Key considerations of orphan products designation and registration regulation

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What is **orphan** meaning

The word orphan comes from the Greek word "**Orphanos**",

"a child who has lost one parent or both, or an adult who has lost a child".

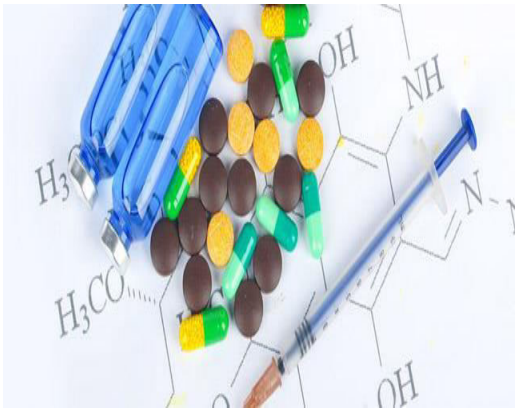
Orphan Drug definition

- What is an **orphan drug**?
- ✓ Drug (or biological product) used for the prevention, diagnosis or treatment of a **rare disease**

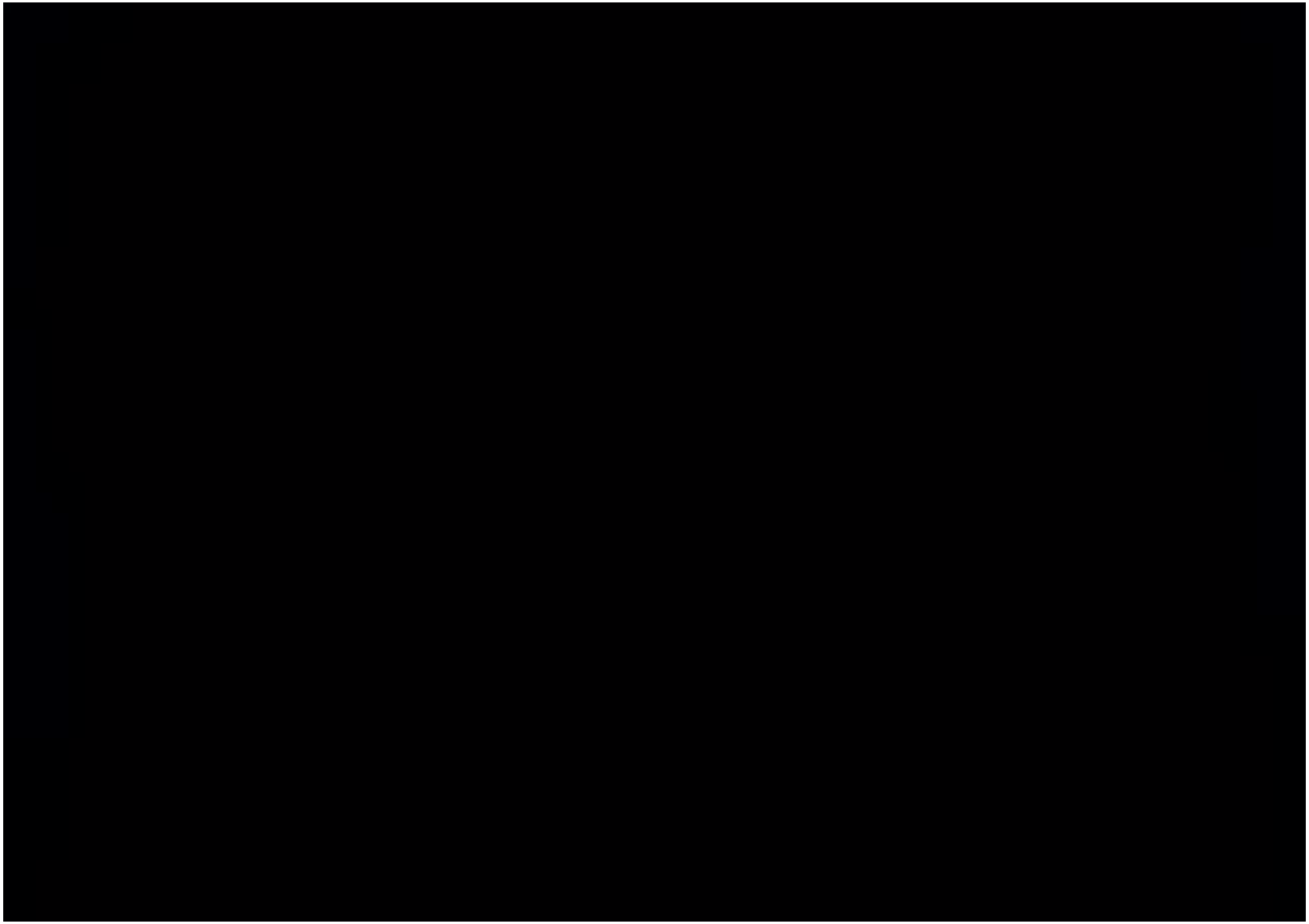
- What is a **rare disease**?
- ✓ Any disease that affects a small percentage of the population.
- ✓ Most rare diseases are genetic, and thus are present throughout the person's entire life, even if symptoms do not immediately appear.
- ✓ Definition of "rare" varies depending on the policies and legislation enacted by each region:

Continue…….

- USA: <200,000 per Orphan Drug Act of 1983
- EU: <1/2,000
- Japan: <50,000
- Australia: <2,000/year
- Singapore: <20,000
- WHO: 0.65-1/1,000
- China: <1/10,000 newborns or <1/500,000 general pop.



Rare disease

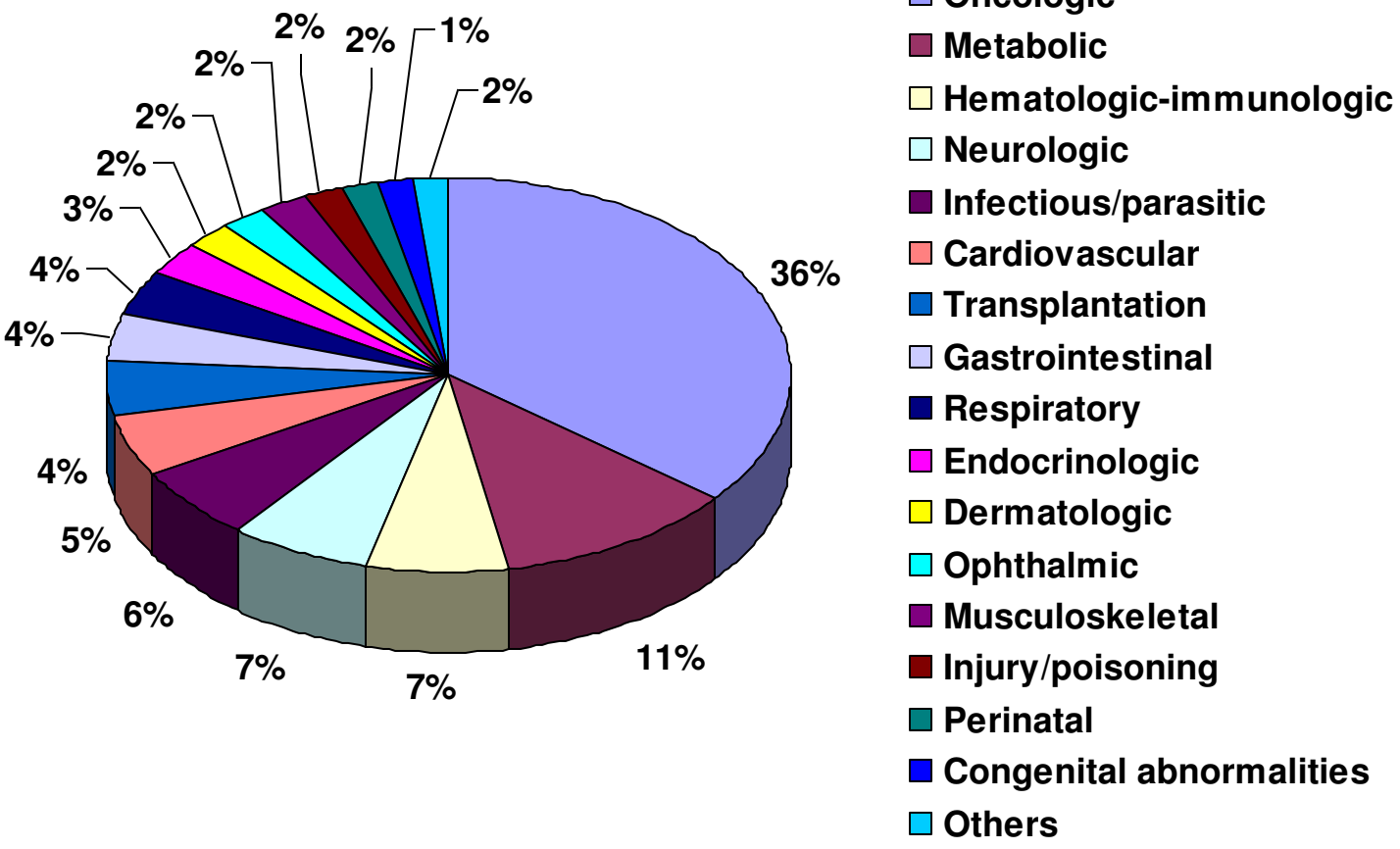


Impact of "Rare Disease"

- Affects 6-8% or more of the world's population
- 600-700 million people worldwide
- >7000 rare diseases currently recognized
- <5% have effective drug therapies available

- **Broad spectrum of illness and etiology…**
- Genetic
- Rare cancer
- Congenital malformation
- Autoimmune
- Toxic
- Infectious
- Degenerative, etc.

Range of Designated Orphan Drugs



Orphan Designation

To qualify for orphan designation, a medicine must meet a number of criteria

- Used for treatment, prevention or diagnosis of life-threatening or chronically debilitating disease.
- The prevalence of the condition in the EU must not be more than 5 in 10,000
- Applications for orphan designation are examined by the European Medicines Agency's Committee for Orphan Medicinal Products (COMP)
- Orphan drug designation does not indicate that the therapeutic is either safe and effective or legal to manufacture and market
- The designation means only that the sponsor qualifies for certain benefits from the federal government, such as reduced taxes.

Benefits of orphan drug designation

- Financial incentives for orphan drug :

  - Tax Credits – 50% of clinical trials costs
  - Waiver of User Fees
