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Orphan drugs: the regulatory environment

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The definition of a rare disease is not universal and depends on the legislation and policies adopted by each region or country. The main objective of this article is to describe and discuss the legal framework and the regulatory environment of orphan drugs worldwide. Some reflections and discussions on the need for specific orphan drug legislation or policies are described at length. Furthermore, some aspects of the history of each region in respect of the orphan drug legislation evolution are outlined. This article describes and compares the orphan drug legislation or policies of the following countries or regions: United Sates of America (US), European Union (EU), Japan, Australia, Singapore, Taiwan and Canada. The incentives described in the orphan drug legislations or policies, the criteria for designation of orphan status and the authorisation process of an orphan drug are also described and compared. The legislations and policies are to some extent similar but not the same. It is important to understand the main differences among all available legislative systems to improve the international collaboration in the field of orphan drugs and rare diseases.

Without incentives many orphan drugs would not be developed and authorised because they are unprofitable for the pharmaceutical industry. This article illustrates and discusses the ratio between the orphan drug designation and approval in Europe, the US, Australia and Japan. The orphan drug legislations and policies have been successful given that more medicines for rare diseases have been authorised since the implementation of these legislations and policies.

Why orphan drugs are a special class of medicines

An orphan drug is a medicinal product that is developed to treat, diagnose or prevent a specific rare disease [1,2].

Rare diseases affect 6–8% of the population in the world [EURORIS, About rare diseases. EURORIS website, 2012: http://www.eurordis.org/about-rare-diseases] [3,4] and are often called orphan diseases because the pharmaceutical industry does not have an interest in developing medicines for a small number of patients [H.E. Heemstra, PhD thesis, University of Utrecht, 2009]. This would compromise its profits and the return on shareholders' investment. Orphan diseases therefore require some attention from governments and the regulatory competent authorities.[a]

In this context, several governments developed specific legislation and policies, which stimulate the research and development of orphan drugs for specific diseases [Heemstra, H.E. PhD thesis, University of Utrecht, 2009] [5,6].

There is no single definition of rare disease. Some of the definitions are based on the number of patients affected by the disease and others take into account other important factors, such as the severity of the disease and the existence of adequate treatments. According to the WHO, and the relevant legislation or policy in the EU, United States of America (US), Australia, Taiwan, Canada, Singapore and Japan a rare disease can be defined as described in Table 1.

The number of patients, necessary for a disease to be accepted as an orphan disease, is clearly related to the population size of these countries (with the exception of Singapore) [5]. A universally

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[a] Authority responsible for granting, controlling and supervising the manufacturing, the marketing, the importing, the distribution of medicines.

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TABLE 1

There are several definitions of rare disease that are accepted by different countries according to their legislation or policy. The number of patients, necessary for being accepted as an orphan disease, is in general related to the population size of these countries (with exception of Singapore)

Country, region or organisation	Relevant orphan drug legislation	Definition	Population per country or region	Low prevalence of the disease	Number of patients necessary for being accepted as an orphan disease	Refs
WHO	–	A disease or a condition affecting 0.65–1 in 1000 inhabitants	–	6.5–10/10,000	N/A	[5,7]
EU	Regulation EC No. 141/2000	A life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 persons in the community; or life-threatening, seriously debilitating or serious chronic condition in EU and without incentives the Sponsor would develop the medicine; and there are no other satisfactory method of diagnostic, prevention or treatment of the condition	502,500,000	5/10,000	Fewer than 251,250	Demographics of the European Union Eurostat: http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/ [8]
US	Orphan Drug Act of January 1983 and amendments	A disease or a condition, which affects fewer than 200,000 patients in US	311,864,524	6.4/10,000	Fewer than 200,000 or more 200,000 patients if the cost of development will not be recovered	US Census Bureau: http://www.census.gov/population/www/popclockus.html [9–11]
Japan	Law 145 – 10 August 1960 (revised in 1993)	A disease that affects fewer than 50,000 patients in Japan	127,950,000	3.9/10,000	Fewer than 50,000	Portal site of official Statistics of Japan: http://www.e-stat.go.jp/SG1/estat/ListE.do?bid=000001032402&cycode=0 12]
Australia	Therapeutic Goods Act in 1989 (revised in 1997)	A disease that affects fewer than 2000 patients per year	22,663,156	≈1/10,000	Fewer than 2000	Australian Bureau of Statistics: http://www.abs.gov.au/ausstats/abs@.nsf/0/1647509ef7e25faaca2568a900154b63?opendocument [13]
Canada	No specific legislation	Canada accepts the WHO definition	34,531,000	≈1/10,000	Fewer than 3300	Statistics Canada: http://www.statcan.gc.ca/ig-gi/pop-ca-eng.htm [14]
Singapore	Medicines Act Chapter 176, section 9)	A life-threatening and severely debilitating illness affecting fewer than 20,000 patients	5,100,000	≈39.4/10,000	Fewer than 20,000	National Population and Talent Division: http://www.nptd.gov.sg/content/NPTD/home.html [15]
Taiwan	Rare disease and orphan drug act	Diseases with prevalence lower than formulated and publicity announced by the central competent authority, and recognised by the orphan drug committee	23,188,078	No specific number of patients is mentioned in the legislation	No specific number of patients is mentioned in the legislation	National Statistics Republic of China (Taiwan): http://eng.stat.gov.tw/mp.asp?mp=5, rare disease and orphan drug act (Twain): http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html

