Health Policy 108 (2012) 1–9

Contents lists available at SciVerse ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

Evaluating and improving orphan drug regulations in Europe: A Delphi policy study

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ARTICLE INFO

Article history:
Received 7 December 2011
Received in revised form 24 August 2012
Accepted 27 August 2012

Keywords:
Orphan drugs
Rare diseases
Delphi techniques
Health policies

ABSTRACT

To encourage the development of orphan drugs, the European Union has implemented specific policies in 2000. However, the political, social, scientific and economic context has changed since the implementation of these policies. For that reason, the aim of this article is to evaluate orphan drug policies in Europe. Firstly, key issues on the orphan drug policy were identified based on desk research. Secondly, a Delphi policy study with 47 European orphan drug experts from different backgrounds was carried out to explore these issues. In the round one of the Delphi, responses were received from 18 experts (38.3%) and from ten (55.5%) in the round two. Experts agree that the orphan drug policies in Europe have not outlived their usefulness. Additionally, the importance of reducing country-dependent inequalities in patient access to orphan drugs has been emphasized. Still, there is room for further refinement of the orphan drug policies. Within that context, we formulated several policy recommendations (e.g. enforcing the policy that is in place to reduce the period of market exclusivity for profitable orphan drugs, stating the level of clinical evidence needed to authorize orphan drugs, etc.) with the overall goal to optimize patient access to orphan drugs.

1. Introduction

In the European Union (EU), rare diseases are defined as life-threatening or chronically debilitating diseases that have a prevalence of 50 out of 100,000 individuals or less. Orphan medicinal products are intended to diagnose, prevent or treat rare diseases [1]. To encourage the development of orphan medicinal products, the European Union has implemented specific policies in 2000.

In the United States, the Orphan Drug Act was installed in 1983 and served as a model for these European policies. Both offer a number of incentives to stimulate the development of orphan drugs. The process of a drug going from orphan designation (i.e. the award of orphan status to a drug) to marketing authorization is governed by the Food and Drug Administration (FDA) in the United States and in the EU by the European Commission. Specifically, the FDA Office of Orphan Products Development (OOPD) is responsible for evaluating scientific and clinical data submissions from sponsors to identify and designate products while the European Commission receives advice from the EMA. Comparisons of the two policies have been well documented [2–5]. Even though both the US and the EU define a rare disease on the basis of rarity or the unlikelihood of return on investment, there remain two critical differences. Firstly, the European definition specifically emphasizes the life-threatening or seriously debilitating nature of these diseases [1,4–7]. Secondly, in Europe, market exclusivity is granted to orphan drugs for a period of ten years, whereas in the US the period of marketing exclusivity is limited to seven years [8,9].

In both regions, the number of orphan designations and authorized orphan drugs has been steadily increasing over

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http://dx.doi.org/10.1016/j.healthpol.2012.08.023

the last years. However, the political, social, scientific and economic context has changed since the implementation of the policies [10]. For example, advances in the field of genomics caused a disaggregation of prevalent diseases into many distinct rare conditions, making orphan status increasingly more common [11,12].

For that reason, the aim of this article is to evaluate orphan drug policies in Europe with key orphan drug experts and formulate informed policy recommendations regarding the future of the European orphan drug policies.

