may impact the availability and accessibility of these medications. Furthermore, the SFDA has implemented a priority review process for drugs that treat RDs to help expedite their approval and availability. The impacts of pricing policies and fast-track processes for drug approval of ODs in SA are complex. While pricing policies could increase the affordability of ODs, they could also lead to a decrease in availability because manufacturers may not find it profitable to develop and market these drugs if prices are set too low. The fast-track process for drug approval could expedite the availability of ODs, but it may not be sufficient to address the issue of OD availability and accessibility, as the limited patient population and market for ODs can remain a challenge, even with established fast-track approval processes.

This raises the question of whether SA must consider publicly officializing the system governing OD approval and availability in the region. A comparison between Canada, which has no established OD policy, and Australia, which has an established policy, was conducted over 10 years to determine whether the availability of the policy had an impact. Notably, the number of approved drugs in Canada was not significantly different from that in Australia, indicating that the lack of OD policy did not limit the availability of ODs in the region (Lexchin and Moroz 2020). Canada has two established and publicly official accelerated pathways through which drugs can be approved based on limited clinical data. However, none of these pathways provide the benefits of formal OD policies (Lexchin and Moroz 2020). A similar comparison was made between China, which has no policy implemented, and the US and the EU; the study found a contradictory result to the Canadian Australian comparison and a result consistent with our comparison, as 35.5% of ODs approved in the US and EU were approved in China (Gong et al., 2016). Our results indicate that OD policies differ regarding the number of drugs being developed, approved, and consequently available to treat RDs in the region, which is crucial to ensure that patients receive timely, adequate, and efficient treatment.

Considering additional factors that contribute to the disparities in OD approval rates between countries is crucial, such as differences in the definition of RDs and their prevalence. Defining RDs is crucial for developing OD policies. However, it can vary across countries. In the US, RD is defined as a disease that affects fewer than 200,000 humans. In the EU, an RD is defined as a disease that affects fewer than 1 in 2,000 humans, and the MOH defines RDs as diseases that affect fewer than 1 in 2,000 humans. The prevalence of RDs plays a crucial role in the development and approval of ODs. Antineoplastic and immunomodulatory agents account for the highest proportion of these products, with 95% of the identified agents being designated in the US, likely owing to the support of basic science research in oncology through the National Cancer Institute at the National Institute of Health (Giannuzzi et al., 2017). This is unsurprising because cancer and rare immune disorders are among the most common indications for OD development. This finding is consistent with Miller et al. (2021), who found that the orphan approvals over the years 2014–2017 are most concentrated in three therapeutic categories: oncology (34%), metabolic and endocrine (15%), and hematology (11%) (Miller et al., 2021).