accepted definition of a rare disease and orphan drugs could be considered by different regions and countries, because it would be easier to develop and submit a designation and/or an application for a marketing authorisation for an orphan drug worldwide [4,5].

A rare disease can be a genetic disease, rare cancer, congenital malformation, auto-immune disease, toxic disease, infection disease, tropical infection disease, degenerative disease and many others [7]. The EU estimates that there are approximately 6000–8000 rare diseases and the majority of them are genetic diseases (80%) [EURORIS, About rare diseases. EURORIS website, 2012: http://www.eurordis.org/about-rare-diseases; ORPHANET, About rare diseases. Orphanet website, 2012: http://www.orpha.net/consor/cgi-bin/index.php] and appear early in life [2,6]. These diseases are life-threatening and/or chronically debilitating and many patients die before reaching adulthood [Heemstra, H.E. PhD thesis, University of Utrecht, 2009; ORPHANET, About rare diseases. Orphanet website, 2012: http://www.orpha.net/consor/cgi-bin/index.php] [7,16]. Rare cancers are one of the most studied diseases and for that reason they have the highest chance to have not only an orphan drug designation but also an orphan drug approved [4]. According to the data available in the EU and the US it can be concluded that 30–40% [4] of the orphan drugs designated or authorised are for rare cancers [4,17,18].

Need for an orphan drug regulation

There is no treatment for many rare diseases because the pharmaceutical industry does not want to invest in medicines, for which the size of the potential market is small. The investment in development might not be recovered by the expected sales without government incentives. In other words, the rarity of a particular disease limits drug development. Patients with a rare disease have an equal right to medicines as other patients with a well known disease (a concept supported by social justice, human rights and equality). Governments and society cannot accept that some patients do not benefit from medical progress, since their specific illness affects a small number of patients [7]. In this context, some governments and authorities have already changed their pharmaceutical legislation and policies [5] to encourage the research and development of orphan drugs through some economic and regulatory incentives [7,19,21]. Incentives to develop new orphan drugs are still needed [20]. Pharmaceutical companies invest in the development of new medicines, and are expected to be rewarded with a reasonable return on their investment [4,19].

USA: US Orphan Drug Act

In the United States of America there was pressure and lobbying by the National Organisation for Rare Disorders to have a specific legislation that would encourage the pharmaceutical companies to develop medicines for orphan diseases [Office of Inspector General, United States Department of Health and Human Services, The Orphan Drug Act implementation and impact, 2001: http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf]. This organisation was established by families and patients with rare diseases with the main objective of lobbying for specific legislation in the area of orphan drugs [Office of Inspector General, United States Department of Health and Human Services, The Orphan Drug Act implementation and impact, 2001: http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf]. In this context, in 1979 FDA established a Task Force on orphan diseases that concluded: ''Whenever a drug has been identified as a potentially life-saving or otherwise of unique major benefit to some patient, it is the obligation of society, as represented by government, to seek and to make that drug available to that patient'' [24]. Finally, in January 1983 the Orphan Drug Act was adopted in the USA [Office of Inspector General, United States Department of Health and Human Services, The Orphan Drug Act implementation and impact, 2001: http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf] [23,24].

