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# EFPIA *IREG* Points to consider in Developing Regulations and Guidance related to Orphan Medicinal Products in Emerging Markets

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# Introduction

To achieve better health outcomes for patients with rare diseases and to have more treatment options for these patients requires innovative pharmaceutical companies to carry out medicine development programs that have a high risk of failure. The development of new treatments for rare diseases involves difficulties linked to the unique characteristics of rare diseases, including the limited number of patients available for clinical trials and treatment and there is often limited information on epidemiology and disease mechanisms of the condition being investigated.

Acknowledging these challenges, a number of countries have developed orphan legislation to foster rare disease drug development. For example, the European Union implemented an EU Regulation on Orphan Medicinal Products in 2000, after similar policy developments had been adopted by the Unites States (US), Singapore, Japan, Taiwan, Australia, Korea and Taiwan. Following the enactment of appropriate regulatory and incentive frameworks for orphan drugs, the availability of safe and effective orphan medicines has increased significantly. Looking at official statistics, orphan drug schemes in the EU and US have led to sustained and increased numbers of designations, clinical trials, and, the approval of new products:

* The number of orphan drug designations has grown substantially with 4663 in the US from 1983-2018[[1]](#endnote-2), 1952 in the EU from 2000-2017[[2]](#endnote-3), and 373 in Japan from 1993-2015[[3]](#endnote-4)
* In the US, according to one estimate, only 34 products were brought to market from 1967-1983 that meet criteria for an orphan drug. Another estimate indicates that industry brought only 10 products to market in the decade prior to 1983[[4]](#endnote-5),[[5]](#endnote-6). Following enactment of the Orphan Drug Act (ODA), there are currently over 600 rare disease indications approved from over 450 different orphan drug products.
* EU designations have resulted in 142 authorized orphan drugs and 20 extensions of indications.2
* A significant and sustained increase in new clinical trials for drugs treating rare diseases has been registered since the introduction of orphan drugs schemes, particularly in the EU, where the number of orphan drug clinical trials grew by 84% from 2005 to 2015.[[6]](#endnote-7)

These data show that well developed and implemented orphan legislation, and research funding have been very successful in stimulating the development of national rare disease plans, medical knowledge and an increase in disease awareness, diagnostics and social services thus innovation by providing incentives to develop treatments for rare diseases that are often un- or misdiagnosed. Ultimately, this has led to significant new research, clinical trials and availability of innovative therapies for severely debilitating and life-threatening diseases.

However, some countries are less advanced in this space, with no or only high-level legislation in place, which addresses the high unmet medical need in rare diseases. As new regulations and guidelines are under development in different countries, we would like to recommend that several key principles as outlined below are included to support global medicine development tailored to population needs that will benefit rare disease patients.

This paper will focus on regulatory considerations only and will not cover medical or market access challenges in the area of rare diseases and orphan drugs.

## Adoption of a standard definition of a Rare Disease and criteria for Orphan Medicinal Product Designation in the legislation

There is no internationally accepted definition of rare diseases.[[7]](#endnote-8) In certain emerging regulatory jurisdictions, defined orphan drug or rare diseases lists exist. However, they often lack clarity on inclusion criteria and methodology for eligibility. Having standard definitions aligned globally will allow standards to be set in a transparent manner and will facilitate regulatory convergence in the designation and approval process. It has been useful to differentiate between a rare disease definition and criteria for orphan medicinal status designation.

In major jurisdictions, medicinal products for rare diseases currently have to fulfil a series of criteria prior to obtaining “orphan” designation and benefit from the corresponding incentives, which are explained in further detail below.

* ***Seriousness of disease***

Orphan drugs have to diagnose, prevent or treat life threatening or chronically debilitating conditions.

In the EU, the Orphan Regulation specifies that the orphan condition should be life-threatening or chronically debilitating.

