Introduction

Key Topics:

- Overview of the Orphan Designation process in Europe and the US.
- Key Incentives of both the European and US Orphan Designation systems
- Some considerations regarding Market Protection mechanisms.

CORRESPONDENCE

LINK TO ORIGINAL ARTICLE

Worldwide collaboration for orphan drug designation

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The growing awareness of the need for pharmaceutical products to treat rare diseases led to the enactment of rare diseases legislation in the United States (Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. *Nat. Rev. Drug Discov.* 9, 510–522 (2010))[1], the European Union[2] and Japan[3] (see also Further information). The European Medicines Agency (EMA) has been

Definition of an orphan condition. The sponsor often plans for development of a drug for a specific therapeutic indication that falls within an orphan disease or condition. Therefore, often the overall orphan disease or condition may be broader than the therapeutic indication that the sponsor plans to study for marketing approval. Although there is some variance between the interpretations by both agen

prevalence has to be based on epidemiological data from the European Economic Area (EEA; consisting of the 28 EU Member States in addition to Norway, Liechtenstein and Iceland) and must not be more than 5 in 10,000 people. In the United States, the number corresponds to a higher prevalence rate (around 7 in 10,000) than in Europe, which means that certain conditions may obtain an orphan designation in the United States but do not qualify in Europe.

Procedural aspects. Text used to describe the rare disease or condition and the medical plausibility and scientific rationale will not vary much in view of the similarity of the requirements, making the only different task the prevalence calculation. In the European Union, once a submission is validated, a start date is given and the procedure lasts a maximum of

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Orphan Medicinal Designation considerations:

Situation in Europe

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Main characteristics Orphan Designation in Europe

- ***Procedure are free of charge.***
- *Submissions can be for a product which is for the treatment, prevention or diagnosis of a rare disease.*
- *A request for designation can be made at any stage of development before the application for an MAA. The product must not have a previous MAA.*
- *The sponsor can be a company, Non-governmental organisation, Academic centre or a private individual who is established in the EEA (EU, Iceland, Liechtenstein)*
- *The COMP assesses the application and sends a recommendation to the Commission who grants the designation thereby opening the incentives.*
- *Designated products are entered into the Community register of OMPs.*
- *Involves a review of the designation at the time of MAA submission regarding granting the 10yr Market Exclusivity.*

Application package

- *Application form (if intention to file with the FDA there is a Joint Application form).*
- *Scientific sections A-E of the application (A-E Template)*
- *Proof of establishment of the sponsor in the EU (passport for private person, certificate of company registration).*
- *Translations of the name of the product and the proposed orphan indication into the official languages of the European Union, plus Icelandic and Norwegian*
- *Bibliography*
- *If applicable, letter of authorisation from the sponsor for the person/company acting on their behalf during the procedure*

Key Considerations: EC Guideline on the format and content of applications as OMPs (ENTR/6283/00)

- Medical Condition under the orphan legislation:
  - *Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome)*
  - *Must be chronically debilitating and /or life-threatening.*
  - *Different degrees of severity- stages not acceptable*
  - *Subset of patients where positive B/R is expected generally neither sufficient to define a distinct condition.*
- Prevalence must be BELOW 5 in 10,000.
- Authorised pharmacological treatments in Europe/Member States should be listed if there are any and European Guidelines highlighted.
- If any are available then the sponsor must show Significant Benefit (either ***clinically relevant advantage*** or ***major contribution to patient care.***)