Australia: Therapeutic Goods Act 1990

In 1989 the Therapeutic Goods Act was amended in Australia to include some incentives which would encourage Australian pharmaceutical companies to develop orphan drugs in Australia. However, the full orphan drug policy was established in 1997 [7,13].

Singapore: Medicines – Orphan Drug 1991

Singapore's orphan drug legislation was the third orphan drug legislation to be published worldwide (Medicines – Orphan Drug – exception order of 1991; Medicines Act Chapter 176, section 9). Singapore recognised early the need for specific orphan drug legislation to help patients with rare diseases. This legislation promotes and enables the importation of orphan drugs for a specific rare disease that has been identified by doctors or dentists and do not provide incentives to pharmaceutical companies that intended to market orphan drugs in Singapore [15,22].

Japan: Pharmaceutical Affairs Law 145

In 1993 Japan revised its Pharmaceutical Affairs Law (Law 145 – 10 August 1960 – Chapter 9-3 article 77-2 to article 77-2-6) with the aim of including important measures that would encourage pharmaceutical companies to develop medicines for orphan diseases in Japan [12,20].

Canadian policies

There are other countries like Canada that do not have specific legislation for orphan drugs. In 1997 Canada rejected the need for specific legislation on orphan drugs [14], because Canadians already have access to orphan drugs approved by the US through the normal approval process. Moreover, there are already some Canadian policies in place, which promote the development of orphan drugs [14]. These policies include some incentives described in Table 2 [14].

European Union: Regulation EC No. 141/2000

On the 30th November 1995 a resolution adopted by the Council of Minister of the EU [19] had requested the European Commission to look into the issue of rare diseases and contemplate specific legislation regarding the orphan drugs [The Council meeting – health Brussels 30 November, 1995: http://europa.eu/rapid/pressReleasesAction.do?reference=PRES/95/344&format=HTML&aged=1&language=EN&guiLanguage=en].

In 1999, the EU followed the same principles of other countries and adopted legislation for orphan drugs [8] (Regulation (EC) No. 141/2000) to encourage pharmaceutical companies to develop and market orphan drugs in the EU. This particular legislation came into force on the 28th April 2000 and set up the EU procedure for

TABLE 2

Comparative incentives describe in the orphan drug legislation or policies adopted by different regions

	Incentives to promote the development of orphan drugs in different countries or regions [Refs]					
	US-FDA [9–11]	**EU-EMA [8]**	**Japan [12]**	**Australia [13]**	**Taiwan [Rare disease and orphan drug act (Twain): http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html]**	**Canada [14]**
Orphan drug legislation	Yes	Yes	Yes	Yes	Yes	No (policy)
Market exclusivity of an orphan drug	Seven years	Ten years (might be reduced to six years), plus two additional years for medicines that complying with the agreed paediatric investigate plan (PIP)	Ten years – extension of re-examination period	N/A (under discussion)	Ten years + two years	N/A
How to break the market exclusivity for similar medicinal product	Clinical superiority and no 'sameness' Or the first MAH are unable to provide sufficient quantities; Or consent of the first MAH	Clinical superiority and no similarity Or the first MAH are unable to provide sufficient quantities; Or consent of the first MAH	N/A	N/A	Clinical superiority and not 'the same kind' Or the first MAH are unable to provide sufficient quantities; Or consent of the first MAH. Or if the price of the first orphan is unreasonable	N/A
Marketing authorisation review process (assessment of a medicine) (not only for orphan drugs)	Allows sponsor to apply for accelerate review	Allows sponsor to apply for accelerate review	Fast track review	Allows sponsor to apply for accelerate review	N/A	Fast track review can be considered
Grants from regulatory competent authorities	Yes	Some incentives by Member States and EC –Community research program - 7th framework program grant	Yes	No	Yes - Determined by the central competent authority	N/A (support research)
Financial incentives	50% federal Tax credit for clinical research	Members states incentives	Tax Exemption Law 12% of expenses(Law no. 26 1957)	No	Determined by the central competent authority	Tax incentives
Fee reduction for MAA	Yes	Fee reduction for an application 100% fee reduction for inspections	Tax reduction (16%)	Yes	Yes	Yes
Scientific advice (protocol assistance and/or consultation for development)	Yes	Yes – 100% fee reduction	Yes	No	Yes	Yes
Special incentives for SME (small and medium sized enterprises) sponsors	N/A	Waiver of market authorisation application fees and for post authorisation activities (50% reduction)	N/A	N/A	N/A	N/A
Regulatory assistance	Yes	Yes	Yes	Yes	Yes	Yes

the designation of an orphan drug, the Committee for Orphan Medicinal Products (COMP), the community marketing authorisation and other incentives are described in Table 2 [8].