2. Methods

2.1. Literature search

Key issues of the orphan drug policy were collected by means of a review of the international literature, of legislative documents, and of the websites of relevant organizations. There was specific focus on definition of rare disease and of orphan drug; orphan designation criteria; possibility of re-consideration of orphan designation application; institution in charge of orphan designation; marketing authorization application; market exclusivity; research funding; incentives; assistance with application file; possibility of accelerated registration procedure; guidance for clinical studies in small populations and procedure for compassionate use. Relevant studies were identified by searching PubMed, Centre for Reviews and Dissemination databases, Cochrane Database of Systematic Reviews and Trip database up to March 2012. Search terms included 'orphan drug', 'orphan medicine', 'OMP', 'registration', 'EMA', 'EMEA', 'FDA' and 'regulation'. MeSH search terms were 'Drug Industry', 'Europe', 'United States', 'Government Regulation', 'Orphan Drug Production/economics', 'Orphan Drug Production/legislation & jurisprudence', 'Drug Design', 'Humans', 'Rare Diseases/drug therapy' and 'Research Support as Topic'. Search terms and MeSH search terms were searched alone and in combinations. Additionally, the bibliography of the articles was checked for other relevant articles or studies. Legislative documents were consulted via the Official Journal of the European Communities, EUR-Lex and the U.S. Government Printing Office. Finally, the websites of several organizations (EMA, FDA, Orphanet and EURORDIS) were also explored for relevant information.

2.2. Policy Delphi study

The methodology of two-rounded policy Delphi study was chosen because it is an efficient and inexpensive way to explore various policy questions and organize group communication [13,14]. As compared to a traditional Delphi study, which is a 'decision-making' tool that relies on participants reaching a consensus, the policy Delphi study is considered a 'decision-facilitating' tool. It does not aim to reach consensus, but rather explores the various opinions on different policy options with a view to informing the decision-making process [13,15,16]. We anticipated a variety of opinions given the diverse backgrounds of the experts [16]. The survey was designed and reported according to the checklist for qualitative research by Anderson [17].

2.2.1. Participants

We sent out the survey to 47 European orphan drug experts who were chosen through selective sampling. The survey is available from the authors upon request [added as additional data]. In order to capture different expertises, experts are academics ($n = 10$), have a regulatory background ($n = 14$), represent patient organizations ($n = 6$) or are members of the pharmaceutical industry ($n = 17$).

2.2.2. Data collection

The first round questionnaire consisted of 25 statements relating to the key issues described above. The 47 experts were contacted by email and directed to the online survey. The questionnaire and two reminders were sent out in February and March 2011. The phrasing of the statements was piloted on three PhD students who were unfamiliar with the subject. Respondents were asked to respond from their personal perspective and indicate their level of agreement or disagreement on a six-point Likert scale on statements like for example "In Europe, market exclusivity for orphan drugs is granted for a period of ten years. Time wise, this is ideal". No neutral response was allowed. Additionally, they were commentary fields throughout and at the end the questionnaire.

The second round questionnaire and one reminder were sent out in May 2011. The questionnaire was personalized and consisted of two sections. Firstly, the comments made in the first round were summarized per statement as controlled feedback. Secondly, for each statement, the answer frequency distribution from the first round was shown in a histogram. Additionally, the experts' original answer was indicated in the histogram. The experts were given the opportunity to change their initial vote in light of others' answers and comments. It was envisioned to allow additional survey rounds until consensus of the expert panel was reached.

2.2.3. Data analysis

Consensus percentages, i.e. the extent to which respondents agree with each other, were calculated for each statement according to the percentage of ratings on either side of the Likert scale. Consensus levels were preset at 75% for 'modest consensus', 80% for 'consensus' and 85% for 'strong consensus'. 'Disagreement' was defined as a consensus level equal to or less than 65%.

The comments made were analyzed in three steps. The first step was aimed at familiarizing with the raw data by reading and re-reading the comments. Secondly, all key issues were identified. In the last stage, the key issues were interpreted and the appropriate quotes were selected. Quotes are indicated throughout the text with a code to identify the background of the cited individual (i.e. A = academic, I = industry, R = regulatory and P = patient organization).

Table 1
Overview of the statements for which consensus (>80%) was achieved.

