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RESEARCH ARTICLE

Effect of EU Regulations on Innovation and Marketing Authorisation of Orphan Drugs for Children

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ABSTRACT

No single definition for orphan diseases exists worldwide, but it is generally a disease that affects a small portion of the world population. Despite the development of science and pharmaceutical technology, the number of rare diseases for which no treatment is available is estimated between 4.000 and 5.000 worldwide. The analysis of the finances that are required for research, development and manufacturing of orphan drugs suggest that these drugs are perhaps the most expensive drugs produced by the pharmaceutical industry. The main objective of orphan regulations is to encourage pharmaceutical companies to begin the process of researching and developing of new drugs intended for treatment of orphan diseases. The first legal framework for defining the rules for the marketing authorization of the orphan drugs was presented by the Food and Drug Administration (FDA) in the 1983. In European Union, the regulation for orphan drugs was introduced by the European Medicines Agency (EMA) in1999.The FDA orphan drugs regulation is based on three laws, while the EU legislation is covered by six regulations and two additional guidelines. The detailed overview of the FDA and EMA orphan drugs regulatory requirements showed that both regulatory authorities provide shortened registration procedure, allow exception from payment of certain fees, provide protocol assistance and stimulate processes of a parallel application for orphan designation. The differences could be seen in the period of market exclusivity, tax incentives and source of the grants.

Keywords: Incentives, orphan (rare) diseases, orphan drugs, orphan drugs regulation

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CONTENTS

1. Introduction

Purpose of the Orphan Drug Act (ODA):

The Orphan Drug Act (ODA), first enacted in the United States in 1983, was set up to encourage the development of drugs for rare diseases. At that time, drug therapies for such diseases were rarely developed. Three decades later, a growing proportion of industry research and development (R&D) and regulatory drug approvals target diseases affecting fewer than 200,000 persons in the United States, the prevalence-based threshold of rare disease under the ODA. Most of the policy and scholarly response to the orphan drug pricing problem to date has been to explore new ways to evaluate orphan drug performance following regulatory approval. However, there is little indication that health care payers are successfully pushing back on drug price points. Meanwhile, the findings of Kesselheim and colleagues underscore how the operation of the ODA upstream at the point of regulation serves to expand the scope of the problem. With the increasing ability to more precisely identify biomarker-defined subsets of disease, it is perhaps time to re-examine how the ODA distinguishes rare versus common forms of disease or, even more fundamentally, what the ODA is meant to achieve[1].

According to the definition by the World Health Organization (WHO), an orphan disease is an illness or condition that occurs from 0.65 to 1 case per 1000 population, with prevalence from 6.5 to 10 cases per 10,000 residents. Up to date, there are found to be between 6.000 to 8.000 known orphan diseases, with almost weekly reporting of newly identified disorders. Annually, approximately 250 new orphan diseases are identified. Despite the fact that orphan diseases affect a small portion of the world population, it is estimated that over 55 million people suffer from orphan diseases at the level of the United States (USA) and European Union (EU). In the USA there are about 25 million people who suffer from an orphan disease, while at European level about 30 million people are registered with orphan diseases, meaning that orphan diseases affect 6% to 8% of the population at European level. The large part of orphan diseases (about 50%) appears during early childhood. Approximately 80% of the known orphan diseases have been identified as genetic in nature affecting between 3% and 4% of the new born[2].

Orphan drugs are defined as drugs that are used for treatment of orphan (rare) diseases. The analysis of the finances that are required for research, development and manufacturing of orphan drugs suggest that these drugs are perhaps the most expensive drugs produced by the pharmaceutical industry. For illustrations, the cost for orphan drugs per patient in the USA for 2014was $ 118.820,00, versus the cost of$ 23.331,00 for non-orphan drugs for the same period. The registration of orphan drugs is in accordance with the special legislation, in literature known as an orphan regulation[3]. The main goal of the orphan regulation is to stimulate the pharmaceutical companies to begin the process of research and production of orphan drugs. Worldwide, the most frequently referred regulations for orphan drugs are regulations set by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in the USA and EU, respectively.

Effects of regulations in different countries:

Rapid growth in pharmaceutical spending is a worldwide phenomenon. According to a recent study, OECD spending on pharmaceuticals has increased by an average of 32% in real terms since 1998, reaching more than US $450 billion in 2003. However, there is wide variation in the growth of pharmaceutical spending across countries. For example, during this period, the annual growth rate of pharmaceutical spending in the US (9.6%) was nearly triple the growth rate of spending (3.5%) in Germany[4].