  - 7-10 years Marketing Exclusivity

Orphan drug designation legislation

Implemented by:

- United States
- European Union
- Japan
- Singapore
- Australia
- China

that offers subsidies and other incentives to encourage the development of drugs that treat orphan diseases.

	USA	Japan	Australia	EU
Legal framework	Orphan Drug Act (1983)	Orphan Drug Regulation (1993)	Orphan Drug Policy (1998)	Regulation (CE) N°141/2000 (2000)
Admnistrative authorities involved	FDA / OOPD (*)	MHLW/OPSR (*) (Orphan Drug Division)	TGA (*)	EMEA /COMP (*)
Prevalence of the disease (per 10,000 individuals), justifying the orphan status	7,5	4	1,1	5
Estimation of the population affected, prevalence rate (per 10,000 individuals)	20 millions 7,3	No information	No information	25-30 millions 6, 6-8
Marketing exclusivity	7 years	10 years	5 years (similar to other drugs)	10 years
Tax credit	yes : 50% for clinical studies	yes : 6% for any type of study + limited to 10% of the company's corporation tax	no	managed by the member states
Grants for research	programmes of NIH and others	governmental funds	no	'FP6' + national measures
Reconsideration of applications for orphan designation	No	yes	yes (every 12 months)	yes (every 6 years)
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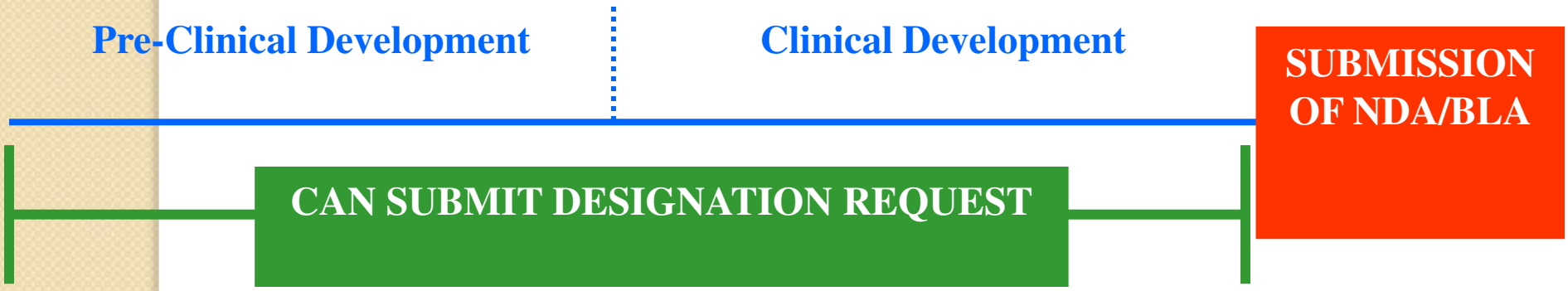
Technical assistance for elaboration of the application file	yes	yes	no	yes
Accelerated marketing procedure	yes	yes	yes	yes (via the centralised procedure)

