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REGULATORY ASPECTS OF ORPHAN DRUGS IN US AND EUROPE

SANIKOMMU TEJASWI[1*], KOUSHIK YETUKURI, RAMARAO NADENDLA

Department of Pharmaceutical Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Chalapthi Nagar Lam, Guntur -522034

***Corresponding Author: Sanikommu Tejaswi: E Mail: stejaswi13579@gmail.com**

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ABSTRACT

Medicinal products for the diagnosis, prevention or treatment of life-threatening or crippling rare diseases are orphan medicinal products. They are 'orphans' because the pharmaceutical industry has no interest in producing and selling medicines intended for only a limited number of patients suffering from extremely rare conditions under normal market conditions. The law on orphan drugs provides the pharmaceutical industry with a number of incentives and conditions for producing medicines for the treatment of rare diseases. Currently, the number of items for orphans approved (centralized level) is far beyond anything seen before the law on orphan drugs. Furthermore, the final stage relates to whether a patient is able to receive care in a timely and reimbursed manner at the level of the payer (decentralized process), resulting in inconsistency between European countries in patient access. The lack of orphan drug control has a negative effect on the economic development of the Indian medicine industry. The present study analyses and increases the orphan drug laws in the United States, the EU. Any of the current problems relevant to their legislation.

Keywords: Medicinal products, Orphans, Life-threatening, Centralized, Decentralized, Legislation

INTRODUCTION

Patients with uncommon disorders should be entitled to care of the same quality as other patients.' This praiseworthy sentiment is enshrined in European law in the landmark European Regulation 141/2000, which implemented in the European Union (EU) a package of commercial incentives to try to promote the production of rare

(orphan) disease products that, had previously been largely ignored by pharmaceutical industry.

There are more than 25 million individuals affected by more than 7,000 diseases in the United States that are considered rare. With only 10 new medicines licensed for rare diseases between 1972 and 1983, lawmakers assisted parents and caregivers, and the Orphan Drug Act (ODA) became law in 1983. The US was the first country to adopt orphan drug regulations, and a number of other countries have followed suit in recent years, such as Japan (1993), Singapore (1997), Australia (1998) and the EU (2000). Other nations, such as Canada, understand the value of orphan drug legislation and, on a case-by-case basis, accept applications for rare diseases, but have yet to do so issue regulations.

Although the rewards have been of great benefit, there is no question that the cause of the recent surge of interest in the production of orphan drugs is likely to be multifactorial. Examples include patent expiry for blockbuster drugs; the lack of novel therapies for well-established diseases; the development of the biotechnology industry; developments in molecular biology; substantial growth in the efficacy of groups of patients with rare diseases; and ubiquitous social media availability [1].

About 6000 and 8000 rare diseases are estimated to occur. While each rare disease affects a relatively small number of patients by itself, rare diseases collectively pose a major health burden. Rare disease patients are entitled to expect the same care standard as other more common disease patients. However, under normal market conditions, it is not expected that the expense of producing rare disease drugs will be recovered from future sales. Therefore, a legislative mechanism exists to promote the discovery and production of 'orphan drug or orphan medicinal product (OMP)' medicines for rare diseases.

In the USA in 1983 (the Orphan Drug Act (ODA)), Japan in 1993 (amended Pharmaceutical Affairs Law), Europe in 2000 (Regulation (EC) No 141/2000) and in other areas, a supportive regulatory framework for medicines for rare diseases was introduced. The law acknowledges the 'anticipated potential' of an OMP by awarding a classification called orphan designation in the care of a rare disease. A sponsor obtains an orphan status for its medicinal product by making a request to the designating authority before applying for a marketing authorisation application (drug licensing). There is no international harmonization of the requirements and procedure for orphan status, and this editorial focuses on main designation features in Europe and the USA [2].

INCETIVES FOR ORPHAN DRUG DEVELOPMENT:

The key incentives of the EU and US orphan drug legislation. Market exclusivity is commonly considered to be the most relevant of the benefits, but this does not take effect until marketing authorisation (MA) has been issued in the EU and the Food and Drug Administration (FDA) has approved a new drug application (NDA) in the US.

