Orphan drug policies in different countries

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Abstract

Objectives Due to the low prevalence of rare diseases (RDs) and the small number of individuals affected with a RD, challenges complicate the development of and accessibility to medications and medical devices to prevent, identify, treat or cure these RDs. The aims of this study were to analyse and compare regulations and policies related to accessibility of orphan drugs (ODs) in different countries which have policies or systems in place which are specific for RDs and ODs in Europe and the United States (US).

Methods A comprehensive literature review was carried out. A total of 20 120 articles which contained information about accessibility and legislations, regulations and governmental policies related to RDs and ODs were retrieved.

Key findings Sixty-eight articles were included in this study. Classification of information related to 24 countries was based on six themes: OD policies, marketing authorisations, incentives offered, pricing of ODs, reimbursement and pharmacovigilance. The EU and United States have adopted policies and regulations aimed to improve OD accessibility in the last 20 years. Although all included countries had an OD legislation, only 16 countries had an OD or RD plan in place.

Conclusions Comparison of different legislations and policies in each country can be used to identify and address deficiencies in the field of RDs and improve accessibility of ODs.

Keywords accessibility; orphan drugs; plans and policies; rare disease

Introduction

Rare diseases (RDs) affect millions of people of all ages, genders and ethnicities worldwide. Over 80% are serious and life-threatening genetic conditions and affect the paediatric population mostly.[1–3] RD classification differs between countries.[4] In the European Union, for a disease to be classified as a RD, the disease must affect <1 patient per 200 000 individuals.[5] The United States (US) defines a RD as one that affects <200 000 patients out of the total population.[6]

Due to the low prevalence of RDs and the number of individuals affected with a RD being relatively small, challenges complicate the development of and accessibility to medications and medical devices to prevent, identify, treat or cure these RDs. The ‘1983 Orphan Drug Act’ in the United States recognised the importance of pharmaceutical research in RDs and allocated special incentives for drug companies and researchers to help develop new treatments in the form of government credit lines and reduced taxes.[7,8] Soon after the Orphan Drug Act was passed in the United States, Japan and the European Union followed with issuing their own acts.[9] The European member states adapted Reg (EC) no 141/2000 (the Orphan Regulation) in December 1999.[10] The regulation stated that a ‘patient living with a rare disease should be entitled to the same level of care as other patients’. In 2009, the European Council emphasised that ‘the principles and overreaching values of universality, access to good quality care, equity and solidarity’ are of paramount value for RD patients.[11]

The ‘Orphan Designation’ is a legal procedure that allows for the designation of a medical substance with therapeutic potential for a RD before its first administration in humans or during its clinical development. The specified therapeutic indication is defined at the time of issuing of the marketing authorisation.[11]

Orphan drugs (ODs) carry a higher price tag than medications used for common conditions. The high cost of ODs has been linked to the complexity of developing therapies...
for RDs and the small population size of patients set to receive treatment.[12] Policy makers and payers in the EU and United States have a challenging situation where the limited resources available have to be prioritised and used to procure cost-effective medications with proved benefits for common conditions.[13]

A report on the ‘economic power of ODs’ published in 2012 stated that there was an increasing investment in the OD market particularly in research driven by the legislations issued in the EU and the United States.[14] It is estimated that the cost per patient for ODs is six times higher than non-ODs, a clear indication of their pricing power.[14] Incentives in the form of tax exemptions can lower drug development costs.[15]

Between 2001 and 2011, the OD market had its ‘most productive decade in the history of OD development, designations and approvals’.[16] A 2017 report declared that OD sales have been increasing and the market will continue growing rapidly, with sales expansion prediction at 11% per year, more than double the rate predicted for non-ODs.[17] It is estimated that the sales of ODs are set to increase by 11% a year and reach $262 billion by 2024.[18]

A recent study by Khosla and Valdez focused on plans, legislations or strategies related to RDs and ODs in 23 different countries in the EU, United States, Canada, South America, Asia and Australia. The authors stated that following the passing of laws on RDs, it is important that not only promotion of the law is dealt with but also the following through with the implementation of the law.[2]

Implementation of the US OD act was a result of combined efforts of medical researchers, government agencies and the pharmaceutical industry, among others. EU countries take government action one step further by not only including treatment and medication for RDs but also access to care for RD patients.[2] The aims of this study were to analyse and compare regulations and policies related to accessibility of ODs in different countries which have policies or systems in place that are specific for RDs and ODs in Europe and the United States.