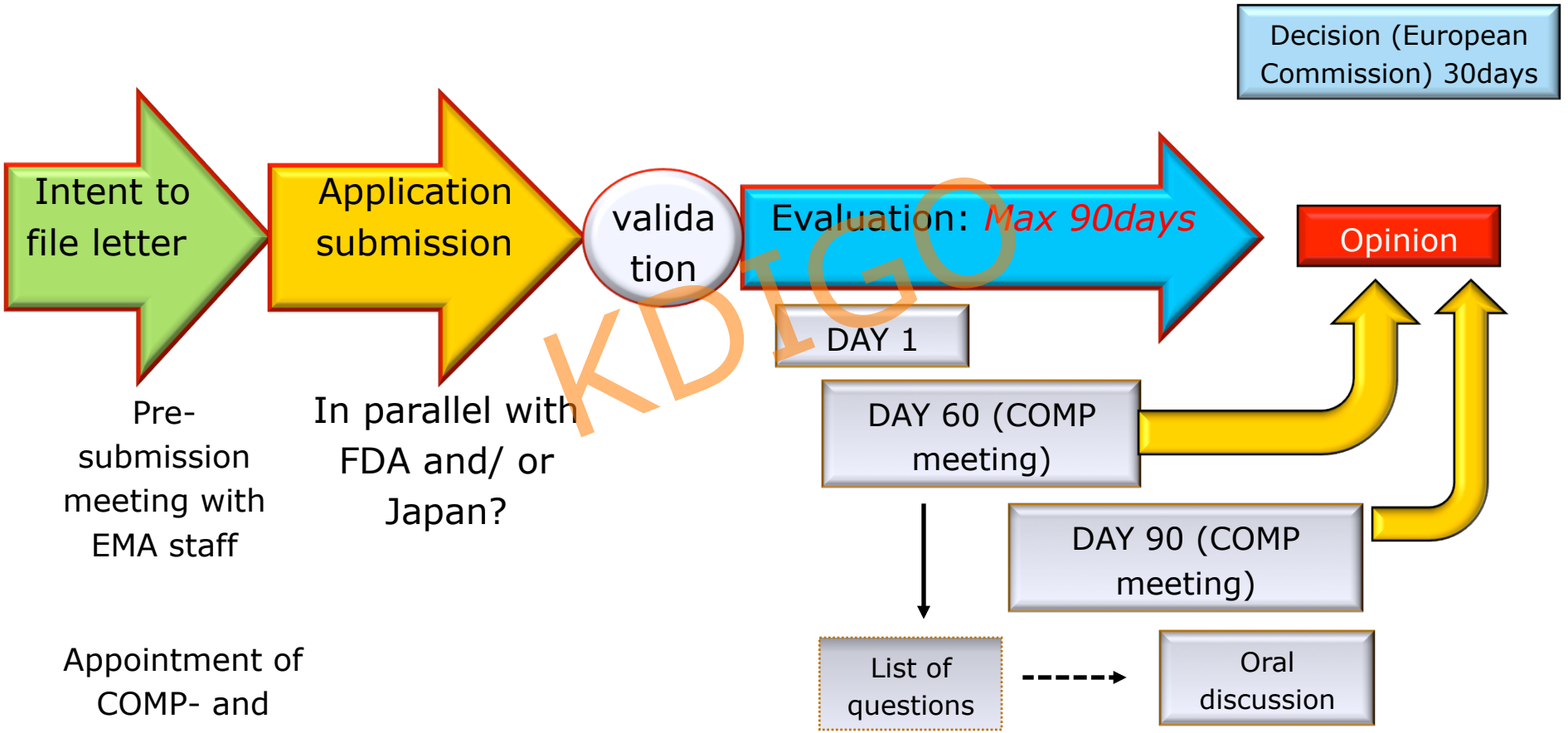
Significant benefit (Exclusive for Europe)

Significant benefit: "*A clinically relevant advantage* or *a major contribution to patient care*"

Based on **assumptions** at the time of orphan designation

- Significant benefit over "satisfactory methods" generally understood to mean authorised medicines for the indications.
- Current European Guidelines regarding how to treat patients with the condition.
- COMP to assess whether or not assumptions are supported by available data/evidence supplied by applicant
- Significant benefit to be **confirmed** at the time of marketing authorisation to maintain orphan status. Data to demonstrate the SB.
- Recommendation document on data for SB and plausibility

The designation process in the EU



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FDA Orphan Designation

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Basic Definitions

What is an **orphan drug**?

- Drug (or biological product) intended for use in a rare disease or condition (21 CFR 316.3 (b) (10);
  - Note: Being an orphan drug is not synonymous with having orphan drug designation

What is a **rare disease**?

- Disease/condition that affects <200K people in the US

Actions Pertinent to Orphan Drugs

1. Designation:
   - is free and requires the sponsor to be established in the US
   - Has no regulatory clock.
   - Must be submitted before obtaining a Market Authorisation
   - Is conducted by the FDA Orphan Office who grants the designation.
2. New Drug Application (NDA)/Biological Licensing Application (BLA) Approval

Content and format of a request for orphan-drug designation

- (1) Statement that the sponsor requests orphan-drug designation for the rare disease or condition.
- (2) Identify the sponsor and the drug
- (3) Describe the rare disease or condition, the proposed use of the drug, and the reasons why such therapy is needed
- (4) Provide:
  - Detailed description of the drug
  - Scientific rationale for its use
- ***Same in Europe***

Additional considerations for a request

(5) If SAME DRUG as an already approved drug for the same rare disease or condition, with or without orphan exclusivity, designation would be inappropriate