Statement	Verdict	Level of consensus
Strong consensus (>85% agreement)		
The orphan drug regulation in Europe has outlived its usefulness. We could rely solely on the market to support innovation for rare diseases.	Disapprove	100%
It is important to reduce country-dependent inequalities in patient access to orphan drugs.	Approve	94%
Disabling the possibility of marketing a product for the same orphan indication would lead to more orphan drugs that cover a broader variety of orphan diseases.	Disapprove	88%
With regard to safety, it is in the patients' best interest to convert off-label use of a drug for a rare disease indication into an authorized orphan drug.	Approve	88%
Consensus (>80% agreement)		
The future of orphan drug research lies within private public partnerships between academia and industry.	Approve	82%
The possibility of marketing different products for the same orphan indication provides the necessary incentive to continue research for that orphan indication.	Approve	82%
In Europe, market exclusivity for orphan drugs is granted for a period of 10 years. Time-wise, this is ideal.	Approve	82%
To achieve equal access to drugs for life-threatening diseases it is recommended that all procedures with respect to compassionate use are a European responsibility.	Approve	81%
Repurposing of previously approved products can give a boost to orphan drug development.	Approve	81%

2.2.4. Ethical considerations

Each respondent participated voluntarily and was not remunerated. Because of the nature of the questionnaire, it was not required to seek approval from a research ethics committee. The anonymity of the participants and confidentiality of the answers were guaranteed throughout the study.

3. Results

3.1. Delphi Policy study

We sent out the first round survey to 47 experts and received answers from 18 experts (38.3%). These were five academics (response rate (RR) = 50%), three people with a regulatory background (RR = 21.4%), one representative from a patient organization (RR = 16.6%), and nine members of the pharmaceutical industry (RR = 52.9%). Together, they made 139 comments on the different statements and came to a consensus (>80%) on eight statements. Among the non-participants there were five people out-of-office, three were too busy and two others did not participate because someone else from the same organization already did. The second round survey was sent out to the 18 experts that participated in the first round. Ten experts (55.5%) responded to the second round survey. Only six experts wanted to change their votes from the first round (results Table 3). Together, they made 13 extra comments. Therefore, two survey rounds were deemed sufficient to achieve data saturation. Consensus was achieved for nine statements (Table 1). Experts disagreed on six statements (Table 2).

3.2. The expert opinion

The key issues of the orphan drug policy and procedures by the European Medicines Agency in Europe are summarized below and discussed in light of the experts' opinions (quotes in italic).

3.2.1. Orphan designation

3.2.1.1. Criteria for orphan designation. Orphan drug designation status is awarded based on a prevalence criterion or an economic criterion [1]. Nearly all orphan drug designations are granted based on the prevalence criterion. Nonetheless, the expert panel does not favour the development of a clear protocol to calculate return of investment because '*companies are not willing to open their books to*

Table 2
Overview of the statements for which there was disagreement.

Statement	Verdict	Level of consensus
Disagreement (≤65% agreement)		
Research on rare diseases and orphan drugs is adequately incentivized in Europe.	Approve	59%
Research on ultra rare diseases and orphan drugs for ultra rare diseases is adequately incentivized at this time at the European level.	Approve	53%
There is a need for more financial support to promote orphan drugs R&D.	Approve	65%
At the time of orphan designation, it is easier to demonstrate significant benefit (E.U.) than it is to demonstrate a hypothesis for clinical superiority (US) over existing methods.	Approve	50%
Over the years, EMA's scientific advice working party has acquired expertise on advising sponsors applying for market authorization. Also, adherence to this advice is positively associated with higher marketing authorization success rates. Therefore, assistance with the application file should be mandatory instead of optional.	Disapprove	59%
It would be appropriate to let the period of market exclusivity depend on factors like level of innovativeness, medical need, etc.	Disapprove	65%

Table 3
Delphi questionnaire results.

