EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Orphan designation and Orphan Medicines in EU

Orphan development support

Workshop on Support for Orphan Medicines Development

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An agency of the European Union

Special circumstances….

From the recitals of Directive 141/2000 by European Parliament and Council of the EU:

(1) some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called 'orphan';


1983


1993


1997


2000

…. same rules!

patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry; incentives for the development of orphan medicinal products have been available in the United States of America since 1983 and in Japan since 1993;

Orphan designation

European law to stimulate the **research, development and bringing to the market** of appropriate medications by the pharmaceutical industry

Application for orphan designation via a voluntary procedure **free of charge** at the Committee for Orphan Medicinal products (COMP) at the European medical agencies (EMA)

Incentives rather than obligations

Orphan incentives - as planned and as in practice

Pre-marketing incentives

- Regulatory/scientific advice
- Fee reductions (depending on sponsor type)
- Eligibility for research funding by the EC
- Centralised procedure (?)

Post-marketing incentives

- Fee-reductions/exemptions
- 10 (+2 if PIP compliant) year market exclusivity (protection against **similar** products)

Not official, but real:

- *External perception*
- *Impact on HTA procedure (DE)*

Orphan criteria (EU)
EC 141/2000

Diagnosis, prevention or treatment of a rare condition

§ 3(a) Paragraph 1: Prevalence of max. 5 in 10 000

§ 3(a) Paragraph 2: insufficient return of investment

that is life-threatening or chronically debilitating

... e.g. genetic diseases, many cancer types

AND

that there exists **no satisfactory method** of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community

OR

if such method exists, that the medicinal product will be of **significant benefit** to those affected by that condition.

* Rarely used in practice

Responsibilities of committees and institutions involved

Committee for orphan medicinal products (COMP)

- Scientific and transdisciplinary committee
- 1 member by each member state
- 3 **patient representatives** with full voting rights
- 3 EC-nominated experts
- Makes recommendations to the European Commission

European Commission (EC)

- Official granting of Orphan-Status (not by default in agreement with COMP)
- Community register of orphan medicinal products (active/withdrawn or expired/refused)

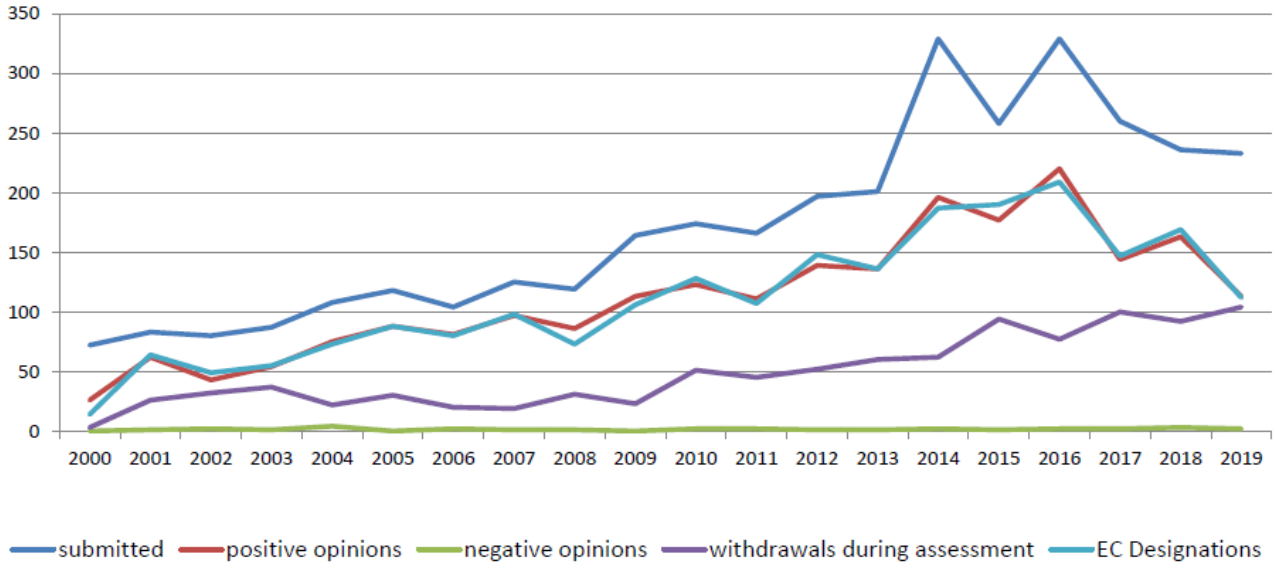
Orphan designation - at least a two step process