- Explain why clinically superior

(6) If the request is for an orphan subset of a common disease, explain why some property of the drug or biologic would limit use of the product to the subset

(7) Summary of the regulatory status and marketing history

(8) Documentation *(similar in Europe)*:

- Prevalence < 200K

Or

- No reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales

Orphan Subsets

No to "salami slicing"

- Example: A drug proposed to be used to treat breast cancer patients refractory to first-line treatment
  - No, unless there is some property of the drug (e.g., toxicity) that would restrict its use
- Example: A drug that will only be tested for those patients that meet clinical trial inclusion criteria
  - No
- ***Same in Europe.***

Orphan Subsets

Yes to orphan subsets

- Example: A drug (monoclonal Ab) that will act against a surface antigen found only in a rare subset of breast cancer cases and would not act in breast cancer cases without the surface antigen.
  - Yes
- Example: A drug that targets a specific genetic mutation found in only a small subset of colon cancer cases
  - Yes
- ***Not always the same in Europe.***

#3 – Is the Scientific Rationale Sufficient?

Required – Evidence that the drug holds promise for being effective in treating/preventing/diagnosing disease

Includes information from:

- Clinical data, OR
- Animal models, OR
- In vitro data (with proposed MOA and pathogenesis of disease when no adequate animal model exists)
- ***Similar in Europe***

Common Incentives between FDA and Europe

Financial Incentives

	FDA	Europe	Japan
Financial incentives	• Tax credits can apply to as much as 50% of qualified clinical development costs (US studies) • User fees paid to the FDA for review of the sponsors' application for marketing authorisation are waived	• No general tax credit on clinical trials and no specific subsidies for clinical trials • Regulatory fee reductions generally favour small and medium-sized enterprises, but are revised from time to time • Member states might offer a variety of price and reimbursement incentives as well as tax credits (see REF. 7)	• Financial subsidies for up to 50% of expenses for clinical and non-clinical research • Subsidies through the NIBIO to reduce the financial burden of product development • User fee waivers, 15% tax credits, up to 20% corporate tax reduction and a 30% reduction in marketing application fees

Grants for Research

	FDA	Europe	Japan
Grants for research programmes	• The FDA Orphan Products Grant Program offers funding for clinical studies (investigating safety and/or effectiveness) that will result in or substantially contribute to market approval • The National Institutes of Health (NIH) also has a grants mechanism for rare diseases	• The European Commission supports rare disease research through its framework programmes and the call for proposals in the rare disease area usually includes Europe-wide studies of the natural history of rare disease, pathophysiology and the development of preventive, diagnostic and therapeutic interventions • Member states offer a variety of grants (see REF. 7)	• Support measures include grants in aid for clinical and non-clinical research programs, price-control policies negotiated by Japanese National Health Insurance and pharmaceutical companies, and medical expense reimbursement for 56 diseases • NIBIO and AMED offer grant programmes to small and medium-sized enterprises and researchers who are developing products for rare diseases

Protocol Assistance

	FDA	Europe	Japan
Scientific advice (protocol assistance)	• Access to free scientific guidance at the FDA • Guidance by the relevant review division at the FDA on the regulatory requirements for quality, non-clinical development and the design of the clinical trials to demonstrate the efficacy and safety of the drug	• Access to free-of-charge protocol assistance at the EMA • Guidance on the regulatory requirements regarding quality, non-clinical development and the design of the clinical trials necessary to fulfil the regulatory requirements for the demonstration of efficacy and safety of the drug	• A 30% fee reduction for protocol assistance • Guidance is given on the regulatory requirements regarding quality and non-clinical development, as well as on the design of the clinical trials necessary to fulfil the regulatory requirements for marketing authorization

Marketing Exclusivity

	FDA	Europe	Japan
Marketing exclusivity	• 7-year marketing exclusivity is granted to a product that, after receiving an orphan designation, goes on to receive a marketing approval as an orphan drug, meaning that the FDA cannot approve another (competing) marketing application for the 'same' drug treating the 'same' orphan diseases or conditions.	• The 10-year market exclusivity protects against a similar drug being authorized for the same therapeutic indication • Three derogations from this rule exist: first, sponsor's consent; second, lack of supply; and third, if a new product (although similar) could be demonstrated to be 'clinically superior', that is, 'safer, more effective or otherwise clinically superior' than the product already on the market	• Extension of the re-examination period to 10 years at marketing authorisation

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Incentives: Additional considerations

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Paediatric Investigational Plan (Europe)

- *EC Regulation (EC) No 1901/2006 Article 37 states that "a Marketing Authorisation Application for an Orphan Medicinal product which includes the results of all studies conducted in compliance with an agreed paediatric investigation plan will be eligible for a **2yr extension** onto the 10yr Market Exclusivity."*
- Sponsors' should come and establish the need for a Paediatric Investigational Plan (**PIP**) with the PDCO.
- The PDCO operates a 120Day procedure with clock-off periods for a PIP. The service is **free**.
- Sponsor's should integrate this consultation into their development planning as failure to have a PIP may invalidate their application at the time of submission for MAA.