Another application for an MA (and even an expansion of an established MA) for the same therapeutic indication, for a particular medicinal product, is precluded by market exclusivity in the EU. For multiple products, it is possible (and indeed very common) to receive an orphan classification for the same indication, but for two identical products, the MA would be given only the first to obtain an MA and the 10-year exclusivity. For example, 16 products received orphan designation for pulmonary arterial hypertension in the EU, but only 4 received orphan designation for MA. An MA for the same indication could be given to a second product if it is not identical to the first product, but it would also be required to show a substantial benefit if the orphan label was to be received. There are exceptions to these regulations if the original MA holder consents, or if the original MA holder is unable to provide an appropriate product, or if the second applicant is able to demonstrate that his or her product is better, more reliable or otherwise clinically superior.

In the United States, the orphan drug designation is conferred on the active moiety in the product and, as in the EU; the first active moiety with the orphan designation to be put on the market enjoys exclusive benefits. If a medication has been licensed for use in an orphan indication for sale in the US, the only way to label another product as an orphan drug for that indication is if the sponsor makes a fair hypothesis that the product is 'clinically superior' to the approved product by means of greater efficacy, greater protection or a substantial contribution to patient care. A head-to-head trial may be appropriate for any assertion of clinical superiority . Key incentives of the orphan drug legislation in Europe and the US are shown in **Table 1**.

In the US, the classification as an orphan drug provides sponsors with an exemption from the fees needed when submitting a new drug or biological application. For fiscal year 2014, the charge under the Prescription Drug Consumer Fee Act for an application that includes clinical data is $2,169,100 (PDUFA).Recent changes in fee reductions in Europe for companies developing orphan medicinal products is shown in **Table 2**.

Table 1: Key incentives of the orphan drug legislation in Europe and the US*

Items	EU	US
Market exclusivity	10 years	7 years
Protocol assistance and follow-up	Yes	Yes
Reduced / waived regulatory fees	Yes	Yes
Tax credit on clinical trials	No	Yes
Specific subsidies for clinical trials	No	Yes

Table 2: Recent changes in fee reductions in Europe for companies developing orphan medicinal products

Items	2013	2014
Protocol Assistance And Follow Up	100 for SME'S 40% for Non SME'S (non pediatric related assistance) 100% for Non SME'S (pediatric related assistance)	100 for SME'S 75% for Non SME'S(non pediatric related assistance) 100% for Non SME'S(pediatric related assistance)
Pre authorization inspection	100% for SME'S	100% for SME'S
Initial marketing authorization approval	100% for SME'S	100% for SME'S 10% for Non SME'S
Post authorization marketing including annual fee in the 1st year after MA	100% for SME'S	100% for SME'S

The ODA is generally known as having succeeded in supporting the production of orphan indication products in the US and the EU. There have been almost 3,000 orphan designations and 448 approvals in the US since it was enacted in 1983. More than a third of all the new chemical entities (NCEs) approved by the FDA were orphan drugs in 2008. There are 1,219 designated and 78 licensed products in the EU (excluding those withdrawn and expired, there are currently 986 designated and 67 orphan drugs approved) **[1]**.

ORPHAN DRUG DESIGNATION:

Orphan drug designation in the EU:

Regulation (EC) 141/2000 outlines the conditions for the classification of an orphan . In Regulation (EC) No 847/2000, more comprehensive rules, guidelines and definitions are given. The criteria to be met for the designation of an orphan are as follows: the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 out of 10,000 persons in the European Union (EU) or the product is intended for the diagnosis at the time of submission of the designation application; It would be unlikely that the prevention or treatment of a life-threatening, severely disabling or severe and persistent illness would result in revenue without benefits that would cover the investment in its growth. Furthermore, no adequate method of diagnosis, prevention or treatment of the condition involved is allowed or the medicinal product would be of substantial benefit to those affected by the condition if such a method exists.