Statements	Results (% round 1/% round 2)					
	Strongly disapprove	Disapprove	Somewhat disapprove	Somewhat approve	Approve	Strongly approve
Research on rare diseases and orphan drugs is adequately incentivized in Europe.	0/0	28/29	11/12	44/41	6/6	11/12
Research on ultra rare diseases and orphan drugs for ultra rare diseases is adequately incentivized at this time at the European level.	0/0	39/41	6/6	50/47	6/6	0/0
There is a need for more financial support to promote orphan drugs R&D.	6/6	6/6	28/24	11/6	28/35	22/24
There is a need for more supporting measures, other than financial, to promote orphan drugs R&D.	11/6	0/0	17/18	17/6	28/35	28/35
In Japan pharmaceutical companies pay 1% tax on orphan drugs sales (if annual profits exceed 100 million yen) until orphan drug subsides have been repaid. A similar initiative should be considered in Europe.	0/0	11/12	17/12	39/41	33/35	0/0
The orphan drug regulation in Europe has outlived its usefulness. We could rely solely on the market to support innovation for rare diseases.	39/47	28/24	22/29	11/0	0/0	0/0
The future of orphan drug research lies within private public partnerships between academia and industry.	6/6	6/6	6/6	22/18	39/41	22/24
Priority review vouchers are an effective incentive to stimulate the development of orphan drugs.	0/0	11/12	11/12	28/24	50/53	0/0
Repurposing of previously approved products can give a boost to orphan drug development.	0/0	12/6	12/13	35/38	35/38	6/6
Most orphan designations are granted based on prevalence data. More orphan drugs would be designated if there were a clear protocol to calculate potential return on investment.	0/0	50/47	22/24	11/12	11/12	6/6
Salami-slicing (the process of dividing diseases into small subsets to obtain orphan designation) is problematic and should be strictly avoided.	6/6	17/18	6/6	17/12	28/29	28/29
Orphan drugs are intended to treat, diagnose or prevent rare diseases. With respect to the diagnosis and prevention of rare diseases, it is contradictory and counterproductive that neither medicinal devices nor health food products are eligible for orphan designation.	6/6	11/6	11/18	39/41	28/29	6/0
At the time of orphan designation, it is difficult to demonstrate significant benefit over existing methods due to the limited amount of data at that time.	0/0	6/6	24/25	24/25	41/38	6/6
At the time of orphan designation, it is easier to demonstrate significant benefit (E.U.) than it is to demonstrate a hypothesis for clinical superiority (US) over existing methods.	6/6	12/13	35/31	24/25	18/19	6/6
The guideline on clinical trials in small populations positively influences the quality of clinical trials with orphan drugs.	11/6	11/19	0/0	44/44	28/31	6/0
Over the years, EMA's scientific advice working party has acquired expertise on advising sponsors applying for market authorization. Also, adherence to this advice is positively associated with higher marketing authorization success rates. Therefore, assistance with the application file should be mandatory instead of optional.	0/0	33/35	22/24	11/12	28/24	6/6
The possibility of marketing different products for the same orphan indication provides the necessary incentive to continue research for that orphan indication.	6/6	6/6	6/6	28/29	44/41	11/12

Table 3 (*Continued*)

Statements	Results (% round 1/% round 2)					
	Strongly disapprove	Disapprove	Somewhat disapprove	Somewhat approve	Approve	Strongly approve
Disabling the possibility of marketing a product for the same orphan indication would lead to more orphan drugs that cover a broader variety of orphan diseases.	28/24	50/53	11/12	6/6	0/0	6/6
In Europe, market exclusivity for orphan drugs is granted for a period of 10 years. Time-wise, this is ideal.	0/0	6/6	11/12	39/35	33/35	11/12
It would be appropriate to let the period of market exclusivity depend on factors like level of innovativeness, medical need, etc.	33/35	17/18	17/12	11/12	22/24	0/0
It is important to reduce country-dependent inequalities in patient access to orphan drugs.	6/6	0/0	0/0	6/6	17/12	72/76
To achieve equal access to drugs for life-threatening diseases it is recommended that all procedures with respect to compassionate use are a European responsibility.	6/6	6/6	6/6	18/19	35/31	29/31
To achieve equal access to drugs for life-threatening diseases, orphan drugs should be conditionally reimbursed by the Member States upon market authorization until adequate data is available to review the reimbursement.	6/6	11/12	6/6	11/12	56/53	11/12
Setting up more disease and/or patient registries is more important than standardizing registries at the European level.	6/6	17/18	44/47	17/12	6/6	11/12
With regard to safety, it is in the patients' best interest to convert off-label use of a drug for a rare disease indication into a proper orphan drug.	11/6	0/0	6/6	28/24	33/35	22/29