When to Submit an Orphan Designation Request



- No IND is required

General principles

Pre-submission

1. **Notification of intent**

   Sponsors should notify the EMA of their intention to submit an application as early as possible, and at the latest two months prior to the planned submission date. This notification should be sent by e-mail to orphandrugs@ema.europa.eu and should include:

   - name of the active substance;
   - proposed orphan indication (i.e. treatment, prevention or diagnosis of a rare disease);
   - name and address of the sponsor;
   - planned submission date for the designation application
   - unique Product Identifier (UPI) number.

2. **Pre-submission meeting**

   The EMA strongly encourages sponsors to request a pre-submission meeting prior to filing an application for orphan medicinal product designation. Pre-submission meetings for orphan designation are free of charge and are held mostly via teleconference

- The following documents should be sent at least one week prior to the teleconference/meeting:

  - draft application form
  - draft scientific sections A-E
  - short PowerPoint presentation about the application (approx. 15 min)
  - list of questions
  - list of participants
  - dial-in number and password for teleconference (if applicable)

- Sponsors will be invited to take minutes of the meeting, which should be provided to the EMA within two weeks after the meeting. The Agency will subsequently review the minutes within 2 weeks, and agree the final (amended) minutes with the applicant.

Application submission

The complete application should include

Document	Format
Cover letter	signed PDF
EMA application form or Common EMA/FDA application form The application should be signed by no other than the sponsor Word and signed PDF	Word and signed PDF
Scientific sections A-E of the application	Word (97-2003)
Proof of establishment of the sponsor in the EU	PDF
If applicable, letter of authorization from the sponsor for the person/company acting on their behalf during the procedure	signed PDF
Translations of the name of the product and the proposed orphan indication into the official languages of the European Union, plus Icelandic and Norwegian	Word
Bibliography saved as single publications and titled as first author and year, such as in 'Smith PH et al 2004.PDF'.	PDF

- The EMA encourages parallel applications for orphan designation for the benefit of global development of medicines for rare diseases.

- If an application has not been submitted in the United States before, the EMA encourages the sponsor to seek orphan designation from both the European Medicines Agency and the FDA in parallel using the common orphan application form.

- If an application has not been submitted to the Japanese authorities before, the EMA also encourages the sponsor to seek orphan designation from the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA)

Validation

- The EMA secretariat will complete the validation of the application.
- In the event that the EMA requires additional data, information or clarification to complete its validation, the sponsor will receive a validation issues letter and will be asked to respond within a 3-month time limit.
- If no response from the sponsor is received within this time frame, the sponsor will be advised to withdraw the application and consider re-submission.
- Once the validation process is successfully completed, a timetable to start the procedure for the evaluation will be forwarded to the sponsor for information.

Evaluation

- During the evaluation phase the EMA coordinator will work very closely with the COMP coordinator and appointed expert(s).

- The EMA coordinator, in association with the COMP coordinator, will prepare a summary report on the application. The summary report will include data reported in the sponsor's application, a critical review, and a conclusion.

- Following agreement between the Agency coordinator and the COMP coordinator, the summary report will be circulated to the COMP members for comments. Members of COMP will forward comments to the Agency in accordance with the adopted timetable