The sponsor must be known within the Group, and must provide the permanent

address documentation. Until applying for marketing authorisation, sponsors can apply for a designation at any point in the production of a product (non-clinical and/or clinical). Orphan designation applications are reviewed by the Committee for Orphan Medicinal Products(COMP) of the European Medicines Agency (EMA). The COMP consists of one delegate from each Member State, three representatives of patients and three appointed members of the European Commission (EC). The EMA strongly encourages sponsors to request a pre-submission meeting (usually by teleconference) before the application is submitted (at least 2 months in advance) and to use the common EMA/FDA application form. The classification process is free of charge and there is a fixed time for the assessment process. Applications should be submitted in compliance with the Guidance on the format and content of applications for orphan medicinal product classification. In the application, sponsors should explicitly substantiate the allegations and support statements made. Specifically,

- Generally, distinct medical entities are known as legitimate conditions. There would be a need for evidence of plausibility to limit use of a subset of a more common disease.
- Medical plausibility is not an explicit criterion for orphan status. In the proposed orphan indication, however, there must be a clear scientific rationale for the use of the product.
- Prevalence must be a particular number, not necessarily suggested as less than 5 in 10,000.
- A significant benefit is defined as a clinically important benefit or a significant contribution to patient care (MC-to-PC). Assumptions should be realistic and based on sound pharmacological principles and cannot be based on theoretical risks with respect to protection.

A brief report is prepared by the EMA/COMP from the evidence provided by the sponsor and a favorable opinion is given following discussion at the COMP if the conditions are found to be satisfactorily fulfilled. However, a list of questions is submitted to the sponsor if there are unresolved issues. To decide the final result, the sponsor presents a written response and is invited to attend an oral hearing. A sponsor can appeal or re-apply with additional data at a later date in the light of a negative opinion. The scientific opinions of the COMP are generally reached by consensus and the opinion is forwarded to the EC, which is the body

responsible for the issuance of binding decisions. The OMP is registered in the EC Registry and there is an online public assessment report available.

Incentives help sponsors with a specified orphan product. The EMA uses a special fund from the EC to award fee cuts (i.e., applications for marketing authorization, inspections and scientific advice). Scientific advice (called protocol assistance) helps increase the possibility at the marketing authorization point of a good result. OMPs benefit from 10 years of market exclusivity following the issuance of a marketing authorization. Member States may not approve another application for the same therapeutic indication for a duration of 10 years with regard to a related medicinal product. During that time, comparable products which are directly competitive (products containing a similar active substance intended for the same therapeutic indication) cannot usually be put on the market. However, three derogations apply: I the marketing authorisation holder (MAH) consents to the original application; (ii) the marketing authorisation holder (MAH) is unable to provide adequate quantities for the original application; or (iii) the second applicant is able to develop clinical supremacy.

Orphan drug designation in the USA:

The Food and Drug Administration (FDA) administers the main provisions of the ODA through its Office of Orphan Products Production (OOPD). The ODA is a federal rare disease law affecting fewer than 200,000 people in the United States or more than 200,000 people, where there is no hope of recovering the expense of the related drug production and delivery by sales in the United States. An orphan drug status for a previously unapproved drug or a new orphan indication for an already marketed drug may be sought by a sponsor. Furthermore, if they can present a reasonable hypothesis that their product may be clinically superior to the first drug, a sponsor of a drug which is otherwise the same drug as an already approved orphan drug may pursue and receive a designation for the same rare disease or disorder. Higher efficacy, greater safety or MC-to-PC refer to clinical superiority. A narrow category is considered to be MC-to-PC and does not concern minor inconveniences.