1) „***Orphan designation***" (initial OD)
COMP decides on orphan indications of medicinal products at "any stage of development before **an application for marketing authorisation (MA)** is made" with assumptions of SB (if applicable) **based on plausible hypotheses.**

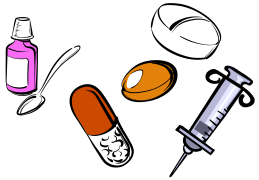
2) „***Review of orphan designation***"
Decides ***before MA* is granted,*** whether product still fulfills orphan criteria to become orphan medicinal product (**OMP**) (higher level of evidence required)

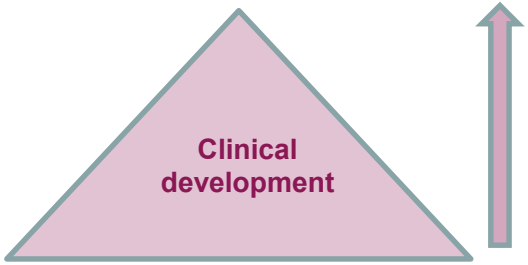
* Initial MA for each underlying condition or major variations

Applications for orphan medicinal product designation



Orphan designation ≠ *authorised orphan medicinal product*





183 OMP since 2000 in EU*

- Ca. 120 with active orphan status*
- **Ca. 130 orphan conditions***
  - OMPs with more than one OD
  - More than one OMP per condition

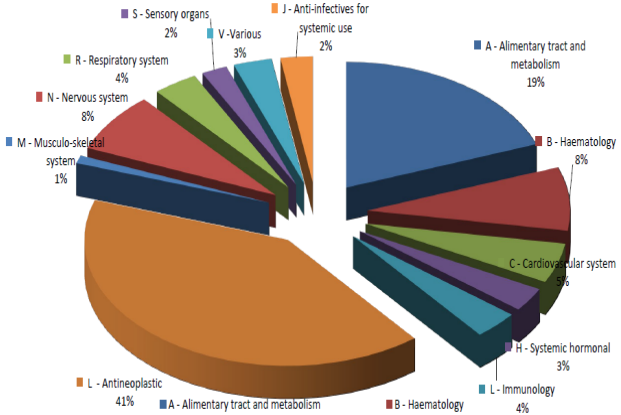
* Moving target: withdrawals possible at all times, expiry after 10-12 years;

> 2200 orphan designations in approx. 550 conditions

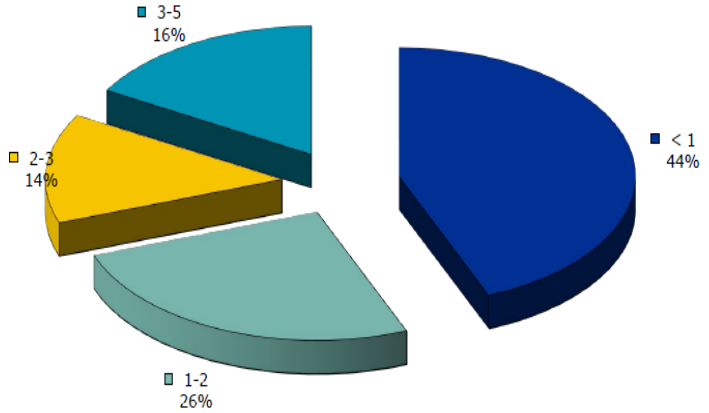
6000 – 8000 orphan conditions

Heterogeneity among authorised orphans

Therapeutic areas



Prevalence



Products

Majority: innovative substances
(chemical vs 35% biotechnology/ATMP)
Known substances (repurposed)

Orphan medicines figures 2000- 2019 by EMA

From EU-Regulation to interpretation

Regulation 141/2000
European Parliament and Council

Implementing Regulation 847/2000
European Commission

Commission Notice on Articles 3,5 and 7 **2016/C 424/03**

Commission GL on Article 8(1) and 8(3) (C(**2008**) 4077)

Commission GL on Article 8(2) (**2008**/C 242/07)