Methods

A comprehensive literature review was carried out between January 2017 and December 2017. Electronic databases (PubMed, Orpha.net, EURODIS, EMA, FDA), available policy documents and disease-specific websites were searched. Regions and countries in the EU and United States with a publicly funded national health service and with policies or systems in place which are specific for RDs and ODs were included. Regions or countries without RD- or OD-specific legislation or policy were not included.

Issues related to accessibility of ODs (regulations, policies, marketing authorisations, reimbursement and pricing of ODs) were compared. The PRISMA[19] flow chart method was utilised.

A search strategy was used and keywords included the following: ‘rare’ or ‘orphan diseases’, ‘orphan drugs’, ‘orphan medication’, ‘orphan medicines’, ‘orphan pharmaceuticals’, ‘access’, ‘availability’, ‘accessibility’, ‘cost of orphan drugs’, ‘regulation’, ‘policy’, ‘Food and Drug Administration (FDA)’, ‘European Medicines Agency.EMA’. The dates of inclusion published literature ranged from the year 2000 to 2017. The year 2000 was chosen since it was the date when the first OD legislation for providing incentives for the development of medicines for RDs was approved in the EU parliament.[11] The search was limited to research published in English.

A total of 20 120 articles which contained information about accessibility and legislations, regulations and governmental policies related to RDs and ODs were retrieved (Figure 1). Peer-reviewed studies and reports which were related to accessibility of ODs in regions with a policy or system in place which is specific for RDs and ODs were included. Literature and reports on countries with a publicly funded national health service were included in the study. Literature which did not address RDs and OD accessibility issues was not included. Literature about countries which did not have an RD- or OD-specific legislation or policy was not included.

Sixty-eight articles that were deemed relevant to be included in the study were identified. Classification of retrieved information was based on six different themes adapted from Gammie et al.[20] The six themes explain the political or regulatory mechanism utilised and the relevant influence with regard to patient access to ODs.[20] The six themes were as follows:

1 OD policies
2 Marketing Authorisation
3 Incentives offered
4 Pricing of ODs
5 Reimbursement
6 Pharmacovigilance

Subthemes were generated from the six themes identified (Table 1).

Results

Sixty-eight articles relating to 24 countries (23 European countries and the United States) were included in the study.

Orphan drugs policies

Subthemes of OD policies included the following: (i) OD legislations, (ii) national RD plans, (iii) cross-border regulation and (iv) OD designation.

OD legislations

The OD act introduced in the United States in 1983 and the EU legislation for OD introduced in 2000 both aimed to ease the burden of cost on patients and make OD development a lucrative decision for pharmaceutical companies.[21] The EU and US legislations contain incentives for research and development of ODs (Table 2). The incentives include the following: market exclusivity, tax incentives and free scientific advice.

Some OD legislations differed from others in terms of incentives offered. Countries such as Austria, Denmark, France and Italy offer free scientific advice to companies...
involved in the development of ODs whilst countries such as Belgium and Portugal do not.\[20\]

In the United States, ‘fast track’ for ODs is available. Drugs which are in the fast track are those which are eligible for priority review and quicker approval.\[22\]

Table 1  Themes and subthemes used to assess accessibility of orphan drugs in the EU and United States