In order to file an application for orphan drug status, a foreign sponsor needs to have a US resident agent. An application is submitted by the sponsor to the OOPD and the application can be submitted at any time before the New Drug Application/Biologics License Application (NDA/BLA) is submitted. The details needed to be included in the application can be found in 21 CFR 316.20(b), shown as nine items. Although all nine items are discussed, items 4 (scientific rationale) and

8 are the most important (population prevalence). If a treatment can be shown to be effective in a small subset of a common disorder, it may also qualify for orphan status (such subsets may be considered invalid according to the EU Regulation). One where the drug's features limit its use in a specific subgroup is a medically feasible subset of a more common disease. The prevalence must be a precise number, not just less than 200,000,000. (If a range exists, the highest estimate should be applied).

A submitted orphan drug application is reviewed by the research staff of the OOPD in order to decide if a drug qualifies as an OMP. The appointed OOPD reviewer completes the evaluation by preparing an analysis following receipt of the submission. This is followed by an examination and rivalry at the second (OOPD team leader) and third level (OOPD Office Director). A letter of designation, a letter demanding more information or a letter of rejection are the findings. The name of the sponsor, the name of the drug and the proposed indication are released after a positive decision. 90 days is the average evaluation period. Incentives support sponsors who receive an orphan designation. Incentives include a 7-year market exclusivity period following marketing authorisation, protocol assistance and production expense tax advantages. User fees charged to the FDA for review of the marketing authorisation application of the sponsors are waived. Furthermore, the FDA Orphan Products Grant Program provides funds for clinical trials (safety and/or efficacy) that may lead to or contribute significantly to consumer acceptance **[2-3]**.

REVIEW PROCESS FOR ORPHAN DRUGS IN COUNTRIES:

USA: The FDA is conducting a new initiative to explore whether it can help establish a more reliable, scientifically advanced, predictable and modern approach to the approval of safe and effective treatments for rare diseases in order to overcome these challenges and to help allow continued progress towards more treatments and even possible cures for rare diseases. This begins with the redesign of our Office of Orphan Drugs Development's mechanism for awarding orphan drug designations. We will modernise the processes in OOPD with their leadership and hard work to make sure we continue to have timely analysis of requests for orphan drug designation. This will provide sponsors with greater certainty and simplify and eventually eliminate some of the time and costs associated with orphan drug development.

As part of this new strategy, the FDA will complete evaluations of all orphan drug designations that are older than 120 days by

September 21, 2017. After those 90 days, the Agency undertakes to respond to 100% of all new requests for orphan drug designation within 90 days of receipt by the FDA. Improvements to the programme and a renewed commitment to prompt analysis of these essential items would ensure that.

The few of programmatic improvements that are further described below in Orphan Drug Designation Plan:

- In 90 days, FDA will complete reviews of all orphan drug designation requests that are older than 120 days (the backlog) while maintaining consistent, scientifically rigorous reviews; and
- After 90 days, 100 percent of all new orphan drug designation requests will receive a response by the agency within 90 days of receipt. FDA will adhere to this 90-day timeline going forward.

Goal-1-In 90 days (by September 21, 2017) complete reviews of all requests older than 120 days.

1. Created a Backlog SWAT Team of senior, experienced, proficient OOPD reviewers to focus solely on reviewing orphan drug designation requests, starting with the oldest ones first.

2. Create and implement a new streamlined Designation Review Template to increase consistency, efficiency, and predictability of orphan designation reviews

3. Minimize discretionary work – i.e., FDA will reduce non-designation and non-grant-specific duties and assignments – for all other reviewers to enable the review teams to focus on core activities

4. OOPD will collaborate with FDA's Medical Product Centers to complete a CDER-CBER Orphan Designation Pilot Project – CDER and CBER reviewers will conduct preliminary primary reviews of a subset of drug designation requests, with OOPD conducting secondary reviews

5. OOPD will collaborate with the Office of Paediatric Therapeutics (OPT) to jointly review rare paediatric disease (RPD) designation requests. In these cases, OPT will conduct the paediatric review and OOPD will conduct the rare disease review. This policy began as of May 15, 2017.