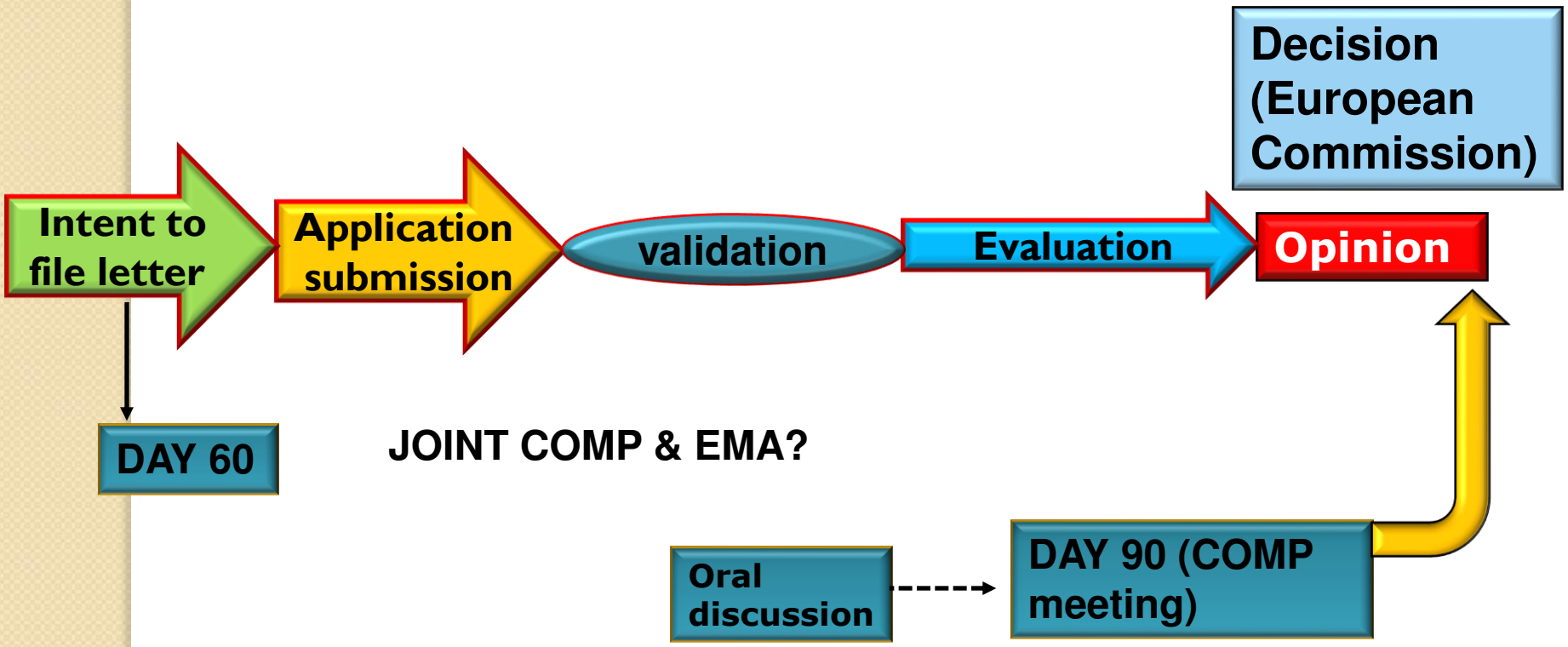
- Where there is a need for a written/oral explanation from the sponsor, this will be highlighted in the summary report. In this case, the report will identify the main issues to be addressed by the sponsor.

- Following the COMP's first discussion the sponsor may be invited to address the list of questions at the next meeting. The list of questions will be forwarded with the draft summary report to the sponsor after the first meeting. The sponsors may be invited to attend an oral explanation at the next COMP meeting.

- For the oral explanation the sponsors will be requested to provide the EMA (one week before the meeting at the latest) with:
  - list of participants;
  - dial-in number for the teleconference if any of the sponsor's representatives/experts wish to participate via teleconference.

- The oral explanation lasts around 1 hour and includes the COMP discussion with the sponsor. The outcome of the discussion will be communicated to the sponsor immediately after the Committee has reached a conclusion.