scrutiny' **[I8]**. Additionally, the policy specifically states that there needs to be an unmet need or a significant benefit over existing methods. At the time of orphan designation it can be difficult to demonstrate significant benefit due to the limited amount of data. Nonetheless, according to the expert panel, '*the current criteria work and should not be loosened nor tightened*' **[P1, A1, A3, A4, R2, R3, I3, I4, I6, I9]**. However, one expert remarked that '*there should at least be a possibility to change or withdraw the designation afterwards if it doesn't seem appropriate after some time when more evidence becomes available*' **[A5]**.

Orphan drug designation can be sought after by dividing an existing disease into several less prevalent subgroups. This is the so-called 'salami-slicing' tactic. However, an indication must be a distinct medical entity [18]. As such, the '*salami-tactic is not allowed in Europe and will be rejected by the Committee for Orphan Medicinal Products (COMP) of EMA*' **[I4]**. Salami-slicing '*is only appropriate if it deals with a medically plausible subset, otherwise it is "gaming" the system*' **[I8]**. The expert panel suggests that apart from the prevalence of the disease, '*the expected value of a technology across all its planned indications should form a part of the assessment*' **[A1]**. Other experts suggested that the determination of a technology's value '*requires critical assessment of the orphan designation status requests*' **[A3]** '*using a protocol*' **[R3]** '*based on a distinct set of aetiology, pathogenesis, clinical features, international classification codes and disease and management algorithms*' **[R2]**.

3.2.1.2. Nature of the designated products. Drugs and biologics are the most commonly designated products, however the policy also allows for cell- and gene therapy products to be designated [3]. One expert suggested that it could be useful to have '*an "orphan drug like" process for medical devices, but not for health food products, as the latter can gain a medical status if performing adequate R&D*' **[I1]**.

3.2.1.3. Institution in charge of orphan designation and procedure. The request for orphan drug designation can be made at any stage of drug development prior to the market authorization application. The request for orphan designation must be directed at the COMP. The European designation procedure takes 120 days (or 90 days if no additional information is requested from the sponsor) to complete. The sponsor can either withdraw the application before a negative opinion is adopted by the COMP (so no information is made public) or start an appeal procedure, within 90 days, if the negative opinion has already been transformed into a Commission Decision [9,19].

3.2.2. Assistance and guidance

The sponsor of an orphan drug is entitled both developmental and regulatory assistance from EMA's Scientific Advice Working Party (SAWP). The request must be made before the marketing authorization application. The sponsor subsequently receives advice on the development of the clinical and non-clinical protocol, the execution of

clinical studies and on follow-up [3,4]. Despite the positive association between protocol assistance and marketing authorization success rates [20], the expert panel were ambivalent on whether or not this assistance should be mandatory (41% agreed) instead of optional. Also, The Committee for Human Medicinal Products (CHMP) published the 'guideline on clinical trials in small populations' in 2007 because trials enrolling several hundred patients may not always be practical or possible. However, deviation from the standard procedure is only allowed when completely unavoidable and needs to be properly justified [21]. One expert wished that the European guideline specified '*more details on time of follow-up*' **[A5].**

3.2.3. Marketing authorization and market exclusivity

3.2.3.1. Procedure for marketing authorization (MA). A request for marketing authorization is directed at the CHMP of EMA. The procedure takes over nine months to complete. Orphan drugs are required to pursue the centralized registration procedure. The review is similar to that for non-orphan drugs. There are three types of marketing authorization, i.e. normal, under exceptional circumstances and conditional. Respectively 56%, 38% and 6% of the orphan drugs approved up to December 2010 followed these routes to MA [8].

