# *Orphan Designation - Key Concepts and Evaluation Criteria*

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## Is there any reason to stimulate development and marketing of drugs for rare diseases?

**“Persons suffering from rare conditions should be entitled to the same quality of treatment as other patients”**

**But…**

**“ the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions”**

**As…**

**“some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product (…) would not be recovered by the expected sales”**

## Orphan Regulations in the EU

- **Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products of 16 December 1999**
  - **Criteria for designation**
  - **Committee (COMP)**
  - **Procedure**
  - **Incentives**

- **Commission Regulation (EC) No 847/2000 of 27 April 2000**

## Orphan designation

- For medicinal products for human use
- Procedure free of charge
- Can be requested at any stage of development
- Sponsor can be either company or individual
  - Established in the Community (EU, Ice, Liech, Nor)
- European Commission Decision gives access to incentives

## Designation criteria

**RARITY (prevalence) / RETURN OF INVESTMENT**

- **Medical condition affecting not more than 5 in 10,000 persons in the Community (around 246,000)**
- **Without incentives it is unlikely that the marketing of the prodcut would generate sufficient return to justify the necessary investment**

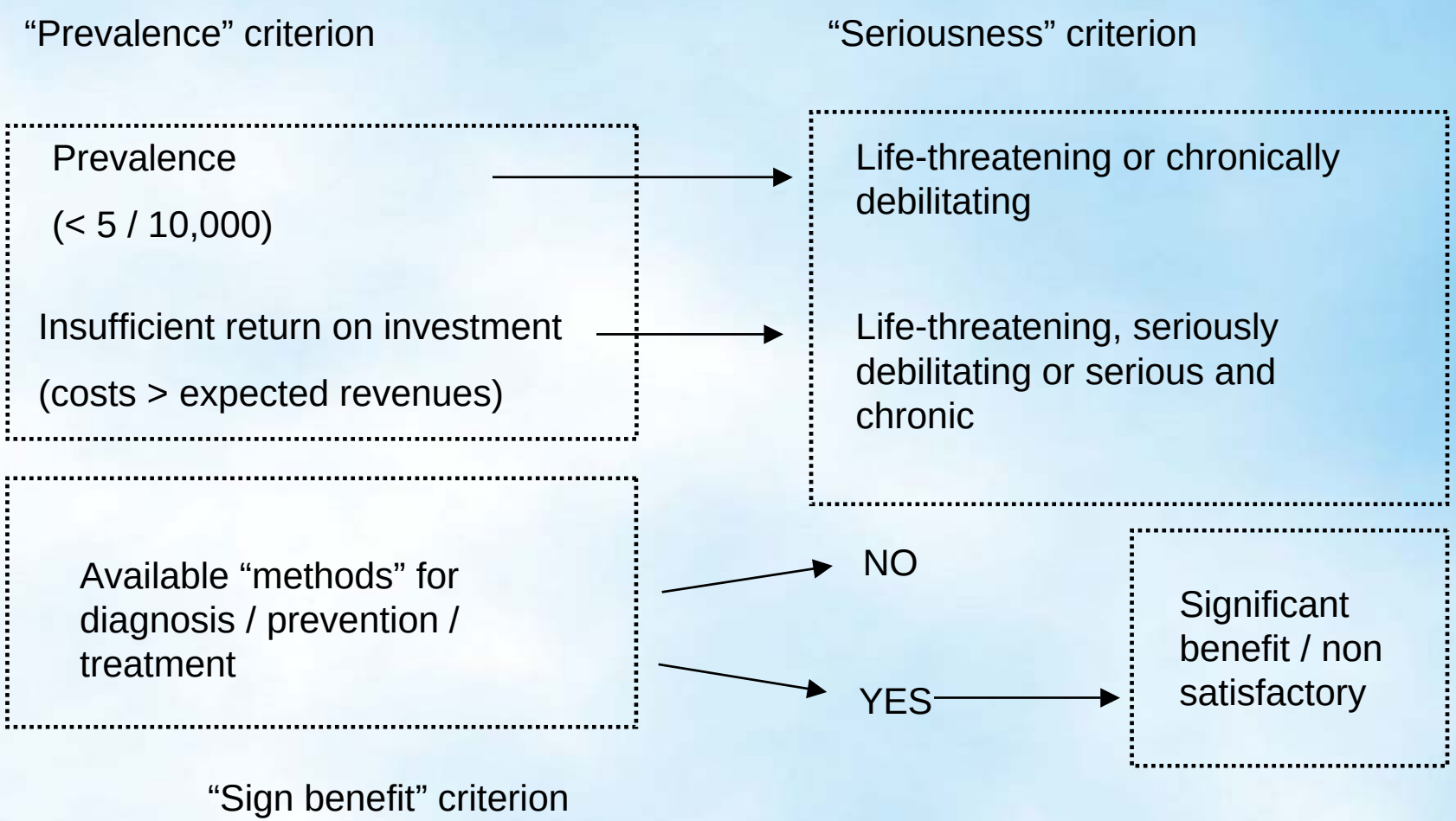
**SERIOUSNESS**

- **Life –threatening or chronically debilitating**

**ALTERNATIVE TREATMENTS AUTHORISED**

- **If satisfactory method exist the sponsor should establish that the product will be of significant benefit**

# Designation criteria



## Significant benefit

- **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 authorised products (satisfactory)**
  - **COMP to assess whether or not sign benefit assumptions are supported by available data/evidence supplied by applicant**
  - **Sign benefit to be confirmed prior to marketing authorisation to maintain orphan status**

## Examples assumption for significant benefit

- Drug has a new mechanism of action
  - Efficacy will have to be demonstrated
  - Opens possibilities for drug combination
  - Therapeutic alternative
- Claims of better efficacy
- More convenient administration route (major contribution to patient care)
- Better safety
  - Most times complementary safety profile
  - Weak assumption for justification of sign benefit (data to support?)