How to obtain additional 2yr extension

- To obtain an additional 2yr Marketing exclusivity extension the sponsor must be compliant with the agreed PIP.
- Each separate orphan designation linked to an orphan condition has its own additional 2yr Marketing Exclusivity Extension.
- The Paediatric Committee conducts the compliance check to ensure that the PIP has been completed adequately.
- The COMP is not involved. The CHMP will assess the data in the PIP.
- A positive opinion from the Paediatric Committee is communicated to the European Commission who the grants the 2yr extension for the indication(s) in the PIP.

Regulatory Support for Small to Medium Size Enterprises

- EC Regulation No 2049/2005 specifically addresses assistance of pharmaceutical SMEs in Europe.
- The EMA operates a Small to Medium Size Enterprises Office whose role is defined in Article 11 of the Regulation No 2049/2005.
- Companies who qualify need to register with the SME Office in order to benefit from these incentives more information is available on the EMA website.
- Article 7 of EC Regulation No 2049/2005 is the basis for free Scientific Advice and Scientific Services for Small and Medium Size Enterprises (SMEs) who have a product with an Orphan Medicinal Designation.
- ***Similar legislation exists in the US for Small Businesses.***

Orphan Similarity (Market Exclusivity)

EU and US considerations

Orphan Similarity Europe

- Paragraph 3 of Article 8 of EC Regulation 141/2000 establishes the basis for Orphan Medicinal Similarity.
- Orphan Similarity involves a orphan designation product which is applying for an MAA where another Orphan Product already has an MAA for the same indication and has the 10yr Market Exclusivity.
- CHMP determines at any stage before EC approval whether there is Orphan Similarity.
- EC Guideline exists which is available on the EMA Orphan Designation legal basis webpage which explains how it works.

Guideline on Orphan Similarity

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 19.9.2008
C(2008) 4077 final

COMMUNICATION FROM THE COMMISSION

Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity

Assessment of Orphan Similarity

- Applies if other orphan medicines authorised for same designated condition
- Need to submit report in module 1.7
  - Molecular structure
  - Mechanism of action
  - Similarity of indication ("significant overlap of populations"?)
- Assessment by CHMP working party competent (BWP or QWP)
- Final opinion by CHMP
- Similarity can be triggered any time before EC decision on MAA.
- Proactive publication on-going procedures

Derogations to market exclusivity if Orphan Similarity applies

Applicable if product is considered similar by CHMP.

Assessed based on sponsor's report

- Specific timetable (parallel to QSE assessment)

Three derogations (Art 8(2))

- First MAH's consent (agreement market sharing)
- Insufficient supply: long term and clinical consequences (presumably)
- Clinical superiority: better efficacy, better safety or exceptionally major contribution to patient care

FDA
Orphan Drug Exclusivity: Orphan Similarity

Sponsor of the "same drug" as an ***already approved drug***

- For Designation – Must provide a plausible hypothesis of clinical superiority
- For Orphan Exclusivity – Must demonstrate the drug is clinically superior

Orphan Drug Exclusivity: Basis

If Orphan Drug Designation is based on a plausible hypothesis of clinical superiority for greater efficacy or safety clinical superiority must be demonstrated at the time of marketing approval in order to receive Orphan Drug Exclusivity.

May require head to head trials.

Orphan Drug Exclusivity

If Orphan Drug Designation is based on a plausible hypothesis of clinical superiority based on a Major Contribution to Patient Care (MC-PC) the product is eligible for Orphan Drug Exclusivity

MC-PC Examples

Oral formulation of a previously approved intravenous drug

Cysteamine, enteric coated (q 12h) vs. Cysteamine (q 6h)

(data showed that strict adherence to q6h dosing was required for therapeutic effect)

Conclusions

- Substantial overlap regarding FDA and Europe regarding orphan Designation criteria
- Post-designation incentives and assistance programmes on both sides to assist in clinical development of the orphan designated products.
- Key Market Exclusivity incentive available in both regions but consideration should always be given to orphan similarity issues which exist in both regions.