<table>
<thead>
<tr>
<th>Themes</th>
<th>Subthemes</th>
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<tbody>
<tr>
<td>OD policies</td>
<td>OD legislations</td>
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<td></td>
<td>National RD plans</td>
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<tr>
<td></td>
<td>Cross-border regulation</td>
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<tr>
<td>Marketing</td>
<td>OD designation</td>
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<tr>
<td>authorisation</td>
<td>Market access</td>
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<td></td>
<td>Market and data exclusivity</td>
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<tr>
<td>Incentives offered</td>
<td>Financial incentives</td>
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<td></td>
<td>Non-financial incentives</td>
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<tr>
<td>Pricing of ODs</td>
<td>Managed entry agreements</td>
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<tr>
<td>Reimbursement</td>
<td>Payment and copayment</td>
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<tr>
<td>Pharmacovigilance</td>
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OD, orphan drugs; RD, rare diseases.

National RD Plans

The primary goal for National RD Plans (NRDP) is to produce a policy that promotes research, improves access to health care and ODs and increases awareness on RDs.\[23\]

Unlike OD legislations, NRDPs do not have a specific legislation in place but show the ‘readiness’ of a country or region to take action in the RD field.\[24\] NRDPs are documents with a vision on how to improve health outcomes for RD patients. Three EU countries (Bulgaria, Greece and Romania) established joint NRDPs which helped outline the needs of RD patients and may impact OD purchasing power and affect government budgeting, pricing and reimbursement.\[25\] Other countries which have a NRDP in place are Belgium, Czech Republic, Estonia, France, Germany, Ireland, Italy, Latvia, Netherlands, Poland, Portugal, Spain and the UK.\[20\]

Cross-border regulation

The EU has a centralised procedure for OD approval and OD designation for all its member states. The centralised procedure aims to improve uniformity in terms of OD accessibility for everyone living within a member state.\[26\]

The 2011/24 European directive states that patients within...
the EU have a right to gain cross-border treatment. The 2011/24 directive allows RD patients within any member state the right to access health care within any EU healthcare service if their national healthcare system cannot provide treatment required regionally within an appropriate time span.\[22\]

Orphan Drug Designation

Orphan Drug Designation (ODD) is usually granted under four criteria which are as follows: severity of RD, prevalence of RD, pharmacoconomics and unfulfilled treatment needs (no treatment available for RD).\[27\]

The prevalence of a RD is dependent on the region’s definition of what an RD is. A pharmacoeconomic approach is considered if the OD will yield a profit and cover development costs. Due to the limited number of RD patients, there are a few ongoing clinical trials involving ODs and this can lead to a lack of robust clinical data.\[28\] ODD permits that drugs gain exemptions from specific aspects of clinical trials or in the case of the EU and get help for research throughout the OD development programme.\[12\]

Marketing authorisation

Figures 2 and 3 show the number of marketing authorisations (MAs) for ODs granted by the FDA (between 1983 and 2017)\[32\] and EMA (between 2001 and 2017) respectively. The FDA granted the majority (n = 50) of MAs for ODs in 2017. The smallest number (n = 2) of MAs for ODs was granted by the FDA in 1983. The EMA granted the majority (n = 15) of MAs for ODs in 2014. The smallest number (n = 3) of MAs for ODs was granted by the EMA in 2001. There were no MAs granted in the EU in the year 2000 when the legislation was implemented.\[33\]

Incentives offered

Financial incentives allow OD manufacturers to recover costs of research and development.\[34\] Blankart et al.\[21\] found that <12% of OD clinical trials would have still been conducted without the financial incentives offered by OD legislations. Financial incentives offered by both the EU and the United States consist of funding of research, tax exemptions, fee reductions and market exclusivity.\[20\]
Non-financial incentives offered by the EU and United States include the following: accelerated procedure schemes, off label use schemes, research advice and scientific and regulatory consultation (protocol assistance). Compas- sionate use is another type of incentive offered in the EU and the United States. The compassionate use programme is a treatment programme that allows the use of unlicensed ODs under strict conditions. The medicine can be made accessible to a patient with a RD when no other licensed medication can be used. In the EU, the compassionate use programme is regulated by the Committee for Medicinal Products for Human Use. Certain EU countries allow prelicensing use of ODs given that there is some clinical evidence. This allows better accessibility for RD patients living in countries where a MA has not been granted yet for the OD.

