Webinar

Orphan Drugs

05 MAY 2022

BlueReg
PHARMA CONSULTING

EU Expertise

How to take advantage of incentives to develop your orphan products in Europe?

Welcome

The speakers

Claire Ray

Director, Regulatory Affairs

Marlène Schuppli Nollet

Director, Business Development

Webinar Agenda

Introduction

Orphan drugs: where are we?

What is the regulatory context for Orphan Medicinal products in EU?

Why use a third party to develop my orphan drug in the EU?

30 min

Q&A session with the BlueReg experts

Please send your questions for the Q&A using the Q&A box

15 min

Introduction

BlueReg
PHARMA CONSULTING

Introduction - Definitions

- **What is an orphan drug?**
  - An Orphan drug is a drug or a biological product used for the prevention, diagnosis or treatment of a rare disease

- **What is a rare disease?**
  - A disease that affects a small percentage of the population
  - This small percentage – and thus definition of rare – varies across countries/legislations
  - Most rare diseases are genetic, and thus are present throughout the person's entire life, even if symptoms do not immediately appear

Introduction - Definitions

- **What is an orphan drug?**

  Definition of « rare » based on prevalence depending on regional/national legislations/policies

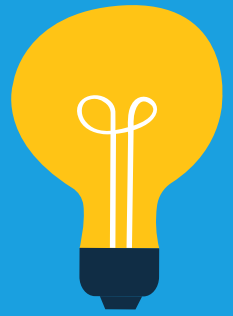
<200,000

per Orphan drug Act of 1983

<5/10,000

per Regulation (EC) No 141/2000 of 16 December 1999

0.65-1/1,000



A rare disease in one region may not be so in another

either for legislative reasons, or because this disease - often genetic - is simply less rare in one region than another

References: Orphanet: The portal for rare diseases and orphan drugs - About Orphan Drugs https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN ; Orphanet: The portal for rare diseases and orphan drugs - About Rare Diseases https://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN

Introduction - Definitions

European alliance of rare disease patient organisations :

https://www.eurordis.org/

1/17

People in the EU has a rare disease

Around 30 million patients suffer from rare diseases out of a population of 510 million in the EU

References: Factsheet: Orphan medicines in the EU – EMA document https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview ; European alliance of rare diseases patient organisations https://www.eurordis.org/

Orphan drugs: where are we?

OMP → Orphan Medicinal Product

BlueReg
PHARMA CONSULTING

Introduction of OMP regulation in EU today shows a visible positive impact

Orphan designation application

80
2001

3678
2020

Authorized OMPs

3
2001

192
2020

For more than 15 years, Orphan drugs have been one of the fastest growing segments of the pharmaceutical market

2021 European Expert Group on Orphan Drug Incentives_Report; EMA annual reports

Rare disease patients have significant unmet needs

30 M
Europeans suffer from rare diseases

6 000
rare diseases - 5 new every week

95%
of rare diseases → no authorized treatments

Most OMP developments focus on disease areas where treatments already exist	OMP development benefits only a limited number of diseases	OMP development is not equally focused	OMP development concentrates on the least rare diseases
Of all the authorised OMPs between 2000 and 2017, only 28% targeted rare diseases without any authorised OMPs	Between 2000-2019, 67% of OMP designation applications targeted same three disease areas (Blood; antineoplastic/immunomodulating agents, dermatology)	No less than 70% of rare diseases occur exclusively in paediatrics. Only 12% of orphan designations between 2000-2019 related to conditions that only affect children	96% rare diseases have a prevalence of <1 in 10,000. Between 2000-2019, 56% of authorised OMPs targeted rare diseases with a prevalence >1 in 10,000

OMPs tend to be developed in certain more profitable therapeutic areas

2021 European Expert Group on Orphan Drug Incentives_Report

Cost of bringing OMPs to the market

Cost of bringing OMPs to the market outweigh potential market revenue

OMPs developed between 2000 - 2017

> 50%

orphan drugs would not have been economically viable in the absence of the OMP regulation and its incentives

Oct 2021 BioProcess International eBooks_Rare Diseases Biopharmaceutical challenges presented by small patient population; Dolon, 2020, Estimated Impact of EU Orphan Regulation on Incentives for Innovation