In the US, the Food and Drug administration (FDA) interprets the term “serious” as a disease or condition associated with morbidity that has substantial impact on day-to-day functioning.[[8]](#endnote-9) Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

* ***Unmet Medical need***

In the EU,an orphan designation can be granted if there is no satisfactory method of diagnosis, prevention or treatment authorised or a sponsor needs to demonstrate the new medicinal product represents a significant benefit compared to existing options.

In the US,a disease with unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e. to treat a serious condition with no or limited treatment) or a longer-term need for society; (e.g, to address the development of resistance to antibacterial drugs).[[9]](#endnote-10)

* ***Prevalence***

Different prevalence criteria have been adopted by different countries and regions. There is no single definition of a rare disease. Some of the definitions are based on the number of patients affected by the disease while others consider different important factors, such as the severity of the disease and the existence of adequate treatments.7

In the EU, rare diseases are those which occur in a maximum of 5 out of 10,000 people. This definition is currently being used in several other countries including for example in Switzerland, Argentina, Colombia, Mexico, and Australia.

In the US, rare diseases or conditions are defined as “any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.” [[10]](#endnote-11)

In Japan the threshold is set at 50,000 but was expanded in 2015 to cover also ‘intractable diseases’ affecting up to 180,000 Japanese (0,1% of population). However, it will be even more challenging to estimate prevalence of rare diseases in emerging markets since epidemiological data for most rare diseases are either not available at all or only in a limited manner. The primary reasons why such epidemiological data are often lacking could be due to inability of, or delay in, diagnosis or the absence of proper classification for rare diseases and the absence of publications and disease registries in those markets. Moreover, the standard of care based on resources, culture and other socioeconomic factors may also play an important role. Until recently there was no systematic effort to establish an inventory of rare disorders. Recognition should, however, be given to the revision of the 11th International Classification of Diseases (ICD), making rare diseases visible in health information systems through appropriate coding. WHO has set up Topic Advisory Groups (TAG) Rare Diseases formed by ORPHANET. Collaboration is expanding to US NIH, Japan, India and South Africa.[[11]](#endnote-12)

In close consultation with various stakeholders including industry, academia, clinicians, and patients, governments should establish a regular and transparent process for reviewing and updating their definition of rare disease and orphan drugs. This consultation should provide adequate time for all parties to consider adjustments and submit feedback and can be organized under a dedicated cross-agency working group or public forum.

***EFPIA recommendations***

*EFPIA believes it is important to ensure alignment and transparency on regulatory pathways for rare diseases and Orphan Medicinal Products in collaboration with industry, regulators and the broader rare disease community. And that for any new orphan medicinal products regulation or guidance being issued in emerging markets there is a common definition of rare disease containing the restriction to life threatening and chronically debilitating conditions with a prevalence that converges towards the EU prevalence criteria of a maximum of 5 per 10,000 inhabitants. This definition can cover most diseases with unmet medical need and can accommodate changes in country population over time. Therefore, a legislative definition and classification of rare diseases and accurate data on the epidemiology of rare diseases, for example via the development of a disease/patient register, are needed at the national and international levels to facilitate global development of innovative new therapies for rare diseases with high unmet medical need.*

## Accelerated review and approval of innovative treatments for rare diseases with high unmet medical need and reliance on other regulatory authorities

In many emerging markets, the lack of both defined review timelines and expedited regulatory pathways for orphan drug designation and registration are major concerns and prevent the regulatory predictability that can facilitate global development of orphan medicinal products. The situation is often further complicated by resource/ capacity constraints within national regulatory authorities (NRAs).

* ***Recognition of Orphan Drug status granted by another health authority***

The orphan designation procedure may require a complex assessment and health authority capacities that are not readily available in all countries. Where these capabilities do not exist, an alternative proposal would be for competent authorities to rely upon and recognise the orphan drug status that has potentially been granted already in another territory. For example, Switzerland will automatically designate a product as orphan if it has already been granted orphan status by another recognized authority. Evidence that the product contains the same active compound, as well as proof of orphan status in the foreign territory must be provided by the Sponsor. If there is a divergence in opinion granted by other authorities’ designations, a full assessment is required.