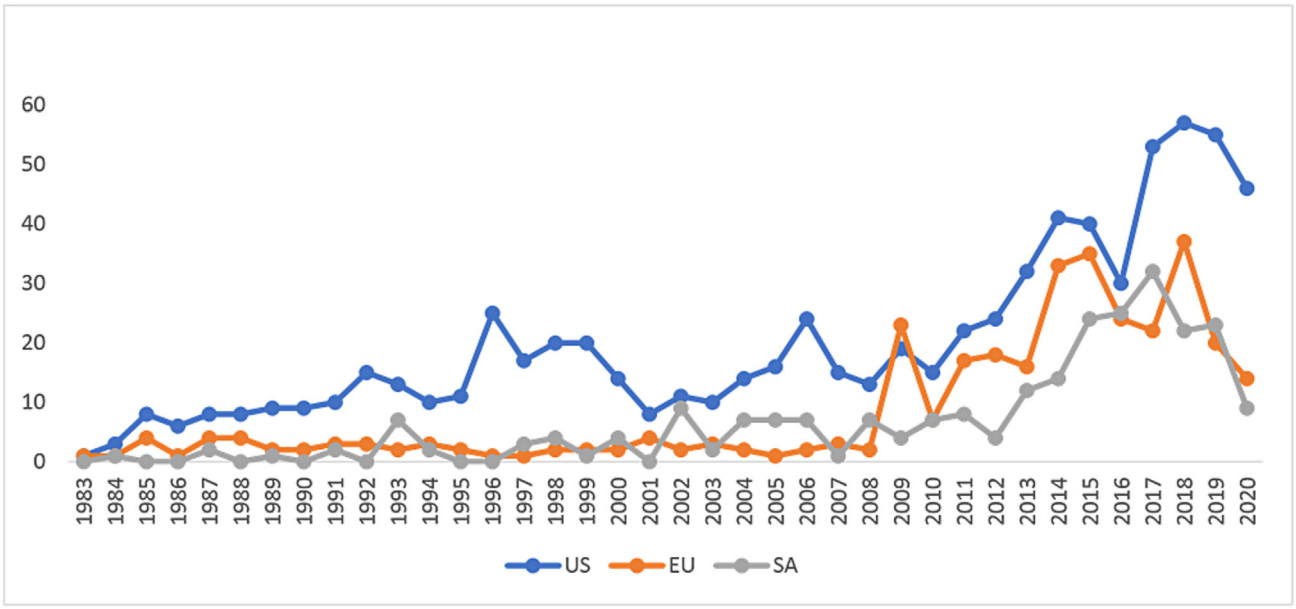

Fig. 1. Approval trend in each country per year.

Table 3
OD indication according to the ATC classification system.

Classification of the products covering approved indications based on the 1st level of the ATC code	Number of approvals per region		
	US	EU	SA
A-Alimentary tract and metabolism	63	50	15
B-Blood and blood-forming organs	63	43	21
C-Cardiovascular system	22	15	10
D-Dermatological	6	2	1
G-Genitourinary system	9	5	4
H-Systemic hormonal preparations excluding sex hormones and insulin	44	30	16
J-Anti-infective for systemic use	48	17	8
L-Antineoplastic and immunomodulating agents	315	210	144
M–Musculo–skeletal system	24	12	9
N-Nervous system	49	24	6
P-Antiparasitic products, insecticides, and repellents	22	0	5
R-Respiratory system	10	5	2
S-Sensory organs	14	5	3
V-Various	44	15	8
Non-coded	20	0	1

Although classifying drugs based on the first level of their ATC codes does not fully reflect the indications of the drug, our findings highlight that neglected diseases that are not being targeted by pharmaceutical developers are still being neglected. A proposed solution is that incentives of ODA should only be offered to companies that conduct drug development research on diseases that have been neglected, known as ultra-rare, or where no treatment options are available (Thomas and Caplan 2019).

The prevalence of RDs may be lower in SA than in the US and EU, which may partially explain the lower number of OD approvals in the country. However, establishing a direct correlation between the prevalence of RDs and the availability of ODs is a complex issue that requires further exploration.

Epidemiological data are essential in determining the need for ODs, and various studies have been conducted in SA to identify the incidence, prevalence, and characteristics of RDs (ElObeid and AlAbdudlkarim 2016, Alsaqa'aby and Ibrahim 2019). Another source of epidemiological data that can be used to generate evidence is the nationwide disease registries (Hollak et al., 2020). In SA, the Department of National Health Disease Registry at the National Health Information Center is responsible for creating national disease databases and patient registries (centre 2021). To date, the center has succeeded in establishing three nationwide disease registries: the Saudi Cancer Registry, the National Registry for Neural Tube Defects, and the National Registry for Hearing Impairment (Center, n.d.; centre, 2021). Because nationwide registries in SA are under development, considering the goal of establishing registries is imperative to attain their maximum benefit. According to Jansen-van der Weide et al. (2018), registries can be classified into three categories: public health, clinical, genetic, and treatment (Jansen-Van Der Weide et al., 2018). Currently, the lack of knowledge regarding the natural history of RDs and disease phenotype heterogeneity, as well as the lack of epidemiological data, poses significant barriers to the development of products for treating RDs (Jansen-Van Der Weide et al., 2018). These data will be of major help in establishing clinical trial endpoints and outcomes that must be achieved because of any intervention. Therefore, registries should focus on long-term goals and include all needed data to maximize benefits and facilitate transparency, which can contribute to the understanding of rare conditions and ultimately impact the availability of treatment options and market access. Because the rationale behind the prevalence threshold established by the FDA OD Act is not entirely clear, it is worth examining whether SA should leverage epidemiological data to establish a prevalence threshold as a criterion for determining drug eligibility for ODD. Additionally, if SA adopts an RD definition, it would be crucial to tailoring the definition to reflect the unique healthcare needs and circumstances of the region.