6. OOPD transitioned secondary review of FOIA requests to the FOIA office, as of May 18, 2017

7. Continue to track weekly progress, adjust as necessary, and report on progress to the public.

Goal-2-After 90 days, 100m percent of all new orphan drug designation requests made to FDA will receive a response from the agency within 90 days of receipt and consistency thereafter

1. FDA will establish an FDA orphan products council to address scientific and

regularly issues related to orphan products to ensure a consistent approach to approach to regarding these products.

2. FDA will work to establish and implement a future state including the below changes. We will report on a full timeline of the progress on these activities within the next two months.

3. Organizational re-structuring to maximize expertise and improve workload efficiencies

4. Leverage the inter-center consult process, involving the medical product centers, that was developed for combination products to develop a streamlined process for consistent and timely orphan consults.

5. Designation and Exclusivity Programs (Orphan Drug, RPD, Humanitarian Use Device (HUD))

- Centralize orphan exclusivity review and determinations
- Continue to enhance the information technology infrastructure, e.g., automating more of the administrative processes for designation reviews
- Improve and implement streamlined "Designation Review Template" across all designation programs to bring more efficiency, consistency, and predictability to these activities
- Complete development of web-based training for sponsors to enhance quality of submissions.

6. Grant Programs: With respect to the Orphan Products (OPD) Grant Program (Clinical Trials + Natural History) and Paediatric Device Consortia (PDC) Grant Program; FDA will:

- Revise grant monitoring processes by increasing utilization of desk-top and virtual tools and by implementing a new risk-based approach for conducting in-person site visits to grant recipients
- Modify and modernize reporting requirements so that FDA can continue to give a high assurance related to appropriate monitoring of federal funds and efficiently measures program success
- Continue to enhance IT infrastructure for continued efficiency and better monitoring

7. Reduce OOPD office-wide workload

- Modify Orphan Cluster meetings with EMA from monthly to quarterly o The impact of the reduction in frequency of meetings with EMA is mitigated by our well established and long-standing relationship with our EMA counterparts, which will allow us to have ad hoc meetings should they become necessary in the intervening months.

- Modify FDA Rare Disease Council meetings from monthly to quarterly o The RDC was established in 2012 to serve as a forum to communicate and collaborate across the agency on rare disease issues. It is chaired by OOPD and includes representatives CDER, CBER, CDRH, OHCA, OL, and OOPD. Quarterly meetings would ensure continuity of cross-agency communication but would help reduce workload in administering monthly meetings. The implementation of more joint reviews and closer regular, ongoing collaboration should reduce the need for the larger, RDC meetings.
- Minimize outreach activities and discretionary projects to only those deemed most meaningful

8. OOPD will create a new "Tracking Dashboard" to monitor and facilitate its efforts to meet the new designation goals and FDA will report on overall workload and progress more regularly.