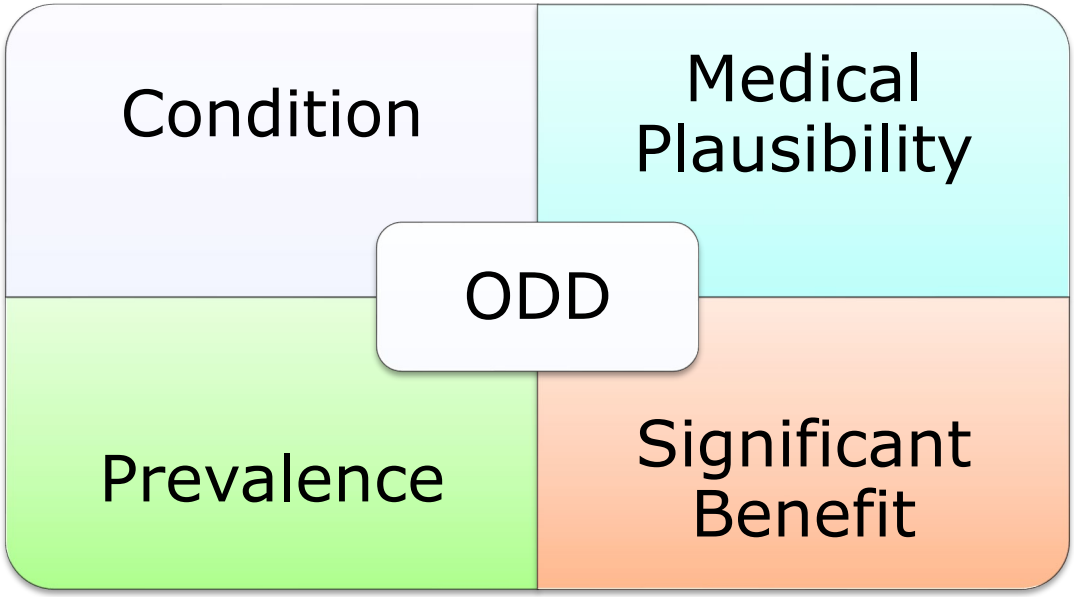
Commission Communication **2003**/C 178/02 – superseeded by **2016/C 424/03**

Commission GL on Article 5 (ENT 6284/00 Rev. 4 - **2014**)

COMP PtC on estimation and reporting of prevalence (2019)

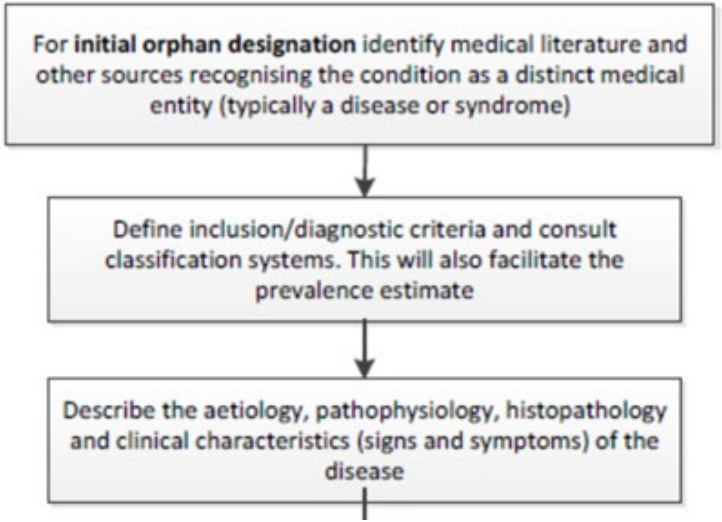
EMA Recommendations on elements required to support the medical plausibiliby and the assumption of significant benefit for and orphan designation (2009).