An additional aspect that contributes to the approval and availability of ODs is the presence of patient advocacy groups. They act as patients voice and advocate for policies and programs that support the development and approval of new treatments. They can help ensure that patients are involved in the drug development process, raise awareness regarding unmet medical needs, and collaborate with pharmaceutical companies and regulatory agencies to streamline the drug approval process and justify insurance and reimbursement options (Dunkle 2014, Hollak et al., 2020)). These groups can also provide insight into the potential contribu-

tions that patient organizations can make toward improving information systems for ODs by sharing natural history registries and providing input on a trial design by suggesting endpoints and the use of reported outcomes and patient-reported outcomes. These efforts by patient organizations can help reduce uncertainties in the decision-making process for ODs and ensure that ODs are developed to meet the needs of patients and their families (Menon et al., 2015). In SA, patient advocacy groups exist, and their impact is remarkable; however, none are dedicated to RDs. Our findings highlight that OD policies are a multistakeholder issue and should be addressed collaboratively from multiple perspectives and in regions where an aspect is lacking. How efficient an OD policy will be if established by regulatory bodies and in the absence of these aspects is unclear.

The assessment and pricing of ODs are another challenge. ODs are often expensive because of the high costs of research and development and the small patient populations they serve. This creates access issues for both patients and healthcare systems (Berdud et al., 2020). Policymakers may need to consider strategies to establish an acceptable price and ensure access while also ensuring that companies are adequately incentivized to invest in research and development (Berdud et al., 2020). OD policies and regulations vary widely between countries, which can create challenges for companies aiming to develop and market drugs globally. Policymakers may need to aim toward greater international harmonization to facilitate access to treatments for RDs. This can include harmonizing the criteria for ODD, reducing regulatory barriers to global drug development, and promoting collaboration between regulatory agencies, which will help streamline the drug development process and promote consistent standards for determining whether a drug qualifies as an OD. Additionally, harmonization can facilitate the global utilization and sharing of Real-World Evidence globally and value-based pricing, particularly because it will be widely used for drug approval (Nishioka et al., 2022). They can also play a crucial role in reducing drug development costs. As companies must meet different regulatory requirements in each country, they may need to conduct multiple clinical trials or invest in additional research to satisfy different regulatory agencies. By harmonizing regulatory requirements, companies can avoid duplicate efforts and reduce the cost of drug development, ultimately leading to more affordable treatments for RDs (Czech et al., 2020).