Summary for the designation process in the EU



COMP Opinion

- Typical review cycle ~ 90 days (often less)

Negative opinion → withdrawal

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Appeal

Original information in the orphan application with new analysis

Positive opinion → **Sponsor claim incentives**

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Proceed with clinical research

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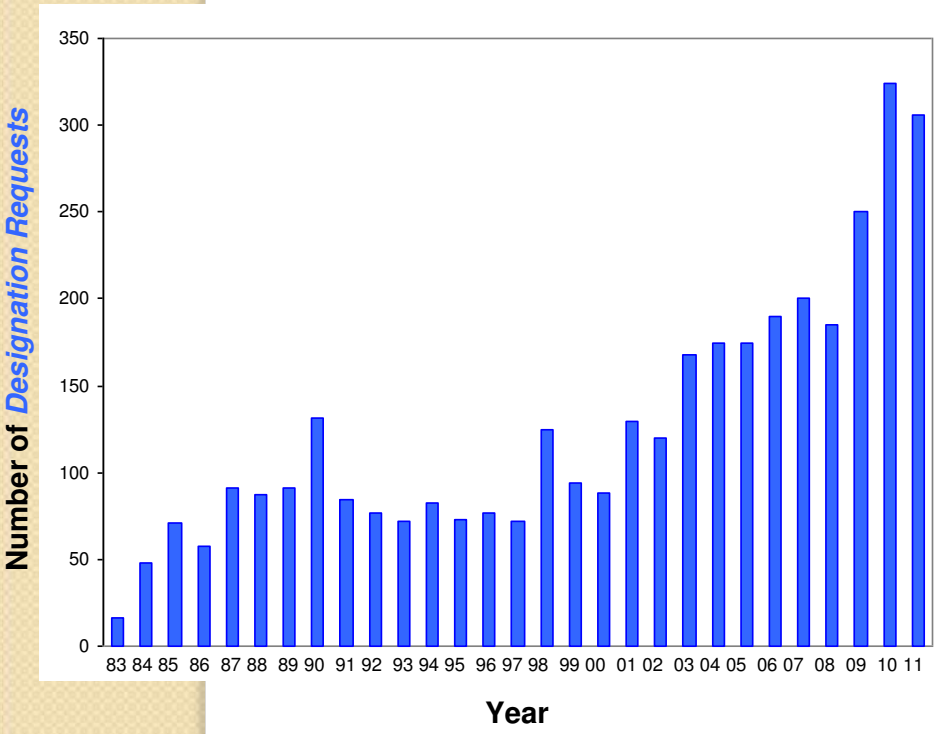
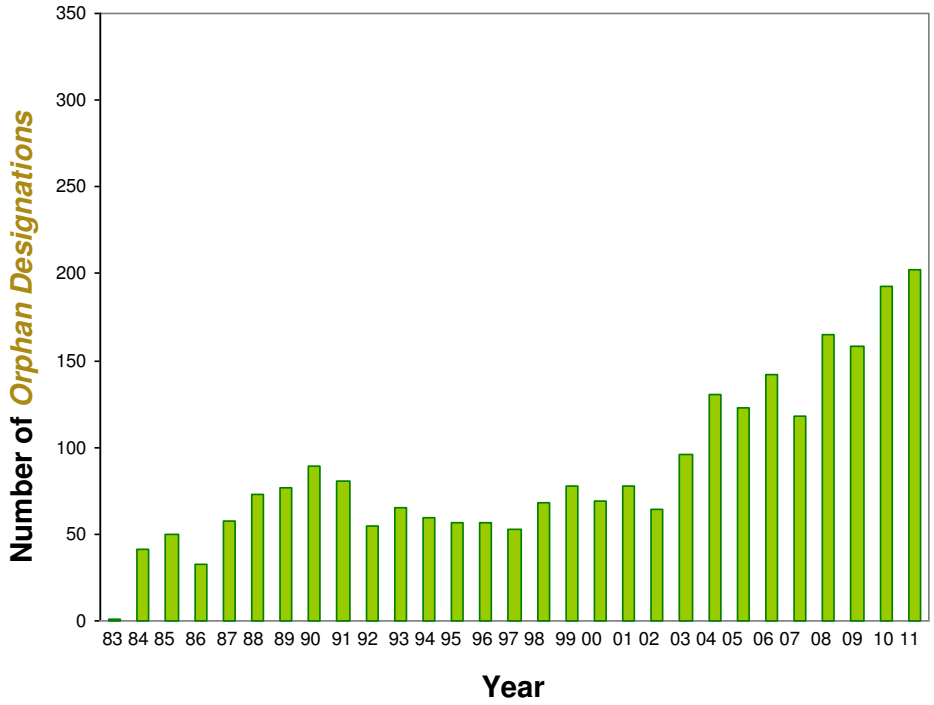
Apply for Marketing Authorization registration

Orphan Designation

~3740 Designation requests

~2600 Products have received Orphan Designation (~70%)





Thank You