* ***Reliance and expedited registration pathways for orphan drugs***

The countries that have put in place incentive-based mechanisms have also focussed on accelerated marketing authorisation approval timeframes. This is notably the case in Australia and Taiwan, as well as the countries that have put in place independent regulatory pathways for orphan drug approval such as Switzerland, Russia, Brazil and Korea. In this context, EFPIA believes that a potent enabler of accelerated review and approval can be the implementation of the concept of reliance or expedited registration pathways at the relevant National Regulatory Authorities (NRAs) as explained in detail in the [EFPIA White Paper](https://www.efpia.eu/media/288592/white-paper-on-reliance-and-expedited-registration-pathways-in-emerging-markets.docx), *‘Reliance and expedited registration pathways in emerging markets’.[[12]](#endnote-13)* EFPIA defines these alternative registration pathways as follows:

* **Reliance pathways to Facilitate Regulatory Decisions**: Registration pathways used by NRAs or regional regulatory initiatives wherein their decisions regarding the approval of any type of product can be accelerated by the reliance on or recognition of prior reviews by stringent regulatory authorities (SRAs; see explanation in glossary).
* **Expedited Regulatory Pathways for medicines targeting unmet medical need:** Registration pathways that speed the development, review and approval of a product which fulfils the national requirements for unmet medical need (see above); typically implemented by a SRA, for a first non-dependent review, where no prior approval exists.

***EFPIA Recommendations***

*EFPIA believes that the recognition of orphan medicinal product designations from other recognized international regulators,e.g. US-FDA, European Commission (EC), should be considered in emerging markets..*

*In addition, the implementation of alternative registration procedures (either reliance or expedited registration pathways) is a potent enabler of accelerated review and approval. Especially the use of reliance pathways is an attractive option to facilitate patient access to orphan drugs (among other products) in emerging markets, as it avoids duplications of efforts across regulators and can thereby contribute to equity of access globally. For orphan medicinal products, regardless of the registration pathway being used, it is critical that regulators allow innovative clinical development approaches. For example, to accept novel trial designs such as basket and umbrella trials, and to accept the use of novel sources of data such as data coming from digital apps/wearables and real-world evidence (RWE) to support decision-making, if scientifically justified.*

*In the interest of public health, EFPIA encourages regulators to offer early scientific dialogue or pre-submission meetings between companies and regulatory agencies wherever available, to define the most appropriate registration procedure for a given medicinal product.*

## Implementation of a Regulatory and Incentives framework enabling innovation and global convergence in the development of orphan drugs

A number of countries around the world aim to improve access to treatments for rare diseases by adopting dedicated rare disease policies or national plans. However, very few countries have included in their regulations appropriate incentives to stimulate innovative research and development of new products and technologies. Those countries that have put in place incentive-based mechanisms have mainly focused on improving development and market approval timeframes. Orphan drug schemes provide different mixes of defined regulatory incentives. Of these, most are related to market exclusivity, fee reductions, accelerated review and approval, development tax credit, and specific pre-licensing support. It is also important to highlight the existence of regulatory challenges that may prevent the introduction of orphan drugs in emerging markets such as the need for a local clinical trial, local Quality Control (re-)testing and local Good Manufacturing Practice (GMP)-, and inspection requirements which introduce ambiguity and complexity in global drug development, potentially leading to a delay in patient access to orphan drugs.

* ***Market Exclusivity***

A defined period of market exclusivity constitutes an important orphan drug incentive but is not commonly included in orphan regulations. While the EU ensures 10-year market exclusivity period versus only 7 years in the US, the orphan status in the EU can be reviewed and thus reduced by 4 years if the designation criteria are no longer met at Year 6. In addition, in the EU, orphan exclusivity may be extended by a further two years upon completion of an agreed paediatric investigation plan (PIP) and the inclusion of the paediatric data within the approved product labelling. In addition, the EU marketing exclusivity clause allows that other similar products may not be approved if they are considered similar. In Japan orphan drugs benefit from an extended data exclusivity period (referred to as ‘re-examination’ period) of ten years, against eight years for NCEs and four years for new indications of drugs already approved. Orphan exclusivity runs parallel to other rules on data exclusivity and market protection.  Market exclusivity should be a key element of orphan regulations and mandatory in countries where local clinical trials are required and/or there is inadequate IP protection.  At a bare minimum, the regulations should include strong data protection provisions to encourage the introduction of orphan treatments into the market.