On the 27th April 2000 the European Commission adopted another new Regulation (EC) No. 847/2000 [25] that lays down the provisions for implementation of the criteria for designation of an orphan drug, definitions of the concepts of similar medicinal products and clinical superiority [8,25]. The above-mentioned regulations are the key regulatory framework of the orphan drug provisions in EU.

Taiwan: orphan drug legislation

In January 1998 Taiwan recognised the need for a specific orphan drug legislation. In this context, several meetings were held to discuss this important public health matter. Based on the discussions and conclusions legislators drafted an Orphan Drug Act that was established in January 2000 and it was enforced on the 9th August 2000 [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html]. This legislation was revised on the 19th January 2005 and recently on the 8th December 2010 [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html] [22].

Incentives to promote the development of orphan drugs

Table 2 describes the major differences in incentives described in the orphan drug legislation and policies adopted worldwide.

Market exclusivity of an orphan drug

In the EU, Taiwan and the US the orphan market exclusivity right is linked to the therapeutic indication that was granted in the marketing authorisation. The market exclusivity is a period of time during which a medicinal product, that is similar or the same and for the same therapeutic indication as an authorised orphan drug, cannot be validated and authorised by a regulatory competent authority.

The same is applicable in the case of a line extension and the extension of an indication of a certain medicine, which is the same or similar to an orphan indication already authorised.

The market exclusivity period in the EU and Taiwan is ten years [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html] [8,26] and in the US is only seven years [9–11]. In the EU, the period of ten years can be reduced to six years, at the end of the fifth year, if a Member State informs the agency that the criterion for designation of an orphan drug is no longer valid [8]. The period of market exclusivity can be extended by two additional years for medicines that comply with the agreed paediatric investigate plan (PIP).[b]

According to the EU, Taiwan and US legislation, it is possible to break the market exclusivity for similar (EU) [8,25–27]/'same kind' (Taiwan) [14]/'same' (US) [9–11] of an orphan drug already authorised if the second applicant proves no similarity (EU) [8,25]/'not the same kind' (Taiwan) [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html]/not the same (US) [9–11] with an orphan drug already authorised for the same indication. Furthermore, it is also possible to break the market exclusivity, if the second applicant proves clinical superiority [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html] [8–11,25]. In other words, a new orphan drug that is safer, more effective, or clinically superior. Moreover, in the EU, the US and Taiwan, it would be possible that the second applicant has the consent of the applicant of the original orphan drug or the authorisation may be granted when the second applicant is able to prove that the first applicant is unable to supply sufficient quantities of the orphan drug [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html] [8–11,25]. The Orphan Drug Act of Taiwan allows the break of the market exclusivity right if the price of the first orphan drug authorised is unreasonable [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html].

The Japanese Authorities grant a re-examination period of up to ten years for orphan drugs [12] and virtually works as protection period.[c] The re-examination period was introduced in 1979 and works like a renewal of a Marketing Authorisation Application in the EU. During this period, no other applicants with the same medicinal products are allowed to submit an application for a marketing authorisation for the same active substance.

In Australia the market exclusivity is still under discussion. In Singapore and Canada there are no specific differences between an orphan drug and a non-orphan[d] drug in regard to market exclusivity.

Process review: accelerate assessment

In all regions the accelerated assessment (accelerated review or fast track review) is possible for orphan and non-orphan medicines. However, only in Japan and Australia is the accelerated assessment process described in the orphan drug legislation.

Funds to promote research on orphan drugs

According to the orphan drug legislation in Japan and in the US, governments are obliged to secure some funds to promote research and development of orphan drugs. In the US the FDA has a grant programme that supports the clinical development of orphan drugs. The grant programme is competitive and only some applications (27%) [26] are successful. Every year between 12 and 15 grants are given to universities or companies [29]. According to FDA this grant programme is important because it helped the authorisation of more than 45 orphan drugs in the US [30]. The FDA follows closely the progress made by the successful candidates and provides adequate training to the investigators [9–11,23,24]. Furthermore, in the US the National Institute of Health (NIH)

[b] Paediatric investigation plan was established by Regulation (EC) 1901/2006 for all medicinal products not yet authorised by 26 July 2008. According to article 7 of this regulation the applicants are obliged to include results of studies that have been conducted in compliance with a PIP or a decision on a waiver or on a deferred PIP in applications for a marketing authorisation.