Pharmaceutical Regulations:

There is no single source of information on pharmaceutical regulations in OECD countries. Some publications report current regulations for several countries, but historical data on regulations is less widely reported. We collected data on pharmaceutical regulations in 19 OECD countries for the years 1992–2004 from a variety of sources. Data were abstracted from peer-reviewed journal articles obtained through a structured search in the PubMed and EconL it databases, in addition to publications from the World Health Organization and OECD, along with grey literature (e.g. IMS), as listed in Appendix A. We verified the data through expert interviews with two researchers and/or policy makers in the field of pharmaceutical regulation in each country, and country experts from a leading multinational pharmaceutical firm. The list of country experts consulted is available from the authors upon request[5]. The 19 countries included in our analysis are: Australia, Canada, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Japan, The Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Turkey, United Kingdom, and United States. There is tremendous heterogeneity in regulations across countries and in some cases historical data on the actual implementation and detailed design of the regulations was not available either from the literature or from the country experts. For example, we know which countries adopted or repealed a maximum annual limit on pharmaceutical expenditures. However, in several cases, we do not know the exact expenditure limit that was implemented or whether it was enforced in practice. To make these diverse regulations amenable to analysis, we grouped them into 10 major categories. Below we describe the regulations in each of these categories[6].

2. Orphan drug regulation in USA and EU

The definition for orphan drugs is in line with the definition for orphan diseases at national level. This means that a drug could receive orphan designation only if it is intended for treatment of patients who suffer from some orphan disease according to national definition for orphan diseases. In the USA some drug may be designated as an orphan drug although it is intended for treatment of larger number of patients, over the allowed limit of number of patients (Table 1). However it should be proven that there is no reasonable

expectation that the cost for development and manufacturing of this drug would be recovered from it sales.

The high price of orphan drugs is due to the negative correlation between the high costs needed for research and their development and the projected relatively small return of the investment from the sale of these drugs, according to a relatively small number of patients that will use these orphan drugs. On the other hand, this high cost is a limitation factor for availability of the product for the small group of already existing and targeted patients. According to the pharmaceutical companies' reports, approximately 21 billion dollars are needed for research and development of a medical treatment[7]. In other terms, it means that about 10 years are needed for a new drug to be released on the market. Reference these economic parameters, the treatment of rare diseases are often characterized as "orphaned" and it is very rarely recognized as a field of interest by the pharmaceutical companies. Comparative data for top 100orphan drugs in USA by sales average and median cost per patient for years 2010-2014 are presented in Table 2. The cost per patient was estimated for the retail cost of a drug to a patient, for a given year, based on a 100% compliance to the treatment guidelines outlined in the FDA label and it does not include off-invoice discounts.

Regulation for orphan drugs in USA, FDA regulation:

The FDA orphan drugs regulation is based on three laws that apply to orphan drugs. The first regulation for orphan drugs is the Orphan drug act, for the first time presented in the far1983.This act seeks to protect an orphan drug which has to be produced and marketed by some pharmaceutical company. It includes not only drugs which are intended for treatment of diseases that affects less than 200.000 people in the USA, but also drugs for any other diseases that affect more than 200.000 people in USA and for which there is no reasonable expectation that the cost of developing and making available these drugs in the USA would be recovered from it sales. On one hand, this act assumes that the drugs intended for treatment of rare diseases need patent protection and on the other hand, this act left the possibility producers of medicines which are not intended for treatment of rare diseases also to obtain patent protection for their final products.

The practical experience of using this regulation shows that it is focused on research and development of new drugs intended for treatment of rare diseases. The loudest critics and opponents of this legislation emphasize that according this act, some drugs could ensure reliable profit of 1 billion US dollars annually, with remark that the same drug will be developed and marketed without receiving any orphan drug designation and without using any incentives connected to this orphan drug designation[8].

The produced by the other pharmaceutical company for the period from five to seven years. The main purpose of this legislation is to discourage the idea for development of non-patent drugs. Considering the fact that generic drug may appear on the market only in case when the company producer of this generic drug submits their own data from their own clinical trials, the scope of full drug protection provided by this legislation is less than the protection provided through the Orphan Drug Act[9].

FDA regulation for orphan drugs is Hatch- Waxman Act. According to this According to this act, the authorized generic company may charge more than the real costs and it is allowed to make an extra profit and to receive other benefits while it challenges the original drug under patent protection. Hatch-Waxman act may tolerate various agreements concluded between the company producer of the original drug and company producer of the generic drug, but it should be noted that only agreements which are focused to the time of entering the generic drug on the market are allowed. Agreements which apply of exchange of funds or any other kind of compensation are not permitted.