3.2.3.2. Market exclusivity for orphan drugs. Market exclusivity is granted to orphan drugs for a period of ten years in all EU countries. During the exclusivity period, no other company is allowed to market a similar orphan drug for the same indication. The expert panel agreed upon consensus that the duration of the market exclusivity period is ideal. Although '*in some cases it might be too long because profits are made much earlier, in others it is not long enough but additional years would not change this*' **[A1, A3]**. The experts did not consider it appropriate nor feasible to let the period of market exclusivity depend on factors like level of innovativeness, medical need, etc. because '*these factors are too difficult to define and assess objectively*' **[P1, A1, A5, I4, I5, I8, I9]**, additionally, '*they are not sufficiently known at the time of market launch*' **[I7]**.

The market exclusivity can be challenged in the case of lack of supply, upon agreement with the sponsor or if another drug is clinically superior [8,22]. The expert panel agreed with strong consensus that disabling this possibility would not lead to more orphan drugs that cover a broader variety of orphan diseases. It would '*increase the barriers to market entry*' **[A1]** and '*would lead to monopoly*' **[A5]**. Additionally, it is '*beneficial for patients and physicians to have access to more than one drug*' **[R1]**. Also, '*companies base their decisions for drug development on their available knowledge for specific disease areas*' **[A2, R3, I6]**.

Market exclusivity can be reduced at the end of the fifth year to six years if the criteria for orphan designation are no longer met, if there is an unreasonable profit, if there is an insufficient stock of the drug or if another product is safer, more effective or clinically superior [3,9]. However, this theoretical provision has never actually been put into practice [23].

3.3. Accelerated procedure

In Europe, orphan drugs do not automatically qualify for accelerated registration. It is only granted upon request of the sponsor and if the following three criteria are met: (1) treating a life-threatening or serious condition, (2) for which there is no available alternative and (3) expecting that the drug has a high therapeutic benefit. An accelerated assessment is carried out in 150 days with a maximum of 30 clock stop days [4,19,24].

The expert panel agreed with modest consensus that an initiative similar to FDA's priority review would stimulate the development of orphan drugs in Europe. Yet, one expert said that the FDA priority review vouchers plan '*has not been successful thus far*' **[I8]** and another remarked that '*it should also target neglected tropical diseases and not any orphan indication*' **[A5]**. A priority review is one FDA's three approaches to making drugs available as rapidly as possible (others are fast track and accelerated approval). A priority review is given to a drug that offers major advances in treatment or to a drug that provides a treatment where no adequate therapy exists. The FDA awards priority review vouchers to the sponsor of a newly approved orphan drug that targets a neglected tropical disease. The (transferable) voucher entitles the sponsor to a priority review (a review within six months) for another product [25–27].

3.3.1. Other incentives

Designated orphan drugs are, apart from ten years of market exclusivity, also entitled to, scientific advice and access to the centralized registration procedure, several financial incentives such as fee waivers, access to EU-funded research and national tax reductions [9,28]. The expert panel agreed, with strong consensus, that the orphan drug policies have not outlived their usefulness. Relying solely on the market would not sufficiently support research and development for orphan drugs.

There was discord (respectively 59% and 53% agreed) among the experts on whether or not research on rare diseases and orphan drugs and on ultra rare diseases and ultra orphan drugs is adequately incentivized in Europe. The '*lack of funds or grants and the lack of coordination and collaboration between the different stakeholders*' were identified as problematic **[P1, A2, A4, I7, R3]**. Furthermore '*both fundamental (basic) research and translational research do not have enough incentives*' **[P1, R3]**. '*Academic trials*' and '*registers*' should be financed better '*to enable the creation of the critical mass necessary for research to proceed efficiently*' **[P1, I7]**. Finally, there is also '*no specific orphan drug pricing and reimbursement procedure that would give some confidence to the industry about return on investment*' **[I2]**. In Japan, profitable pharmaceutical companies pay one percent taxes on orphan drug sales until their orphan drug subsidies have been repaid. The expert panel agreed with modest consensus that a similar initiative should be considered in Europe.