OMP regulation encourages pharma and biotech to develop OMPs

RESEARCH

Access to EU grants

Improved communication & cross border collaboration

orphanet
Know the rare for better care

REGULATORY ENVIRONMENT

Benefit from protocol assistance

Important fee reductions on regulatory activities

Tax reduction/exemption

Access to centralized procedure, potential conditional approval, compassionate use program

Additional incentives if SME

COMMERCIAL

Enhanced exclusivity period 10 years market exclusivity +2 if PIP completed

Pricing committee may agree to a high price

Orpha.net; EMA.europa.eu; orphan inv. Report 2016

Incentives in concrete numbers

EU Funded research

> 620 M€

in funding over 120 research projects between 2007 and 2013

Fee reductions

78 M€ between 2000 and 2015

2000
700 K€

2010
6,7 M€

2015
13 M€

2020
> 11 M€

Access to “High” price

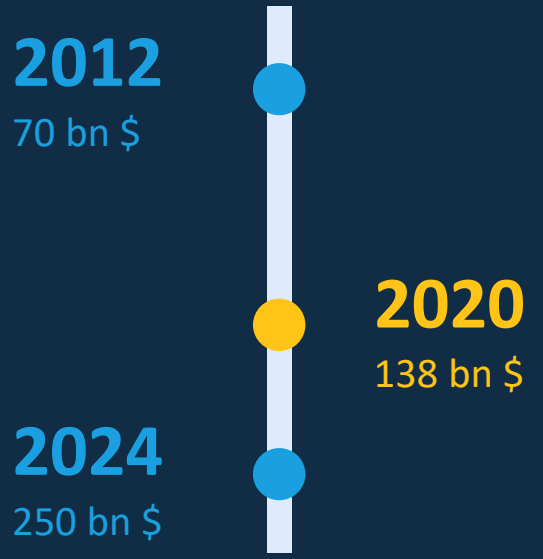
annual per patient treatment costs of OMP range between **755€ to over 1M€** in the EU (24% >10 000€, 18% >100 000€, 58% between this range)

OMP Regulation, EU driven funding and access to high price have made OMPs a cornerstone of pharmaceutical markets

Orpha.net; EMA.europa.eu; orphan inv. Report 2016; 2021: https://od-expertgroup.eu/

Orphan drugs – a highly profitable market

Orphan drug market



Growth/year

+7%

/ year since 2010

+12%

/ year between 2019 and 2024

Rate forecasted for the market of non orphan drugs, 6.4 %

Market share

2024

OMPs capture

20%

of all WW prescription drug sales

OMP regulation stimulated pharma/biotech to enter the rare disease space

Evaluate pharma 2019, Orphan drug report

Is there a limit to the system?

From a patient perspective: left with 95% of rare diseases without authorized treatment options

Heath system - growing economic burden of orphan diseases not indefinitely sustainable

Regulations have not adequately managed to support development in areas where the need for medicines is greatest

EU orphan legislation is currently being revised and is expected to enter into force in the coming years.

OMP regulation in the EU has been largely inspired by the US Orphan Drug Act but the EU can be very complex when it comes to regulation

Our goal today: to raise your attention to the complexity of the system in EU

What is the specific regulatory context for Orphan Medicinal products in the EU?

BlueReg
PHARMA CONSULTING

Orphan Drug Designation – Legal basis

- **What is the legal basis?**
  - US as a pioneer in Orphan drug regulation
  - Complex and multiple documents, particularly for EU
  - Differences between US & EU

	USA	EU
AGENCIES / COMMITTEES	FDA / OOPD	EMA / COMP
LEGISLATION	• Orphan Drug Act (1983) codified in 21 CFR Part 316 • Orphan Drug Regulations Final Rule 6/12/2013	• Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products of 16 December 1999 • Commission Regulation (EC) No 847/2000 of 27 April 2000 • Commission Communication July 2003 (2003/C 178/02) • Commission Communication on Art 8(1) and (3) (C(2008) 4077)

References: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation/legal-framework-orphan-designation ; https://www.fda.gov/industry/developing-products-rare-diseases conditions/designating-orphan-product-drugs-and-biological-products