* ***Pre-licensing support***

Early and close interactions with Health Authorities on orphan medicinal products, including access to scientific and regulatory advice during drug development allow manufacturers to gain an understanding of what regulatory authorities are expecting in terms of product development, including clinical endpoints. Due to the complexity of drug development for rare diseases and the limited number of disease experts, pre-licencing discussions are also an opportunity for authorities to better understand the product and bring relevant experts early enough into the evaluation/ authorization process.

* ***Local clinical trial waiver***

In some countries clinical data in the local population is required to be able to register medicinal products. Given the frequent challenge to find sufficient numbers of rare disease patients at the country level that satisfy clinical trial entry criteria, clinical trial waiver exemptions and limited post approval trials should be encouraged.

A good example is provided by countries such as Taiwan and Korea, which accept global clinical data and provide for the systematic waiver of requirements to conduct local clinical trials for orphan medicinal products.

* ***Import testing and local GMP & inspection requirements***

For orphan medicinal products, the number and size of batches produced per year are often small and the number of involved manufacturing sites is usually very limited. EFPIA encourages national regulatory authorities (NRAs) to support global convergence of pharmaceutical regulations and guidance, and not to impose additional local/ national requirements beyond internationally recognized standards, such as ICH, on the manufacturers of medicinal products and active pharmaceutical ingredients.

This consideration is of even greater relevance for companies active in orphan indications, since it could have a pronounced negative effect on innovation in this space. In concrete terms this means NRAs should consider, for example, exemptions of current requirements regarding local manufacturing, import (re-)testing, national GMP inspections etc., as applicable. Following the theme of supporting global convergence of regulatory standards, EFPIA also encourages NRAs to rely on inspections done by other health authorities which have demonstrated the relevant competencies, for example as a member of PIC/S.

***EFPIA Recommendations***

*EFPIA believes the right incentive scheme is essential to encourage investment in developing treatments for rare diseases, leading to significant new research & development, global clinical trials and new innovative drugs. A well-defined period of market exclusivity constitutes the backbone of orphan drug specific incentives as well as waivers of local clinical trial data, local manufacturing, import testing, and national GMP requirements, as applicable.*

# Conclusion

Patients in all countries worldwide would benefit from having a dedicated regulatory framework and including common definitions and incentives in place for orphan medicinal products, including standard criteria for orphan designation. This would foster global development and local registration of new therapies for rare diseases. As technology advances, it is also expected that regulatory requirements and standards should converge globally to streamline the regulatory path to market for highly innovative medicines for diseases with unmet medical need.

This EFPIA document contains key points to consider relevant when drafting new laws or regulations for orphan medicinal products, in particular in emerging markets. We recommend taking into consideration as well the recent EFPIA White Paper on reliance and expedited registration pathways in emerging markets as a way to mitigate potential capability constraints at the level of national regulatory authorities and to avoid potential disadvantages to patients in those countries.

**Glossary**

*Stringent Regulatory Authority (SRA) [or newly named “WHO listed countries”]*

*According to the current WHO interim definition, a Stringent Regulatory Authority is referred to as a regulatory authority that is:*

*a) a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or*

*b) an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or*

*c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway.*

1. # References

 [FDA Orphan Drug Designations and Approvals Database](https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm#Search_param_field) <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm267378.htm> [↑](#endnote-ref-2)
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11. <https://ojrd.biomedcentral.com/articles/10.1186/s13023-015-0251-8> [↑](#endnote-ref-12)
12. EFPIA White paper on reliance and expedited registration pathways in emerging markets (23/11/2017), available under:

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