Pricing of orphan drugs
There are no reference prices issued by sponsors for ODs. Prices of ODs are generally comparable in the EU and United States but differences in reimbursement and copayment can affect accessibility. Patients in the United States can face a higher cost of ODs due to copayment and reimbursement issues. ODs with multiple RD indications for chronic RDs or for which an increase in overall survival or health-related quality of life has been demonstrated are associated with a higher annual cost of illness. There were no associations found between annual cost of illness of ODs across countries and the different pricing and reimbursement systems. Prices of ODs are influenced by elements such as accessibility to an alternative drug treatment, repurposing and reimbursement.

Unlike the United States, most EU member states have adapted a fixed pricing method which involves having a reference price set by the manufacturing company. The price requested by the manufacturer can be compared to the price in other regions or can involve a set price agreed on by the government or regulatory body. These two examples of setting a fixed price ensure equality between countries when it comes to access to ODs. Germany and the United States have a free pricing market which allows the manufacturer to name the price.

Reimbursement
A barrier to RD patient access to ODs is the reimbursement factor. ODs that are too expensive for the patient or not paid for by the patient’s insurance or government can be inaccessible. The pharmacoeconomical values of ODs are assessed by the Health Technology Assessment (HTA) in both the EU and the United States. The cost-effectiveness of the OD is assessed by the HTA under two

![Figure 3](image-url) Number of marketing authorisations for orphan drugs granted by the EMA (N = 142).

<table>
<thead>
<tr>
<th>Year</th>
<th>Per cent expenditure, %</th>
<th>Country</th>
</tr>
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<tbody>
<tr>
<td>2006</td>
<td>1.2</td>
<td>Netherlands</td>
</tr>
<tr>
<td>2007</td>
<td>1.9</td>
<td>European Union</td>
</tr>
<tr>
<td>2010</td>
<td>3.2</td>
<td>United States</td>
</tr>
<tr>
<td>2012</td>
<td>11.2, 21</td>
<td>European Union</td>
</tr>
<tr>
<td>2013</td>
<td>2.7</td>
<td>Global</td>
</tr>
<tr>
<td>2014</td>
<td>3.1</td>
<td>Netherlands</td>
</tr>
<tr>
<td>2016</td>
<td>4.7</td>
<td>Sweden</td>
</tr>
<tr>
<td>2018</td>
<td>9.7</td>
<td>France</td>
</tr>
<tr>
<td>2020 predicted</td>
<td>5</td>
<td>European Union</td>
</tr>
</tbody>
</table>

Table 3 Percentage expenditure on orphan drugs from total health budgets

5
themes: quality-adjusted life years and incremental cost-effectiveness ratios. Due to lack of clinical data for ODs, it is difficult to conduct HTA, and as a result of this, many countries make exemptions when it comes to OD assessment. Other factors taken into account by the United States and the EU are clinical impact, medical ethics, impact of the OD on the budget, number of patients affected and political pressure. Italy and France reimburse 95% of the ODs available on the EU market whilst Sweden reimburses 70% due to differences in HTA. Countries in the EU do not rely entirely on data by the manufacturer, rather they take into account cohort studies and published literature on ODs. France looks into the value of preserving a patient’s morality regardless of the cost of the OD. Table 3 shows the percentage expenditure on ODs from total health budgets in different countries and regions during different years.

**Pharmacovigilance**

Pharmacovigilance or postmarketing surveillance of an OD is an important step to continue to assess the safety and clinical benefit of the OD. In the EU and the United States, pharmacovigilance is utilised to establish if the OD is clinically efficacious, and if it is found that it is not, the OD is withdrawn from the market. Pharmacovigilance plans are followed by regulatory bodies in the EU and the United States to gather information on areas specific to ODs such as identified and potential risks and safety issues related to pharmacokinetics.
Discussion

The study aimed to give information about different policies, regulations, incentives and pricing in different countries in Europe, which are regulated by the national regulatory bodies and EMA and the United States which is regulated by the FDA. Comparison of different legislations and policies in each country can be used to identify and address deficiencies in the field of RDs and improve accessibility of ODs.