Orphan Drug Designation – Guidance

- Guidance
  - Numerous publications covering all aspects of orphan drug development, registration, maintenance and incentives

USA	EU
Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases Guidance for Industry	Points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation EMA/COMP/436/01 Rev. 1 (June 2019)
	Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation EMA/COMP/15893/2009 Final (March 2010)
Meetings with the Office of Orphan Products Development - Guidance for Industry, Researchers, Patient Groups, and Food and Drug Administration Staff	Decision of the Executive Director on fee reductions for designated orphan medicinal products EMA/135645/2020
	European Medicines Agency Guidance for Applicants EMA/4260/2001 Rev. 12 (February 2022)
FDA Webpages: • Developing Products for Rare Diseases & Conditions • Public Identification of Orphan Drug Designation – Notice to Certain Orphan-Drug Designation Holders • Designating an Orphan Product: Drugs and Biological Products • Frequently Asked Questions (FAQ) About Designating an Orphan Product • Orphan Drug Designation: Disease Considerations	Procedural advice for orphan medicinal product designation EMA/420706/2018 Rev. 11 (Sept. 2021)
	IRIS Guide to registration and RPIs – Preliminary requirements for all IRIS submissions, including substance and Research Product Identifier registration (Feb. 2022)
	Procedural advice for post-orphan medicinal product designation activities EMA/469917/2018 Rev. 11 (Jun. 2021)
	European Medicines Agency pre-authorisation procedural advice for users of the centralized procedure EMA/821278/2015 (Feb. 2022)

Orphan Drug Advantages

		USA	EU
Financial incentives	Fee	Fee waivers (NDA/BLA)	Fee reductions/waivers (SMEs) (PA, MA, PV, ...)
	Tax credits	Yes, 50% on clinical research costs	No (EMA)
	Grants for research	FDA Orphan Products Grant Program NIH grants	EC framework Programmes (Horizon Europe: EU Framework Programme for Research & Innovation); EJP RD
Scientific advice		Yes	Yes, Protocol assistance
Regulatory tools to accelerate approval		Fast-track approval; Breakthrough designation; Accelerated approval pathway; Priority review designation	Priority medicines (PRIME); Mandatory access to the Centralised Procedure; Conditional approval; Approval under exceptional circumstances; facilitated access to accelerated assessment
Marketing exclusivity		7 years	10 years (+2 if PIP)