The study also examined the average market exclusivity for the identified approved indications under each ODD in the US and EU. The average duration of market exclusivity was 7.32 y in the US and 9.29 y in the EU. Drugs covering indications with market exclusivity that lasted for over 7 y in the US were primarily antineoplastic and immunomodulating agents. In the EU, drugs covering indications with a market exclusivity of over 10 y were primarily alimentary tract and metabolic agents. However, the market exclusivity for approved indications in SA could not be determined because of a lack of available information. Our study also identified the factors that contributed to the extension of market exclusivity for indications in both regions. In the EU, the extension of use to the pediatric population within the approved indications was a significant contributing factor. Meanwhile, in the US, the factors that led to the extension of market exclusivities were the extension of the approved indications to include different populations, including younger or older age groups or different populations with the same disease based on what they previously received or their conditions. These findings have crucial implications for SA. This suggests a need for greater consideration of factors that contribute to market exclusivity extensions and their impact on the access of patients to these drugs. However, a balance should be maintained between these regulations and the need for affordable access to life-saving medications. According to Padula et al. (2020), several highly profitable drugs have been granted exclusivity periods of over 10 y, resulting in delayed access to generic or biosimilar alternatives for patients with RDs. This delay can lead to increased medication costs and limit patient access to life-saving treatments (Padula et al., 2020).

Based on the results of this study, OD policies have been established in response to public health needs. These needs are neglected unless they are incentivized. These policies are not optional but are essential. Policymakers must implement appropriate policies, allocate research funding, provide incentives, and engage stakeholders to encourage the development of ODs. These findings suggest that SA has significant gaps and challenges in its OD policies and availability compared to the US and Europe. These gaps create significant uncertainty for healthcare professionals and policymakers and limit the access of patients with RDs to ODs, thereby compromising their health outcomes. Thus, it is crucial to develop ODs for RDs that require significant investment from pharmaceutical companies. It is also crucial to balance incentives for the development of ODs to ensure that they are accessible to patients in need. Of worth mentioning, in SA, the SFDA recently released guidelines for ODD on 04 June 2023. The implementation of these ODD guidelines is scheduled for 04 September 2023. This new development is a progressive step in addressing the needs of patients with rare conditions and advancing orphan drug research and availability in the country. The availability of ODD guidelines will have a positive impact on meeting the specific healthcare needs of patients with rare conditions, and it is expected to lead to increased research and availability of orphan drugs in Saudi Arabia.

The study limitations include the fact that the FDA and EMA were considered as standards against which we compared SA; if other jurisdictions were included, a higher number of approvals in SA would likely be found. The SDI does not include all identified drug information; therefore, if the medication was registered and the label could not be accessed, it was considered approved for the intended indication. If the label did not include use for an orphan indication, we regarded the medication as not approved for an orphan indication. The years of approval in the SA include only the year of product registration because this is the only date that can be accessed. In the EC register for approved medications, the approved indications were available only for centrally approved products, and some medications were approved nationally, for which approval of indication and date of approval could not be investigated. In addition, we classified drugs based on the first level of their WHO ATC code, which denotes the anatomical location where these drugs act and often does not indicate the therapeutic area. Finally, the data were extracted from official public databases, which may not be inclusive. Notably, our study focused on approved indications and did not address the availability or accessibility of these drugs in each country. Despite these limitations, our study provides valuable insights into the global landscape of OD development, highlighting the importance of continued efforts to address RDs. Furthermore, further evaluation of the new ODD guidance will be warranted to assess its implementation and impact. It will be essential to monitor how the guidelines are being integrated into the regulatory framework and how they influence the process of orphan drug approvals in Saudi Arabia. Additionally, measuring the impact of these guidelines on patient access to orphan drugs, research advancements, and the overall healthcare landscape will be crucial in understanding their effectiveness.

5. Conclusions

In conclusion, the findings of this study highlight a significant gap in the availability of ODs in SA compared to the US and EU,

indicating a crucial need for policy development to support the innovation and development of ODs. The implementation of such policies would help fulfill the unmet medical needs of patients with RDs, improve the availability and accessibility of ODs in SA, and ultimately lead to improved health outcomes. Addressing the issue of OD policies is a multi-stakeholder problem that requires attention from societal, governmental, and regulatory perspectives. Since governments have created OD policies to address public health needs, prioritizing RDs and OD areas by establishing policies in regions that attract the pharmaceutical market to meet unmet needs is essential. Therefore, the region should assume responsibility to improve the availability and accessibility of ODs by establishing and publicizing incentive policies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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