[c] Period of time during which a specific biosimilar, generic, hybrid cannot be placed on the market.

[d] Non-orphan medicines are conventional medicines that do not apply for or get the orphan designation.

promotes and supports some research in the area of orphan drugs. In the EU, the European Medicines Agency (EMA) does not have a grant programme. However, there are some national and European incentives, which may promote the research and development of orphan drugs [7,8,21]. Applicants may apply for funds from the EU Framework Programmes (FP) for research and technological development in the area of rare diseases (at the moment there is FP7 programme on going) [28,31]. At national level there are some EU countries, such as France, Germany, Hungary, Italy, the Netherlands, Spain and Portugal that have some funding opportunities in the area of rare diseases [European Union Committee of Experts on Rare Diseases, 2011 Report on the state of the art of rare disease activities in Europe of the European Union Committee of Experts on rare diseases, 2011: http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivities.pdf].

In Taiwan, the central competent authority can promote the research and development of orphan drugs through some financial incentives and grants [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html]. In Australia and Canada there is no grant programme in place. In the US, the EU, Taiwan, Japan and Canada there are some more financial incentives described in Table 2, which may encourage the development of new orphan drugs.

Other important incentives

Fee reductions and regulatory assistance are provided by all regions. Free scientific advice and/or protocol assistance is provided by all regulatory competent authorities with the exception of Australia. In the EU, there are some further financial incentives for small and medium sized enterprises (SME) [8].

All above mentioned orphan drug incentives will only have an impact on the development and market authorisation of an orphan drug if the reimbursement by different regulatory competent authorities is approved [4]. In other words, if the orphan drug is too expensive and if there is no reimbursement approval, patients will not be able to afford the orphan drug [4] and pharmaceutical companies would not have the expected return on their investment. In EU there are some differences in the reimbursement policies among Member States that might have an impact in the final price, reimbursement ceilings and affordability of orphan drugs [32,33]. In the USA the patients and industry are facing same pressures from public and private insurances regarding the reimbursement of orphan drugs [34].

Important aspects of orphan designation

To qualify for the incentives described in the legislation, the applicant must obtain an orphan designation before the submission of a Marketing Authorisation Application (MAA). Having been issued an orphan designation the regulatory competent authorities acknowledge that an orphan disease has been identified [30]. There is no orphan designation process described in the Canada policy, or in the Singapore and Taiwan legislations [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html] [15]. In the Singapore legislation it is clear that the doctor or dentist identifies and designates orphan diseases. In Taiwan it is the Committee of orphan drugs that is responsible for the identification and control of rare diseases [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html]. In both regions regulatory competent authorities accept an orphan drug for a particular rare disease that was approved by other competent regulatory authorities [Rare disease and orphan drug act (Twain), 2011: http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html] [15].

Table 3 illustrates the major differences in the criteria for designation as orphan drugs in the EU, the US, Japan and Australia.

Having looked at the data in Table 3, it is acknowledged that the prevalence of the orphan disease is one of the criteria common to the four regions. It is only in the EU and Australian legislation that the severity of the rare disease is crucial for the orphan drug designation. In the EU the plausibility of the proposed orphan indication might be a relevant criterion when assessing the orphan designation. The EU and US legislation foresaw that an important criterion for the orphan designation could be the improbable development of a particular orphan drug without incentives (due to lack of economic viability), which was not considered by Japan and Australia.

The high priority of certain orphan drugs and their significant benefit to patients are important criteria considered not only by Japan but also by the EU. Japan considered the feasible development plan of an orphan drug as a crucial criterion for the orphan designation, and this is not considered by other regions. Australia might refuse the orphan drug designation if the same designation was rejected by FDA, EMA and Canadian authorities. The Australian legislation mentions other European National Competent Authorities (NCAs) such as the UK (MHRA), Sweden (MPA) and the Netherlands (MEB), which may have refused the orphan drug designation. However, the orphan designation is granted by the EU Commission following a positive opinion by the EMA. Furthermore, orphan drugs must be approved centrally according to Regulation (EC) 726/2004. Therefore, the Australian legislation is not accurate on this matter and a revision might be considered.