Key steps in Orphan drug status designation



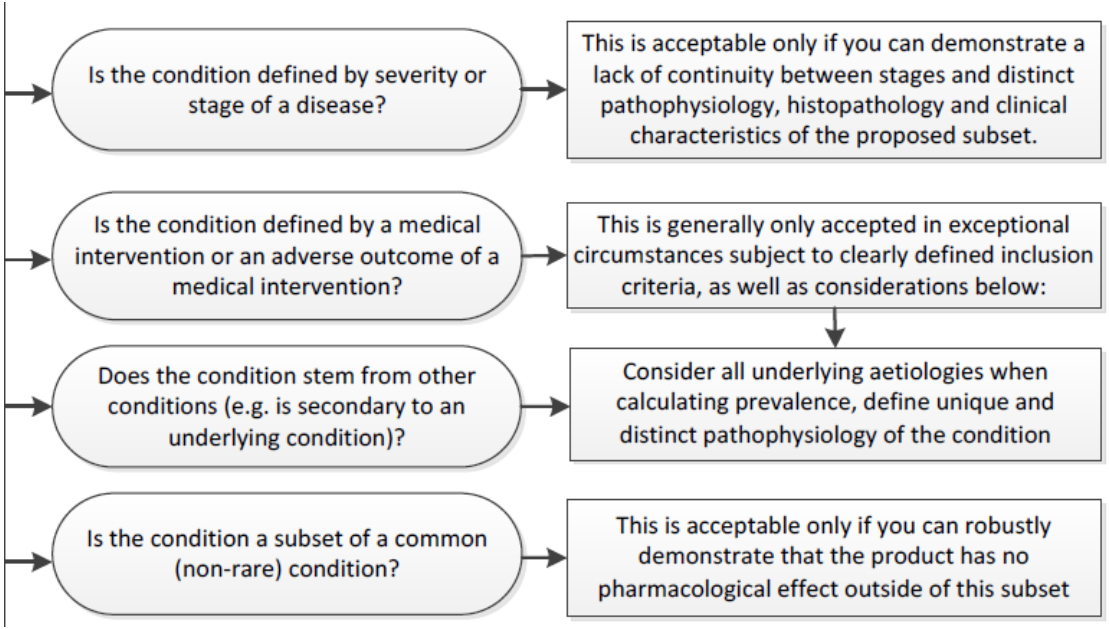
Defining a Condition

Condition:
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).



1. ENTR/6283/00 Rev 4; 2014
2. O'Connor DJ et al., Nat Rev Drug Discov. 2019 Jul;18(7):479-480

Additional considerations when defining a condition



1. ENTR/6283/00 Rev 4; 2014
2. O'Connor DJ et al., Nat Rev Drug Discov. 2019 Jul;18(7):479-480

Challenging areas in defining a condition

- an essential manifestation of a condition

Symptoms of a disease

Subsetting based on severity/stages or biomarkers

- subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition

  and

- if such characteristics are essential for the medicinal product to carry out its action

- biomarkers

O'Connor DJ et al., Nat Rev Drug Discov. 2019 Jul;18(7):479-480

Challenging areas in defining a condition

- treatment or prevention of environmental intoxication – YES
- Intoxication with drugs - NO

Iatrogenic and adverse reactions to a medicinal product

Treatment modalities

- haematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT)