As for financial support to promote orphan drug research the existing '*fee waivers and ten years exclusivity*' are considered '*OK*' **[I2]**. However, some experts call for '*more financial support from either public and/or private bodies*' **[A2, R3, I3]**. When it comes to non-financial supporting measures, several options were put forward. Some experts

suggest '*regulatory adaptations with regard to clinical trials and clinical evidence*' **[I1, I2, I5]**. Also the '*recognition of expert centres and the continued professional development of health care providers*' was advised **[P1, A4, R3]**. Finally, it was proposed to '*facilitate interaction between academia and industry*' **[A2, I3]**. The expert panel agreed upon consensus that the future of orphan drug research lies within private public partnerships between academia and industry. '*This is often already the case now, so the trend will continue*' **[I7]**. However, '*financial support of some type is also needed*' **[I8]**.

3.3.2. Compassionate use

Compassionate use is a way to make an unauthorized drug available to a patient with a serious or life-threatening disease for which there is no available alternative. Additionally, the unauthorized drug should be undergoing clinical trials. Compassionate use can be granted to either a single patient or a group of patients. In Europe, compassionate use is regulated at a national level. The European procedure is supplementary and offers merely optional advice to the Member States [9,29,30]. The expert panel agreed with strong consensus that it is important to reduce country-dependent inequalities in patient access to orphan drugs. One expert disagreed, saying that '*inter-country inequalities reflect legitimate differences in budgets, social preferences and therefore the opportunity costs of orphan drug access*' **[A1]**. The panel considered that one way to reduce these inequalities could be through making all compassionate use procedures a European responsibility (upon consensus). Other suggestions were '*a harmonized assessment of clinical added value for pricing and reimbursement decisions*' **[I1, I2, I9]** and '*a common EU fund for reimbursement*' **[I7, R3]**. The above can be problematic due to '*Member States*' *territorial interests and healthcare systems and budgets'* **[I4]**.

4. Discussion

This study evaluates orphan drug policies in Europe. Firstly, key issues on the orphan drug policy were identified based on desk research. Secondly, a Delphi policy study with European orphan drug experts was carried out. Based on the results, we formulate policy recommendations regarding future European orphan drug policies.

The results from this study suggest that the orphan drugs policies in Europe have not outlived their usefulness. Relying solely on the market would not sufficiently support research and development for orphan drugs. Market exclusivity, the largest incentive for orphan drug sponsors, is in general positively perceived. Although intuitively perceived as more fair, we do not suggest letting the period of market exclusivity depend on factors like for example level of innovation, medical need, etc. as these are difficult to assess. Instead, we advocate the enforcement of the European policy that is in place to reduce the period of market exclusivity to six years if the drug is sufficiently profitable [31–34]. However, further guidance is needed on the concept of 'sufficiently profitable'. As it is the responsibility of one of the Member States to inform EMA on this matter, one action could serve as an example to others [35]. Also, because calculating return on investment for one drug can prove difficult, pharmaceutical companies should be willing (or compelled) to provide the necessary financial data.

The high number of designated orphan drugs demonstrates that the policies stimulate the development of drugs for rare diseases. However, less than 10% have (yet) received marketing authorization [35]. Therefore, we suggest further enhancing the other incentives offered to orphan drugs. In Australia, designated orphan drugs are, instead of being offered marketing protection, granted a priority review at the time of authorization [36]. The introduction of a system of priority review vouchers in Europe, as proposed by Ridley, could further stimulate the development of new orphan drugs [26]. Nonetheless, this apparently attractive method is associated with substantial costs and should be carefully considered before putting into practice [37].