Many orphan designations are granted but only a small number of these designated orphan products are authorised (Table 4), because the orphan designation is requested early in the research phase and some of these potential orphan drugs will not complete their clinical development. Pharmaceutical companies would like to obtain an orphan designation to promote their research and to attract new investors and shareholders [35,36].

Having looked at the data in Table 4 and Fig. 1, it can be concluded that the ratio between orphan designation and approval is quite different in the four regions. Surprisingly, the ratio is quite high in Japan (64.3%), which might be correlated with one of the criteria of orphan designation (feasibility of research program). In other words, pharmaceutical companies in Japan might apply for designation on the basis of a robust drug development with high feasibility of development. In Australia, the ratio between orphan drug designation and approval is 26.8%, which can be considered high. This value can be related to the fact that Australia accepts orphan drugs which were not refused by other competent authorities (Table 3). The ratio between orphan drug designation and approval is higher in the US (15.4%) than in the EU (7%), because the US Orphan Drug Act was adopted 17 years earlier than the EU Orphan Drug Regulation. Therefore, more orphan designation and possible orphan drugs were accepted and approved in the US during this period.

TABLE 3

To qualify for the incentives described in the orphan drug legislation of Europe, the US, Japan and Australia, the pharmaceutical Industry must obtain an orphan designation. The major differences in criteria for designation of orphan status are described in this table

Criterion for designation as an orphan drug	Country or region			
	EU [8,28]	**US [9–11]**	**Japan [12]**	**Australia [13]**
Severity of the disease	The life-threatening or chronically debilitating nature of the condition	N/A	N/A	To treat, prevent or diagnose a rare disease
Prevalence of the condition	The prevalence of the condition in the EU not more than 5/10,000	The disease or condition affects fewer than 200,000 patients	The disease or condition affects fewer than 50,000 patients	The disease or condition affects fewer than 2000 patients
Non return on investment	It is improbable marketing a medicinal product in EU, without incentives	Lack of economic viability when the prevalence exceeds 200,000 patients	N/A	N/A
High priority in the health care needs	No satisfactory method of diagnosis prevention or treatment exist, or if exist, the new medicinal product will be of significant benefit to the patients	N/A	No alternative medicine and the new medicinal product will be of significant benefit to the patients	N/A
Feasibility of research program of a medicine	N/A	N/A	High possibility of development due to a feasible drug development plan	N/A
A medicine refuse by competent authorities	N/A	N/A	NA	No refuse by other Competent Authorities (FDA, Canada, EMA/EC)

TABLE 4

The Orphan Drug Designation and approval in the EU, the US, Australia and Japan (June 2012) are described in this table

Region/country where orphan drugs have been designated or approved as orphan drugs	Orphan drugs		
	Designation as an orphan drug	**Approval of an orphan drug**	**Ration (%)**
EU	1000	70	≈7.0%
US	2609	403	≈15.4%
Australia	231	62	≈26.8%
Japan	269	173	≈64.3%

Obtaining an orphan drug designation in the US

In the US the Orphan Drug Designation is issued by FDA [Office for Orphan Product Development (OOPD)] [30]. Having submitted a request for an Orphan Drug Designation FDA will assess and issue a decision. During the period of evaluation FDA can raise some questions to the applicants. Having obtained the orphan designation the applicant is obliged to submit a comprehensive report on the present and future progress of the development of the orphan drug within 14 months and annually thereafter [23,24]. Based on the assessment of this report FDA can withdraw the orphan drug status [23,24].

Obtaining an orphan drug designation in Japan

In Japan the Minister of Health, Labour and Welfare (MHLW) grants the Orphan Drug Designation based on the opinion of the PAFSC (Pharmaceuticals and Food Sanitation Council). The opinion given by PAFSC is based on a scientific report prepared by Pharmaceutical Medical Devices Agency (PMDA) [12], an independent regulatory agency. In Japan the orphan designation process can take between three and six months and the final outcome is published in the *Government Gazette*.