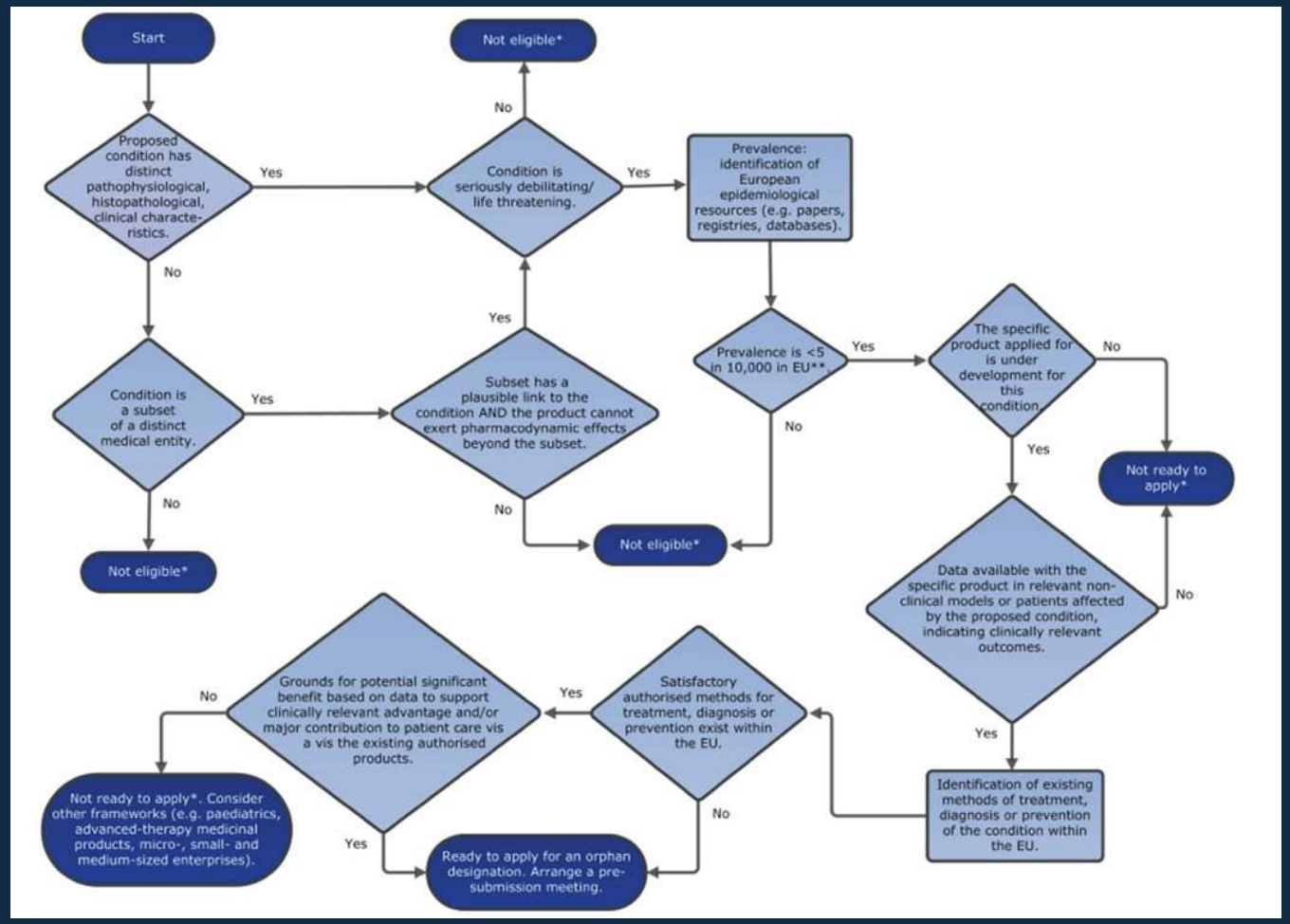
References: Recommended Tips for Creating an Orphan Drug Designation Application - A Webinar by the Office of Orphan Products Development (OOPD) 2018 https://www.fda.gov/media/111762/download ; Decision of the Executive Director on fee reductions for designated orphan medicinal products EMA/135645/2020 https://www.ema.europa.eu/en/documents/other/decision-executive-director-fee-reductions-designated-orphan-medicinal-products_en.pdf

Orphan Drug Designation - Eligibility

EU	USA
Rarity (prevalence) Medical condition affecting not more than 5 in 10, 000 persons in the community	A drug/biologic may be "designated" by the Office of Orphan Products Development if it is to prevent, treat, or diagnose a disease/condition that occurs in <200,000 people in U.S.
OR	OR
Seriousness / return of investment - Life –threatening or chronically debilitating - Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment	Drugs that will not be profitable within 7 years following approval by the FDA
AND	
Alternative methods authorized If satisfactory methods exist, the sponsor should establish that the product will be of significant benefit	

References: Recommended Tips for Creating an Orphan Drug Designation Application - A Webinar by the Office of Orphan Products Development (OOPD) 2018 https://www.fda.gov/media/111762/download ; EMA website: Applying for orphan designation https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-orphan-designation

Orphan Drug Designation - Eligibility



References: Recommended Tips for Creating an Orphan Drug Designation Application - A Webinar by the Office of Orphan Products Development (OOPD) 2018 https://www.fda.gov/media/111762/download ; EMA website: Applying for orphan designation https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-orphan-designation