O'Connor DJ et al., Nat Rev Drug Discov. 2019 Jul;18(7):479-480

Demonstration of medical plausibility

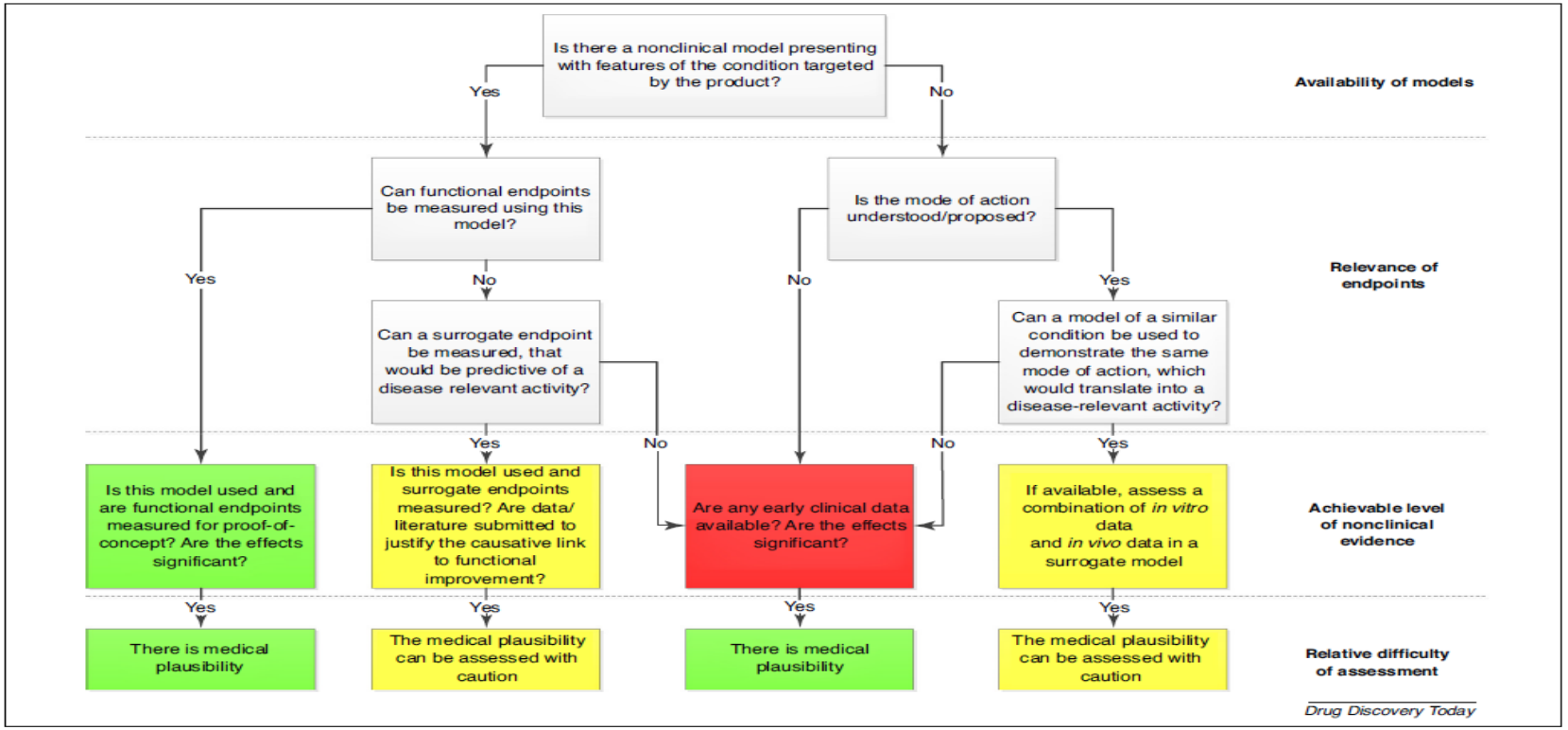
Key aspects:

- experimental design – treatment vs preventive approach
- the claimed mechanism of action (as proposed or demonstrated) effectively translates into disease-relevant functional improvements in the animal model.

It might be not sufficient:

- *in vitro* data only
- novelty of mechanism of action

Demonstration of Medical Plausibility



From Sheean ME et al.; Drug Discovery Today, Jan 2018; 23 (1):26-48

Prevalence

- Prevalence is defined as the number of persons affected by a condition at a specified instant in time in a given population.
- Exceptions:
  - Diseases of short duration, (i.e. less than a year)
  - Prevention/Diagnosis as orphan indication: the number of persons that are candidates for being administered the product on an annual basis

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

Significant benefit

- **Significant benefit based on an assumption of a clinically relevant advantage**
  - improved efficacy
  - improved safety
- **Significant benefit based on an assumption of a major contribution to patient care**

ENTR/6283/00 Rev 4; 2014

Significant benefit based on efficacy or safety

- **Efficacy**
  - If nonclinical models are used, it is preferable that the comparison is derived from direct comparative experiments rather than from results published in the literature.
  - If clinical data exist, presentation of the effects observed in exploratory studies and comparison with the data available in the literature may be appropriate to justify the assumption of significant benefit. In some situations quantitative methods for indirect comparison may be used.
- **Safety**
  - If safety is argued to justify significant benefit, it is important that safety issues with current methods are documented

Significant banefit based on major contribution to patients care

- Ease of self-administration
- If new pharmaceutical form of already authorized medicinal product, difficulties with existing from need to be documented and data need to show improved clinical outcome (e.g. QoL) (Commission Notice on Articles 3,5 and 7 2016/C 424/03)

Additional sources of information

Defining orphan conditions in the context of the European orphan regulation: challenges and evolution. D.J. O'Connor et al. Nat Rev Drug Discov. 2019 Jul;18(7):479-480;

Non-clinical data supporting orphan medicinal product designations: lessons from rare neurological conditions. M.E. Sheean et al. Drug Discovery Today Volume 23, Number 1 January 2018: 26-48;

Non-clinical data supporting orphan medicinal product designations in the area of rare infectious diseases. M.E. Sheean et al. Drug Discovery Today Volume 25, Number 2 February 2020: 274-291.

Thank you very much for your attention!