Obtaining an orphan drug designation in Australia

In Australia the applicant is advised to discuss with the relevant Clinical Evaluation team of the Australian Regulatory Agency (Australian Government – Department of Health and Ageing Therapeutic Goods Administration) before the submission of an application for an orphan designation. After submission the application will be assessed by a Committee and the Therapeutic Goods Administration, which will issue a decision

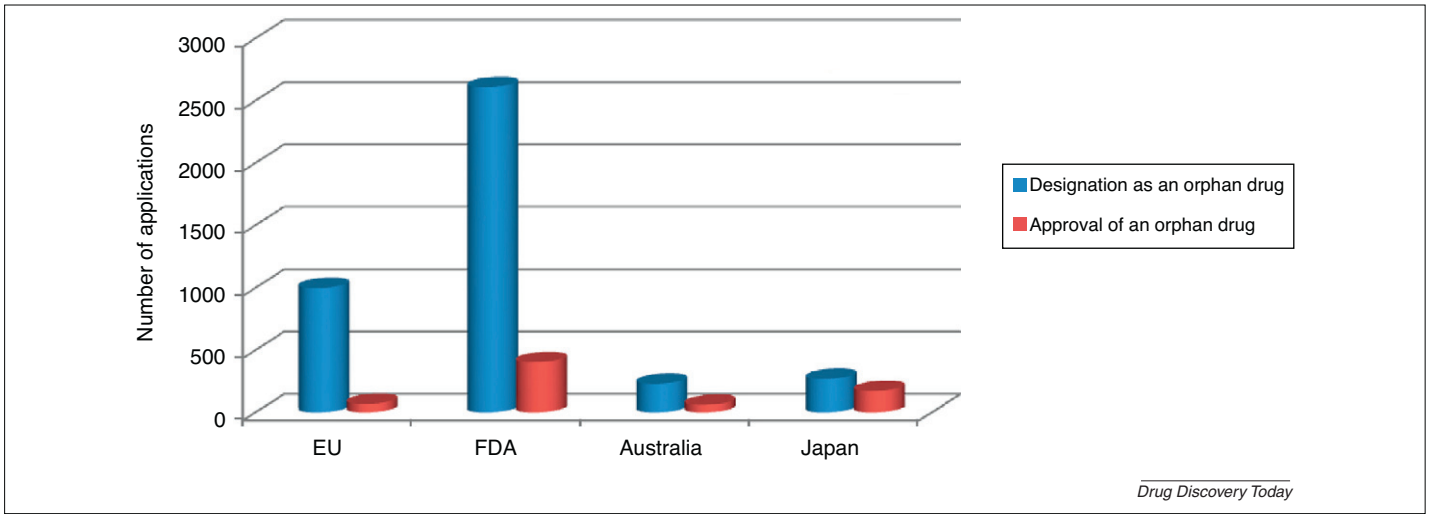

FIGURE 1

Due to different reasons the number of orphan designations and approvals of orphan drugs in 2011 is quite different among the four regions (EU, US, Australia and Japan). The number of approvals and orphan designation are illustrated.

[13]. This decision will be published in the *Commonwealth of Australia Gazette*.

Obtaining an orphan drug designation in the EU

In the EU the orphan designation is granted by the European Commission following a positive opinion by the Committee for Orphan Medicinal Products [8,35,36].

During the pre-submission phase, two co-ordinators (one member of COMP and one scientific administrator from the orphan drug section of EMA) will be appointed for each application. Before the submission the applicant may use the common EU/FDA application form, which is strongly recommended to facilitate the collaboration between both regulatory competent authorities.

Following submission the Agency validates the application and might raise comments or request further data that should be provided within a maximum of a three-month period. Once the validation process is finalised the COMP will have a maximum of 90 days to evaluate the Orphan Drug Designation. However, it is possible to evaluate an Orphan Drug Designation within 60 days. The final opinion (positive or negative) will be forwarded to the European Commission, which will adopt the commission decision within 30 days [37,39]. Following a favourable decision the orphan designation must be entered in the Community Register of orphan drugs [8,37,39]. An annual report concerning progress of the development of the designated orphan drug must be submitted to the agency [8].

Orphan medicinal product marketing authorisation

As already described, the applicant must apply for a designation before the submission of MAA in the EU, the US, Japan and Australia. In Japan, the US and Australia there is no need to reconfirm the Orphan Drug Designation before the authorisation of an orphan medicine. Moreover, it was noted that there is no difference in the process of evaluation and authorisation between an orphan and non-orphan medicine in Japan, US and Australia.