Regulation for orphan drugs in EU, EMA regulation

At the European Union level, the first known regulations related to the definition of rules for obtaining orphan drug designation is EC Regulation 141/200 (Orphan Regulation), adopted in December 1999. Today, the total legislation for orphan drugs in EU is covered by six regulations and two additional guidelines for implementation of the regulations[10]. According to EMA regulations, a drug which is intended for treatment of rare disease or condition which affects not more than 5 in10.000 people in the EU is defined as an orphan drug. The medicinal product would be designated as an orphan medicinal product in EU if its sponsor could demonstrate:

- That it is intended for diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in10.000 people in the Community when the application is made; or
- That it is intended for the diagnosis, prevention or treatment of a life- threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and
- That there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.
- Reference to EMA regulations and EMA rules, the company which is producer of a potential orphan drug, first has to submit an application for evaluation to the EMA's Committee for orphan medicinal products (COMP).
- The task of this Committee are: To examine any application for the designation of a medicinal product as an orphan medicinal product which is submitted to it

in accordance with European regulation for orphan drugs;

- To advise the European Commission on the establishment and development of a policy on orphan medicinal products for the European Union;
- To assist the European Commission in liaising internationally on matters relating to orphan medicinal products, and in liaising with patient support groups;
- To assist the European Commission in drawing up detailed guidelines.

After reviewing the submitted application, COMP gives its opinion to the European Commission whether this drug meets the requirements for receiving an orphan designation. Based on this opinion, the European Commission may give or not an orphan designation for some drug. Reference this rule it could concluded that the COMP has the right to decide and the European Commission has a right for assigning a drug as an orphan drug.

Influence of EU acts:

Rare diseases are defined as life-threatening or chronically debilitating conditions with such a low prevalence that special combined efforts are needed to ensure adequate medical care. As a guide, a prevalence of less than 5 per 10,000 citizens in the European Union (EU) is considered low. A low prevalence still equals to approximately 250,000 patients in the Community for diseases near the cut-off point. Much rarer diseases only affect a few dozen patients in the whole EU. There are between 5000 and 8000 rare diseases identified so far, affecting an estimated 30 million EU citizens. Over 80% of rare diseases have a genetic background, with the great majority being single-gene defects, although multi factorial and chromosomal defects exist. Other non-genetic rare diseases are due to degenerative and proliferative causes, infectious diseases, treatment-related toxicities, alimentary deficiencies, rare poisonings and injuries[11]. Rare diseases can occur at any age but approximately half of these have their onset at birth or during childhood.

The European Regulation (EC) No 1901/ 2006, hereinafter referred to as the 'Pediatric Drug Regulation' came into force on 26 January 2007 with the objective to improve the health of European children by facilitating the development, accessibility and safe use of new drugs for children aged 0 to 17 years, through clinical studies. These objectives should be achieved without subjecting children to unnecessary clinical trials and without delaying the authorization for other age populations[12]. This regulation obliges applicants to submit study results to the EMA for each new medicine, new indication, and new route of administration or new formulation, according to an agreed Pediatric Investigation Plan (PIP). This PIP describes the planned pediatric studies and their timelines. It should ideally cover all age groups from birth to adolescence. Pediatric studies may be (partially) 'waived' if studies are not feasible, appropriate or safe for (a subset of) the pediatric population or 'deferred' if it is appropriate to conduct studies in adults prior to initiating studies in children or if studies in children will last longer than studies in adults. The PIP should also describe the need for the development of age-appropriate formulations and/or additional non-clinical information (such as developmental toxicity studies in juvenile animal). When the PIP is completed and all requirements are met, applicants are rewarded with a six month extension of patent protection. Off- patent products developed exclusively for use in children is granted eight year data and ten year market exclusivity for the pediatric indication (the Pediatric Use Marketing Authorization (PUMA)). ODs are rewarded with two additional years of market exclusivity. The Pediatric Drug Regulation was introduced in stages (see Table 3) distinguishing new medicinal products from already authorized medicinal products.

3. Orphan drug designations and marketing authorizations

From the implementation of the OD Regulation in 2000 until December 2012, 1088 ODDs were granted, 670 (62%) were intended for children (either exclusively for children (n = 161) or for both children and adults (n = 509)) and 418 (38%) were for adults only (Figure 1). As of November 2013, 81 of all granted ODDs had obtained MA. Sixty-five of these were identified as having a potential pediatric use at the time of ODD. Forty of these have indeed become available for children ('on- label'); 25 potential pediatric products were still off label for children at the time of MA and 16 products were for adults only.