With respect to performing clinical trials in small populations, we suggest to further extend the provided assistance and the guideline. For example by clearly stating the level of clinical evidence needed to authorize an orphan drug and by defining the time of follow-up. A similar guideline was already established for cytostatic agents [38]. Regardless of whether or not the assistance ever becomes mandatory, the higher success rates of compliant sponsors could incite small companies to ask for assistance more frequently. At the moment, they are less compliant and less likely to ask for assistance [39].

Furthermore, the increased collaboration between different research centres, by setting up multinational clinical trials and registers, could provide the level of evidence needed for approval. For example, EUTOS, a European Treatment and Outcome Study for Chronic Myeloid Leukemia has been set up to collect treatment outcome data across Europe [40]. In some cases, resources to support (independent) registries are lacking. However, some ideas (e.g. NIH's internet-based registries for rare diseases) have been put forward with a view to reducing the cost of developing and running a registry [41]. Additionally, there is a need for better coordination of additional national incentives that Member States put in place to support the development of orphan drugs. For example, the Italian Medicines Agency (AIFA) launched a programme to specifically promote independent research on (orphan) drugs [42]. Throughout the 2012 report on the state of the art of rare disease activities in Europe the necessity for European- and international-level coordination and resource-sharing was emphasized [43].

Also, experts call for increased coordination and collaborations between academia and industry. These alliances should not be limited to fundamental research but should extend into translational research and clinical trials. However, it is clear that the facilitation of interaction between academia and industry is only possible by providing the necessary funds. Recently, the International Rare Diseases Research Consortium (IRDiRC), a consortium that gathers researchers, funders, patient advocacy groups and regulatory agencies, announced its ambition to find treatment for 200 rare diseases by 2020. To achieve its ambitious goals, funding is provided by the US National Institutes of Health and the European Commission [44].

Also, several pharmaceutical companies (i.e. Pfizer and GlaxoSmithKline) adopted a business model to develop orphan drugs through such private public partnerships [45].

Finally, it is important to reduce country-dependent inequalities in patient access to orphan drugs. Therefore, we advocate the following two measures. Firstly, by regulating compassionate use of (orphan) drugs at a European level, negotiations with pharmaceutical companies and access to yet unauthorized drugs would be facilitated. Nonetheless, compassionate use would still remain constrained by the available budget of the health insurance system [35]. Secondly, pricing and reimbursement decisions made at a National level reflect genuine differences in pharmaceutical budget en health care preferences. Therefore, we support the idea, as proposed by EURORDIS, of installing a European reimbursement assessment procedure that provides assistance to the Member States [46]. This would lead to some harmonization of the national reimbursement procedures and better patient access to drugs for life-threatening disorders. This could be supported by the European Network for Health Technology Assessment, a network aiming to foster European collaboration in health technology assessment with a view to enable the exchange of information and to support drug reimbursement decisions by Member States [47].

This study has several strengths and weaknesses. On the one hand, the study design of a Delphi policy survey allows a diverse group of orphan drug experts to interact in an inexpensive and flexible way. Additionally, experts have the opportunity to formulate their ideas without the interference of peers as compared to for example in a focus group discussion. A group size between 10 and 50 respondents is considered optimal [13]. We were able to contact 18 European experts from the academic world, regulatory agencies, patient organizations and the pharmaceutical industry. For conceptual and practical reasons, experts from the United States were not consulted. On the other hand, policy Delphi studies can be time consuming. The information obtained in a survey can be difficult to summarize and present in a clear fashion. Due to the diversity of questions and answers, overall trends may be difficult to discover [13]. Also, one researcher (E.P.) occupied a dual role in analyzing and reporting the data. The risk of selection bias was reduced by substantiating research findings with appropriate quotes.

5. Conclusions

Notwithstanding the importance of the orphan drug policies for the development and availability of drugs for rare diseases, the changing political, social, scientific and economic circumstances, call for further refinement of orphan drug policies. In that context, we formulated several policy recommendations (i.e. enforcing the policy that is in place to reduce the period of market exclusivity for profitable orphan drugs) with the overall goal to optimize patient access to orphan drugs.

Conflicts of interest

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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