Orphan Drug Designation - Eligibility

- **Databases**

Community register of orphan medicinal products for human use

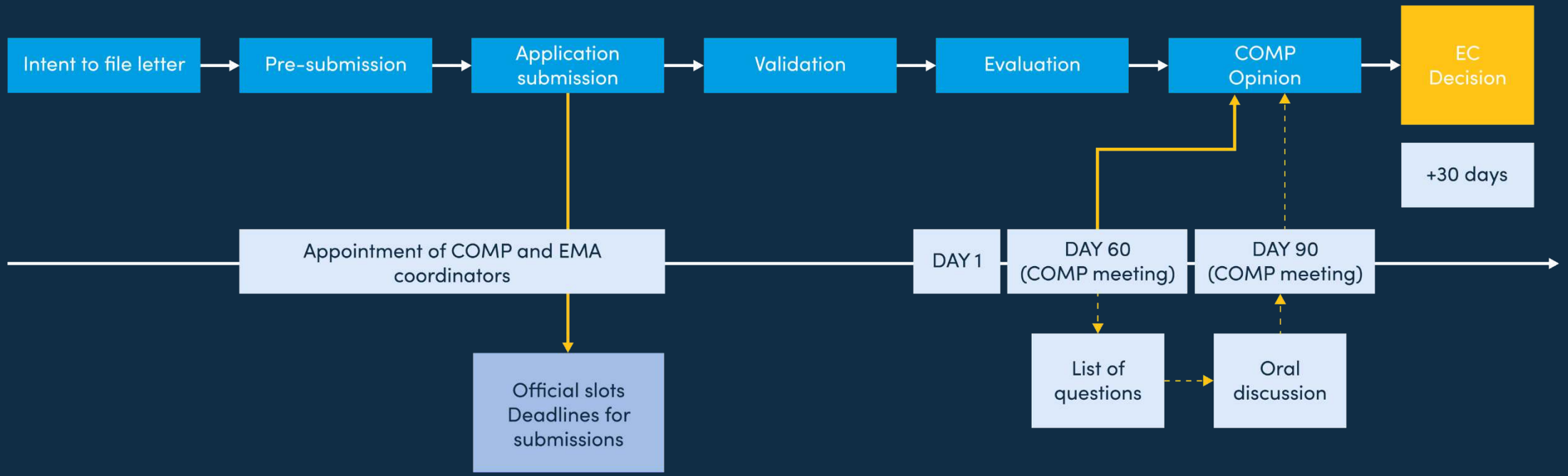
https://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a

Orphanet

https://www.orpha.net/consor/cgi-bin/index.php?lng=EN

- **Bibliographic research**

ODD Application – Regulatory Procedure – EU



COMP meetings timetable for valid applications (available on https://www.ema.europa.eu/en/committees/comp/comp-meetings)

References: EMA website: Applying for orphan designation https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-orphan-designation ; EMA Orphan medicinal product designation 2015 ; EMA workshop - Orphan designation key concepts and evaluation criteria https://www.ema.europa.eu/en/documents/presentation/presentation-orphan-designation-key-concepts-evaluation-criteria-dr-jordi-llinares_en.pdf ; COMP meetings https://www.ema.europa.eu/en/committees/comp/comp-meetings

ODD Application – When and how to submit in the EU

Sponsor of an Orphan designation

- Sponsor **should be established in the EEA** (EU, Iceland, Liechtenstein, Norway)

  If the sponsor is an organization: the sponsor should have a permanent physical address in one of the countries of the EEA with a contact person at the sponsor premises able to receive any documents in person, if needed.

BlueReg can be your Sponsor!

References: EMA website: Applying for orphan designation https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-orphan-designation

ODD Application – When and how to submit in the EU

IRIS Portal

- From September 19, 2018, **sponsors must use the EMA's IRIS system** when applying for orphan designation and to submit all post-designation activities

- **Pre-submission requirements:**
  - Do you have an active EMA customer account number?
  - Is your organization registered in the EMA's Organization Management Service (OMS)? (SPOR database)
  - Is the active substance registered in SMS?
  - Is the RPI (Research Product Identifier) already created?