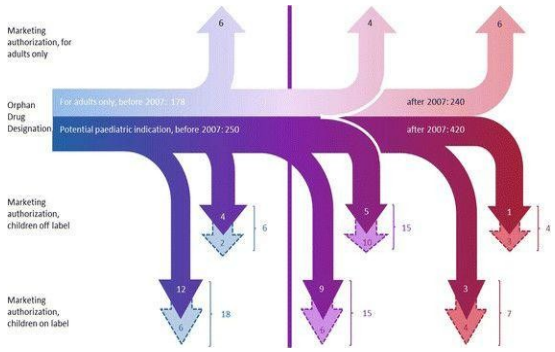

Fig 1: Schematic overview of potential and authorized treatment populations

The horizontal pipeline indicates the orphan drug designations (ODDs) for either adults only (upper line) or with a potential pediatric indication (lower line) over time (2000 – 2012) and the arrows represent those that obtained MA. The thick vertical line represents the year 2007. Arrows to the right of the thick line are all ODDs that obtained MA after 2007 (middle section: designation date before 2007, rightmost: designation date after 2007)[14]. Arrows with broken outline represent ODs that are undergoing further research in the pediatric population (i.e. with an agreed PIP after having received MA, while solid arrows are not undergoing further research in children). Of the 40 on-label pediatric ODs, 16 are currently under further development for a subset of the pediatric population. The PIP details of these ODs are specified in Table 4.

Pediatric investigation plans (PIP)

For 36 authorized ODs no decision or information about a PIP was found. For the majority of the products a PIP was not required because approval was granted before the Pediatric Drug Regulation came into force (n = 19) or because application for MA was submitted before the implementation of article 7 (n = 4) or article 8 (n = 1). Unless the applicant files for extension or variation of the initial MA, these medicinal products are likely to remain off label to children. The remaining 12 products with- out a PIP were developed for (a subgroup of) children[15].

For 34 authorized ODs, the PIP was required to include development and testing of an age appropriate formulation or conducting non-clinical and clinical studies. Most of these (30/34) were granted a partial waiver, the remaining four products were re- quired to develop and assess treatment for the complete pediatric population. None of the PIPs were completed at the time of application for MA as some of the re- quirements in the PIP were deferred. Partial waivers were mostly granted based on the expectation that clinical studies would be of no significant therapeutic benefit or fulfil no therapeutic need of the pediatric population.

Half of the 34 products with a PIP were required to either develop an age-appropriate formulation or to assess the acceptability of the existing formulation (Table 5). The majority of these measures applied to oral formulations (n = 13). An age-appropriate diluted formulation was required for intravenous (n = 1) and subcutaneous (n = 2) formulations. For 15 products non-clinical studies had to be performed. The required measures mostly included juvenile animal studies to determine pharmacokinetics, tolerability, toxicology and/ or toxicokinetics. In some cases, specific pharmacology, exploratory or dose ranging studies were required in vitro or in other animal models[16].

Discussion

The comparison of the regulatory requirements relating to orphan drugs between FDA and EMA shows that in the USA they are defined by three laws that apply to orphan drugs: Orphan Drug Act, Protection from generic competition and Hatch- Waxman Act. In the EU these regulatory requirements are defined by six regulations and two additional guidelines with instructions for their individual implementation. According to the defined regulatory requirements, if a drug is designated as an orphan drug, the company producer of this medicine could use a variety of incentives defined by FDA and EMA, for USA and EU, respectively.

The centralized procedure for marketing authorization in the EU is obligatory in the case of orphan drugs. At the EU level, EMA clearly defines the criteria by which some pharmaceutical company may be defined as a micro, small or medium-sized company, but generally companies must be established in the European Economic Area (EEA), employ less than 250 employees and have an annual turnover of not more than 50 million euros or an annual balanced-sheet total of not more than 43 million euros. According this, there are different types of incentives which the company may receive after obtaining an orphan designation. Both regulatory authorities, stimulate the process of parallel application by advising the companies to use the "common orphan application form" in order to obtain orphan designation in both in USA and EU.EMA also has special arrangements for parallel application with Japan, with their Ministry of Health, Labor and Welfare.