In the EU, in accordance with Article 3(1) and point 4 of the Annex of Regulation (EC) No. 726/2004 [38], all applications for a Marketing Authorisation of a designated orphan drug must be submitted through the mandatory scope of the centralised procedure. This procedure has some advantages because a single evaluation will result in a single authorisation granted by the European Commission, which will be valid throughout the single market of the EU. This single authorisation throughout the EU will increase the availability of orphan drugs in the EU [40] (http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm). Therefore, patients with a rare disease will have equal access to a particular orphan drug independently of their place of residence in the EU.

Before the granting of a marketing authorisation for an orphan drug by the EC the COMP must evaluate the report submitted by the applicant demonstrating that the orphan designation criteria are still valid and maintained by the specific medicinal product. During the evaluation of a Marketing Authorisation Holder (MAH) by the Committee for Human Medicinal Products (CHMP) the orphan indication can be changed and might have an impact in the orphan designation granted. However, this particular scientific matter will be evaluated by the COMP.

Furthermore, the COMP should evaluate the significant benefit in the case of existing potentially satisfactory methods of diagnosis, prevention or treatment of a particular orphan condition or indication authorised in the EU [39,41].

A satisfactory method, in the context of the EU legislation, means any authorised medicinal product or other non-pharmacological treatments that might be considered satisfactory (e.g. transplantation, surgery) for a particular orphan condition or indication [7,39].

Significant benefit does not necessarily mean better efficacy in terms of therapeutic indication or even a different mechanism of action, which could be a possible alternative [41]. In particular cases a specific orphan drug can have some benefits for a particular population or the new orphan medicine could have a better pharmacokinetic profile, which could be clinically relevant. Significant benefit can be interpreted in terms of safety [42]. In other words, different safety profiles could have, in rare cases, an important benefit in the context of interactions with other commonly used medicinal products [42]. Different route of administration that could be beneficial to the patient (e.g. oral versus parental), or

in exceptional cases new formulation might be a major contribution to the patient care (e.g. a new formulation may decrease the possible overdosing or the frequency of dosing), or even in rare cases the market availability (there is a possibility that the alternative medicinal product for a specific disease is only authorised nationally by one or a few Member States) can also be considered a significant benefit to the patients [8,42]. Nevertheless, it is important to emphasise that significant benefit is defined by the Commission [Commission regulation (EC) 847/2000] as 'clinically relevant advantage or a major contribution to patient care'.

Concluding remarks

Patients with a rare disease have an equal right to medicines as do other patients with a well-known disease. In this context, orphan drugs are a special class of medicines because they would not be developed and marketed if there were no incentives and specific orphan drug legislation to promote their development.

Only eight medicines in the EU and ten medicines in the US, which could have been classified as orphan drugs, were authorised before the adoption of the orphan drug legislation [17,19]. After the implementation of the orphan drug legislation 70 and 403 new orphan drugs have been authorised in Europe and the US, respectively. The orphan drug legislations and policies have been successful because more orphan drugs have been developed and approved. This success can be measured by the number of the orphan drugs authorised and not by the number of orphan designations, because many pharmaceutical companies apply for an orphan designation at an earlier stage of development. Nevertheless, Orphan Drug Designation is important for the industry to get further incentives and support from the stakeholders. Having obtained an orphan designation the regulatory competent authorities recognised that the industry identified an orphan disease in a certain region or country.

For many rare diseases there is still no treatment available. Orphan drug incentives will only be effective if the orphan drug is approved, commercialised and the reimbursement process is approved. Otherwise the patients will not be able to afford an expensive medicine.

A clear and common definition of a rare disease and drug is needed because this would facilitate the designation process and the marketing authorisation of an orphan drug worldwide. Moreover, similar criteria for an orphan drug legislation would facilitate the Orphan Drug Designation process. In this review it can be concluded that the market exclusivity is an important incentive that should be considered by other legislators when reviewing their orphan drug legislation, because this gives an extra protection to the orphan drug.

There is already some cooperation between Member States (CAVOD – Advocating to improve orphan drug access and MOCA – Mechanism of coordinated access to orphan drugs among Member States) and regulatory competent authorities (e.g. EMA and FDA) but more international regulatory competent authorities and health authorities should work together and exchange knowledge and experiences in orphan drugs and orphan diseases to avoid duplicating work, avoid inconsistencies in assessment and decisions, and ensure the best available use of the expertise in rare diseases.

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