Multiple registration steps

References: IRIS Guide to registration and RPIs – Preliminary requirements for all IRIS submissions, including substance and Research Product Identifier registration (Feb. 2022)

After Orphan Drug Designation – EU

Several activities can take place after ODD

- Annual report
  - Sponsors must submit an annual report to the Agency summarising the status of development of the medicine
- Additional indication or extension of the existing orphan designation
- Changing of the name or address of a sponsor
- Transferring a designation to a new sponsor
- Marketing Authorisation application (+ protocol assistance)
- Maintenance of the orphan designation/Evaluation of orphan similarity
  - At the time of a MA, sponsors need to submit an application for maintenance of the OD and an evaluation of orphan similarity

References: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

After Orphan Drug Designation – EU

Maintenance of the OD at the time of the MA application

- **Evaluation of Orphan similarity**

  Sponsors need to submit an evaluation of orphan similarity if needed

  - Check the Community register of orphan medicinal products
  - **Complex regulatory and scientific report** addressing the possible similarity between drug candidate for MA and orphan medical product(s) which already have a MA

- **Review of Orphan designation at time of MA**

  Sponsors also need to **submit a report on maintenance of OD** in order to be eligible for the ten-year market exclusivity incentive. Thus, the EMA can assess whether a medicine continues to meet the criteria for maintaining its orphan status in parallel with assessing the MA application.

References: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/orphan-medicines/applying-marketing-authorisation-orphan-medicines#orphan-similarity-section ; European Medicines Agency pre-authorisation procedural advice for users of the centralized procedure EMA/821278/2015 (Feb. 2022)

Summary: ODD key differences in the US vs the EU

	USA	EU
Legal framework	Orphan Drug Act (1983)	Regulation (CE) N°141/2000 (2000)
Administrative authorities involved	FDA / OOPD	EMA / COMP
Sponsor establishment	Not required	Proof of establishment in the EU
Timetable	No timetable - Any time	Timetable published by EMA (COMP meeting)
Prevalence of the disease/condition	< 200, 000 patients in the US	< 5 in 10,000 patients in the EU
Key application criteria	Prevalence, Scientific rationale	Prevalence, Medical plausibility, Significant benefit
Incentives	Fee waivers, Tax credits, Grants for research, Scientific advice, Regulatory tools to accelerate approval, Marketing exclusivity for 7 years	Fee reductions/waivers (SMEs), no grants from EMA but EC framework Programmes, Protocol assistance, Regulatory tools to accelerate approval, Marketing exclusivity for 10 years (+2 if PIP)
Translation	Not required	Translations of product name and proposed orphan indication into the 24 official languages of the EU

ODD in the product lifecycle in EU

References: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

Why use a third party to develop my orphan drug in EU?

BlueReg
PHARMA CONSULTING

Why outsource such key activity?

ORPHAN DRUG DESIGNATION

INCENTIVES

SME STATUS

ODD status and the related incentives will be key to the viability of your OMP program
by reducing the RnD costs and leading to a reasonable return on investment

It is a major milestone in your journey to bring the OMP to the patients

Why outsource such key activity?

- You are a mid-size US company, developing an innovative orphan product
- Limited EU structure and not financially/business viable to have EU structure prior to product launch
- You were granted the orphan designation in the US, your development plan in the US is all set and you are now preparing development in the EU

EXPERTISE & ADVICE

- You are responsible for delivering a development path that is cost-effective, optimizes time to market and maximizes probability of success
  - Alignment of the EU with US strategy (capitalize, minimize change & cost) while ensuring compliance with EU regulation – mitigate risks
  - Understand pathway towards approval in the proposed market and targeted therapeutic indication
  - Take advantage of your orphan status; SME status
  - Engage with regulators at the right moment

EU REPRESENTATIVE

Why outsource such key activity?

TAILORED SOLUTIONS

EXPERTISE & ADVICE

- Expertise in OMP regulation in the EU
- One program regulatory lead – EU single point of contact – strategic/operational
- Facilitation of Competent Authority interactions – protocol assistance, MAA, annual reports etc

EU REPRESENTATIVE

- Support access to ODD – BlueReg as sponsor
- Support access to SME status and SME incentives

FULL MANAGEMENT

Why outsource such key activity?

- You will take advantage of European Knowledge & Expertise to optimize EU development and secure compliance
- You will secure access to all the incentives you are eligible for
- You will ensure your product reaches the patient at the earliest opportunity

Early access is an important path to provide patients with treatment before marketing authorisation

Q & A Session

BlueReg
PHARMA CONSULTING

Let’s stay in touch !

- www.blue-reg.com
- contact@blue-reg.com

Thank you !