Differences in pricing and reimbursement of costs related to RDs exist between different European countries. RD patients might experience differences in OD accessibility and RD treatment across EU member states. Although all included countries had an OD legislation, only 16 countries had an OD or RD plan in place. The United States does not have a national plan for ODs or RDs. Countries lacking a national OD or RD plan have incorporated their plan for ODs in the national OD Legislation. Reasons why certain EU countries do not have a national plan for ODs might be due to lack of enforcement by the EU and EMA. The implementation of a national OD or RD plan is a topic that individual EU countries deal with independently of other member states.

The EU and United States have a centralised MA procedure for ODs and have specific procedures for applying for OD designation. The EU and United States have accelerated authorisation procedures which depend on the severity of the RD and the unmet medical needs of the patient. Accelerated access procedures can help decrease MA timeframes, thus improving RD patient access to treatment.

Financial incentives to companies involved in the research development and marketing of ODs were offered by all countries included considered in the study. Prelicensing or compassionate use programmes allow patients to access unlicensed medications for RDs. Prelicensing access does not mean that the drug is available for everyone. Compassionate use programmes are usually carried out on an individual named patient basis and are not usually reimbursable by the insurance or public health care.

Market exclusivity is highly lucrative for the OD manufacturer and can be problematic for research and development of new ODs. OD designation should not be used to hinder the development, licensing and marketing of other products which have demonstrable clinical potential for the same condition. The existence of market exclusivity remains an important incentive for research and development of ODs but can pose risks, particularly monopolisation and over-pricing of ODs, which can impact RD patients’ accessibility to treatment.

Accessibility to treatment can also be hindered by the inflated prices of ODs. The fixed price model was implemented by some of the countries (n = 10) included in the study. Fixed pricing can be limiting and prices given can be affected by international purchasing power parity differences.

Table 4 gives information about ODs and RD-specific findings by country or region.

Reimbursement also affects accessibility to ODs. The cost-effectiveness factor of the HTA primarily influences reimbursement. All of the EU countries and the United States consider cost-effectiveness when carrying out assessment on ODs and ODs are sometimes made available even with minimal clinical evidence when compared to non-ODs.

RD patients in the United States are faced with copayment issues which can pose a financial burden. Although the United States has the highest number of ODDs globally, RD patients might face challenges when accessing ODs due to their high cost and this might imply that availability does not guarantee accessibility.

The role that patient advocacy groups and alliances play in accessibility to RD medication is paramount. The US-based National Organisation for Rare Diseases (NORD) and its European counterpart EURORDIS focus on improving care of RD patients by improving access to information and on some occasions, access to ODs. Patient advocacy groups can lobby third-party payers or governments which fund health care to provide full reimbursement of ODs regardless of their high price. Patient advocacy groups may form partnerships with regulatory agencies, for example EURORDIS with EMA.

The main limitations in the study were that only literature available in English was considered between the years 2000 and 2017. Review of OD and RD regulations and policies in languages other than English was not conducted. Only peer-reviewed journals were included, and grey literature was excluded.

Conclusion

The EU and United States have adopted policies and regulations aimed to improve OD accessibility in the last 20 years. There are differences between countries in the types of policies and regulations implemented, and this can have an effect on accessibility and availability of ODs. Future amendments to existing policies and regulations and pricing of novel therapy for RDs should be made, keeping the goal of increasing accessibility and improving the quality of life of RD patients in mind.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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Authors’ contributions

AA designed study, analysed data. JVS helped design study, supervised study and drafted paper. LMA reviewed study...
and reviewed paper. ASI helped design study, supervised study and reviewed paper.

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