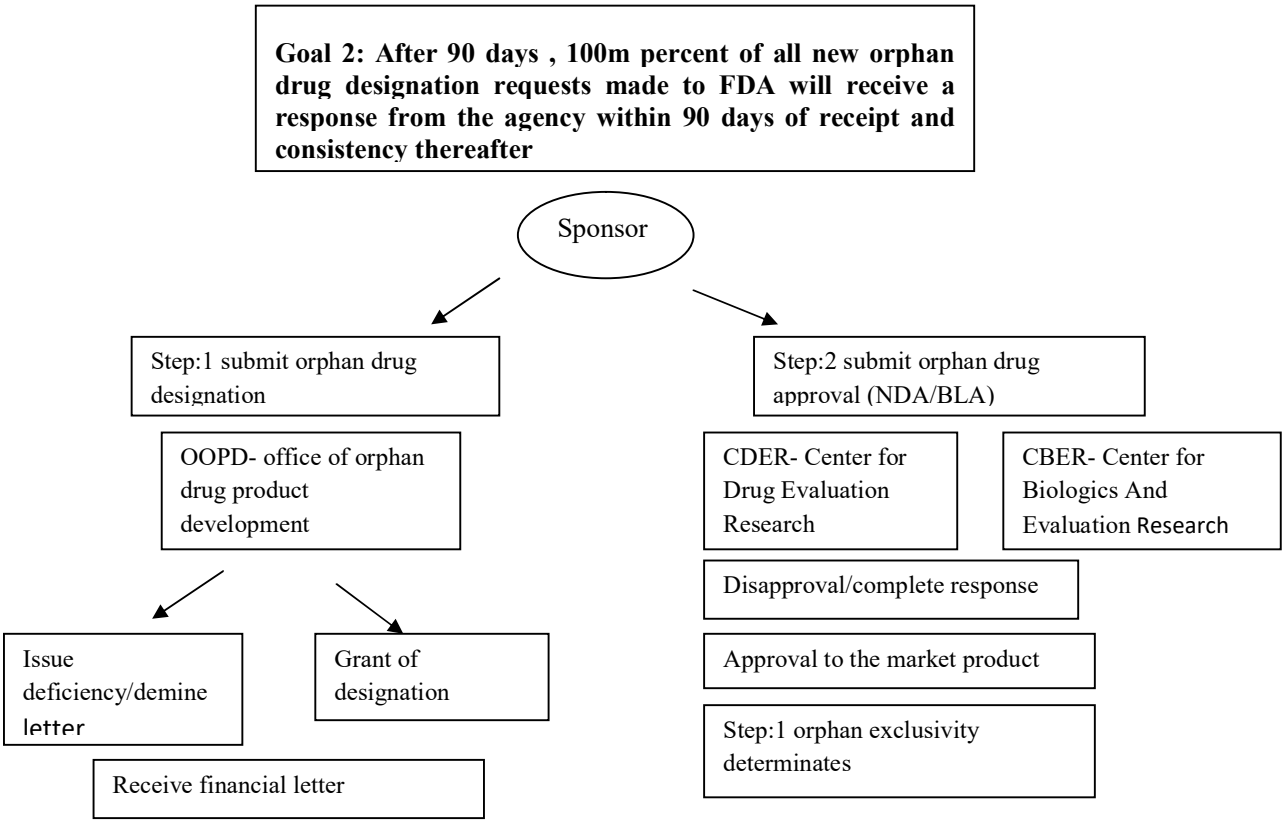

Figure 1: Goal 2 - After 90 days , 100m percent of all new orphan drug designation requests made to FDA will receive a response from the agency within 90 days of receipt and consistency thereafter

European Union: Sponsors are no longer required to send a notification of intent to file an orphan drug application for designation to the EMA. Sponsors should follow one of the two options listed below instead **[6]**:

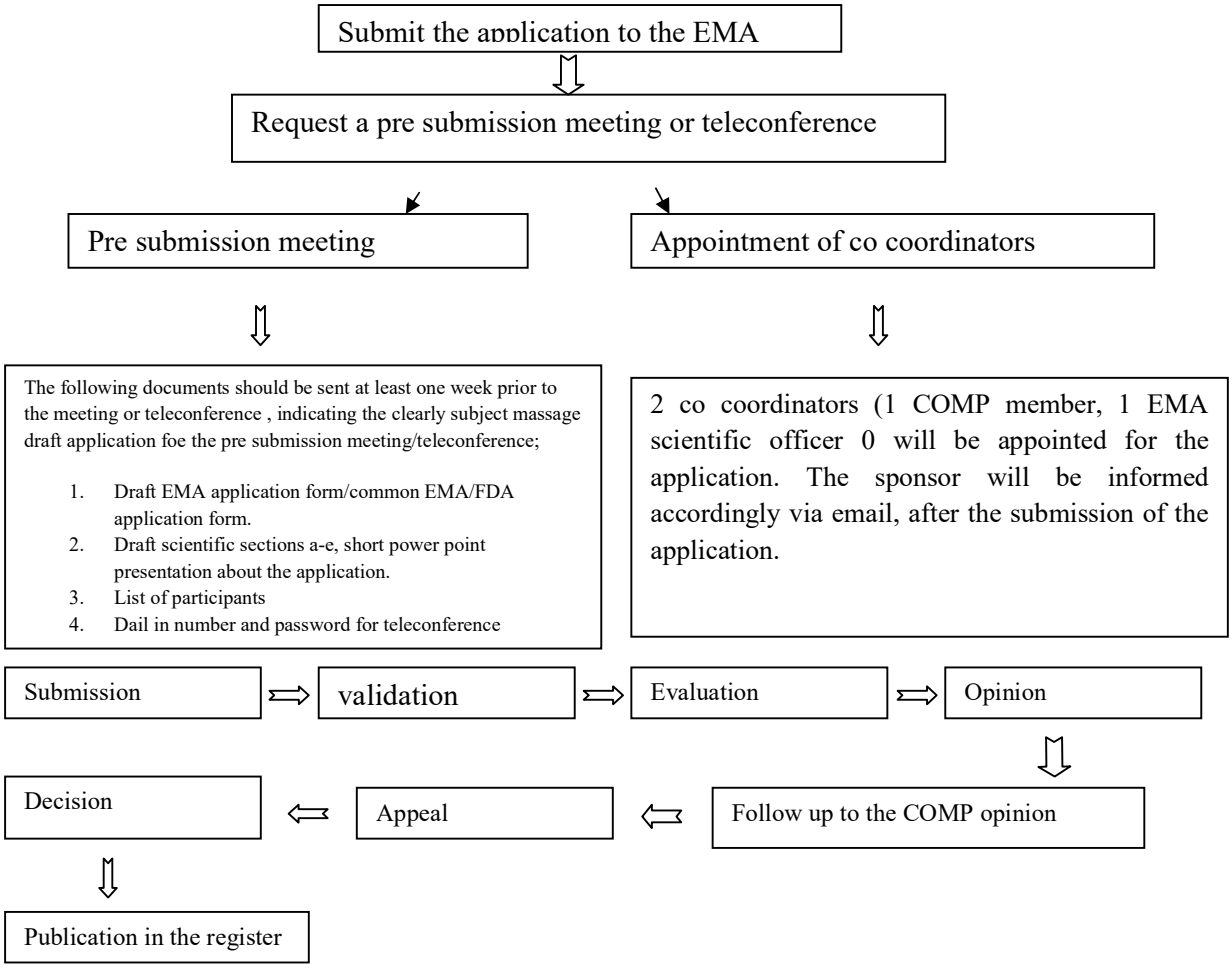

Figure 2: Review Process for Orphan Drugs in European Union

PRICING AND VALUE OF ORPHAN DRUGS

It is probable that if, as in the case of orphan drugs, the potential demand for the new medication is very limited, the price paid by the manufacturer is likely to be considerably higher than for medicines for the treatment of common diseases. In certain cases, the cost per patient per year is several hundred thousand dollars / Euros. The reimbursement bodies have begun to look very critically at the cost-benefit ratio for orphan drugs with ever growing constraints on health budgets, leading to a situation where many orphan drugs, while approved across Europe, are not available in certain countries due to lack of funding.

Different methods have been suggested to resolve the "value" problem for orphan drugs, see, for instance, Hughes-Wilson et

al., but none have been accepted to date. The prospect that orphan drugs could find it increasingly difficult to get reimbursed in the future is a potentially negative outcome of an otherwise very positive step towards providing care for rare disease patients **[5]**.

CONCLUSION

The US and EU orphan drug law has been effective in allowing rare disease patients to access drugs that otherwise would never have been created. This has led to the approval of 448 orphan products in the US and 78 in Europe, more than 30 years after the ODA was authorised in the US and 14 years after the European Regulation. Besides the benefits inside the Original Legislation. Additional regulatory pathways are now available that help to speed up the production and approval of medicines under conditions of unmet medical need. Moreover, patient organisations' deeper involvement in the drug development process itself, rather than merely as lobbyists, is changing the way orphan drugs are created.

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