Table 1: Orphan diseases definition in USA and EU

Country	Total population	Prevalence of the rare diseases	Minimum number of patients necessary for being accepted as an orphan Disease
USA	311.864.524,00	6.4 / 10.000 Residents	Less than 200.000 or more than 200.000 but there are not reasonable expectation that the costs for research and development of the drug will be recovered
EU	502.500.000,00	5 / 10.000 residents	Less than 251.250 Patients

Table 2: Average cost per patient ($) per year (2010 – 2014) for orphan drugs in USA

Average Cost per Patient ($) per year	2010	2011	2012	2013	2014
Orphan drugs	83.550	87.990	97.379	107.316	111.820
Growth per Year		5.3%	10.7%	10.2%	4.2%
Median price	37.767	42.329	50.352	63.435	66.057

Table 3: Implementation phases of the Pediatric Drug Regulation (EC) No 1901/2006

Category	Application	Jurisdiction	Implementation
Off-patent medicine	MA for a pediatric use	Article 30	26 July 2007
New medicine	MA that includes a pediatric indication	Article 7	26 July 2008
On-patent medicine	To include a pediatric indication in an existing MA*	Article 8	26 anuary 2009

Table 4: PIP details of ODs that are authorized for use in children

Medicine name (active substance)	Pediatric use		Pediatric investigation plan			
	Potential pediatric*	On label †	Decision‡	Condition and age covered by waiver	Ground for waiver	Expected date of completion §
Elaprase (idursulfase)	Yes	All	PW	Mucopolysaccharidosis II (Hunter syndrome) (Girls birth to < 18 y)	Condition does not occur in the specified pediatric subset	December 2015
Exjade (deferasirox)	Yes	2	PW	Chronic iron overload requiring chelation therapy (birth to < 2 years)	No significant therapeutic benefit	June 2015
Ilaris (canakinumab)	Yes	2	PW	Juvenile idiopathic arthritis (birth to < 24 months)	Condition does not occur in the specified pediatric subset and no significant	June 2015
Kuvan (sapropterin)	Yes	4	PW	Hyperphenylalanine mia (4 to < 18	No significant	January 2014
Mozobil (Plerixafor)	Yes	All	PW	Myelosuppression caused by chemo- therapy to treat malignant disorders, which requires an autologous hematopoietic stem cell transplant (birth to < 12 months)	No significant therapeutic benefit	June 2017
Xagrid (anagrelide)	Yes	All	PW	Essential Thrombocythaemiaa (birth to < 6 years)	Condition does not occur in the specified pediatric subset	March 2013
Kalydeco (ivacaftor)	Yes	6	FP	NA	NA	December 2016
Orfadin	Yes	All	FP	NA	NA	May 2013
Revatio	Yes	1	FP	NA	NA	July 2014

*Intended for the pediatric population at time of ODD (yes/no).
†Minimum age (in years) on SmPC at time of MA. All: age range not specified and/ or no age contraindication.
‡PIP decision granted by EMA: PW: partial waiver, FP: Full investigation plan, for the entire pediatric population. NA: Not applicable.
§Expected date of PIP completion for the remaining population.

Product was authorized before 2007 however the MAH applied for or had the intention to apply for an extension of the authorized indication. Consequently, pursuant to Article 8 of Regulation (EC) No 1901/2006, the MAH submitted a PIP. **FCAS:** Familial Cold Auto inflammatory Syndrome; **FCU:** Familial Cold Urticaria; MWS: Muckle-Wells Syndrome; NOMID: Neonatal-Onset Multisystem Inflammatory Disease; CINCA: Chronic Infantile Neurological, Cutaneous, Articular Syndrome.

Table 5: Studies agreed upon in the PIPs of ODs

Measure	**N**
Quality	
- Development of age appropriate formulation	14
- Assessment of acceptability/ palatability	2
- Bioequivalence	1
Measure	N
- Microbiological testing	2
Total	19
Non-clinical	
- Juvenile toxicity study	20
- Other	8
Total	28
Clinical	
- Meta-analysis	1
- Randomised, double blind, placebo controlled	25
- Comparative, open label	20
- Uncontrolled	41
- Observational	3
- Bioequivalence/ bioavailability	5
- (PB)PK	2
- Pooled data	3
- Extrapolation	3
- Other	1
Total	104

4. Conclusion

The detailed comparative overview of the FDA and EMA regulatory requirements, respectively for USA and EU, emphasizes several similarities and differences between the incentives that these two regulatory bodies give to the companies that produce orphan drugs. Both regulatory authorities provide grants to pharmaceutical companies, but the difference is in the source of these means. In the FDA these means are provided by the FDA orphan product grant program as a part of FDA. Contrary to FDA, EMA does not provide any grants from its own budget. The companies in EU level could provide grants through European commission and other sources such as Horizon 2020, the EU Framework Program for Research and Innovation; E-Rare, a transnational project for research programs on rare diseases and International Rare Diseases Consortium (IRDIRC).

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