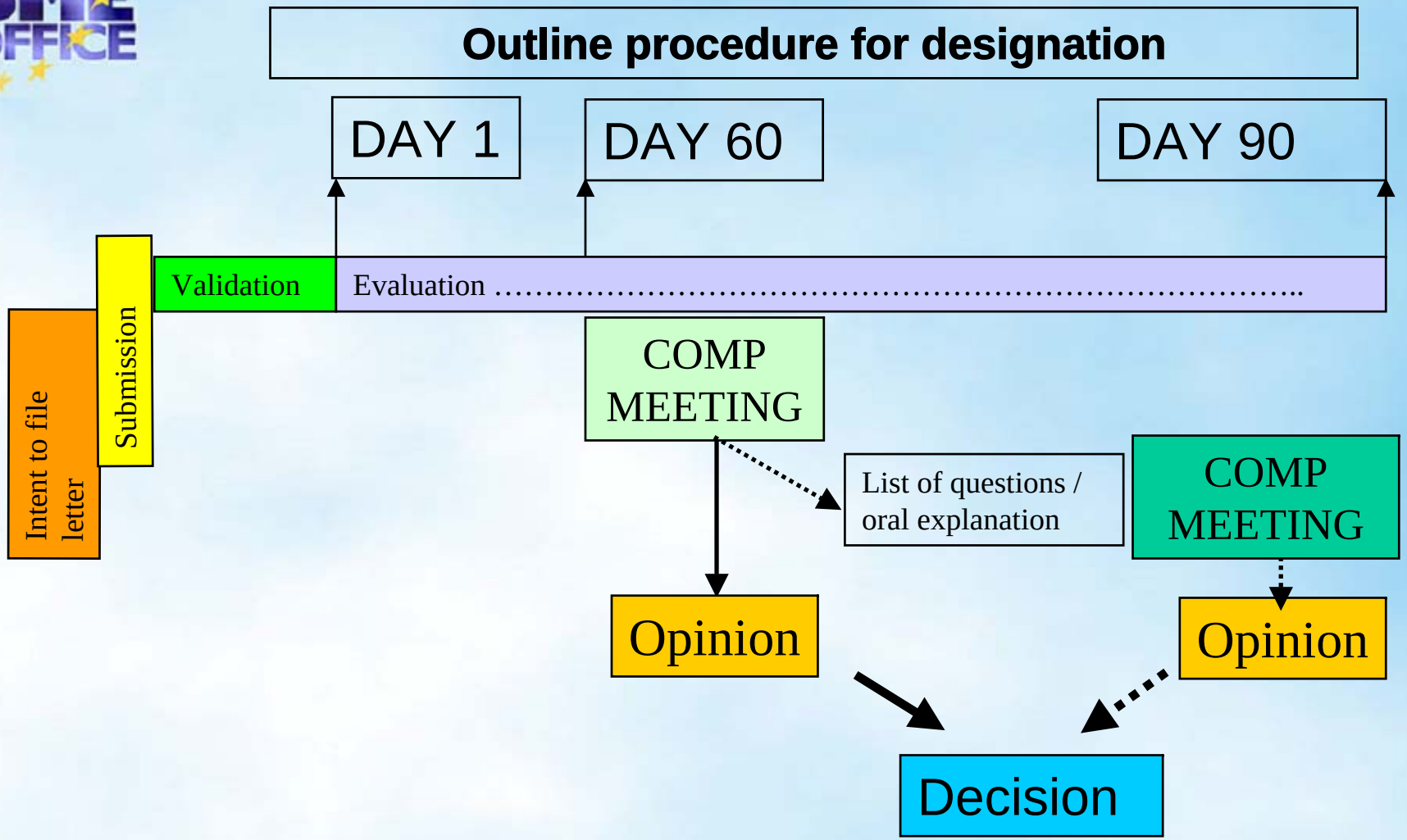
## Incentives

- Economic / marketing
  - Fee reduction / exemption
    - Extended incentives for SMEs (post authorisation)
  - Market exclusivity
- Product development
  - Protocol assistance
- Community marketing authorisation
- National incentives (EC inventory)

## How to obtain orphan designation?

- Applications submitted either by companies or individuals (sponsors)
  - Established in the EU
- Application form +
  - Description of the condition
  - Description of the medicinal product
  - Prevalence calculation of the condition
  - Justification of severity
  - Justification of “significant benefit” (when applicable)
  - Description of product development (current and future)

# Outline procedure for designation




- Publication of public summary of opinion (lay language) on EMEA website

## Committee for Orphan Medicinal Products (COMP)

**EMEA Committee: 33(+2) members + chairperson**

- **1 member per Member State (27)**
- **6 members nominated by the European Commission**
  - **3 patient representatives**
  - **3 members proposed by EMEA**

  **Non voting members (Ice and No)**

**COMP tasks:**

- **Opinions on designation**
- **To advise Commission on establishment and development of a policy on orphan medicinal products**
- **To assist Commission in liaising internationally and with patient support groups**
- **To assist Commission on guidelines**

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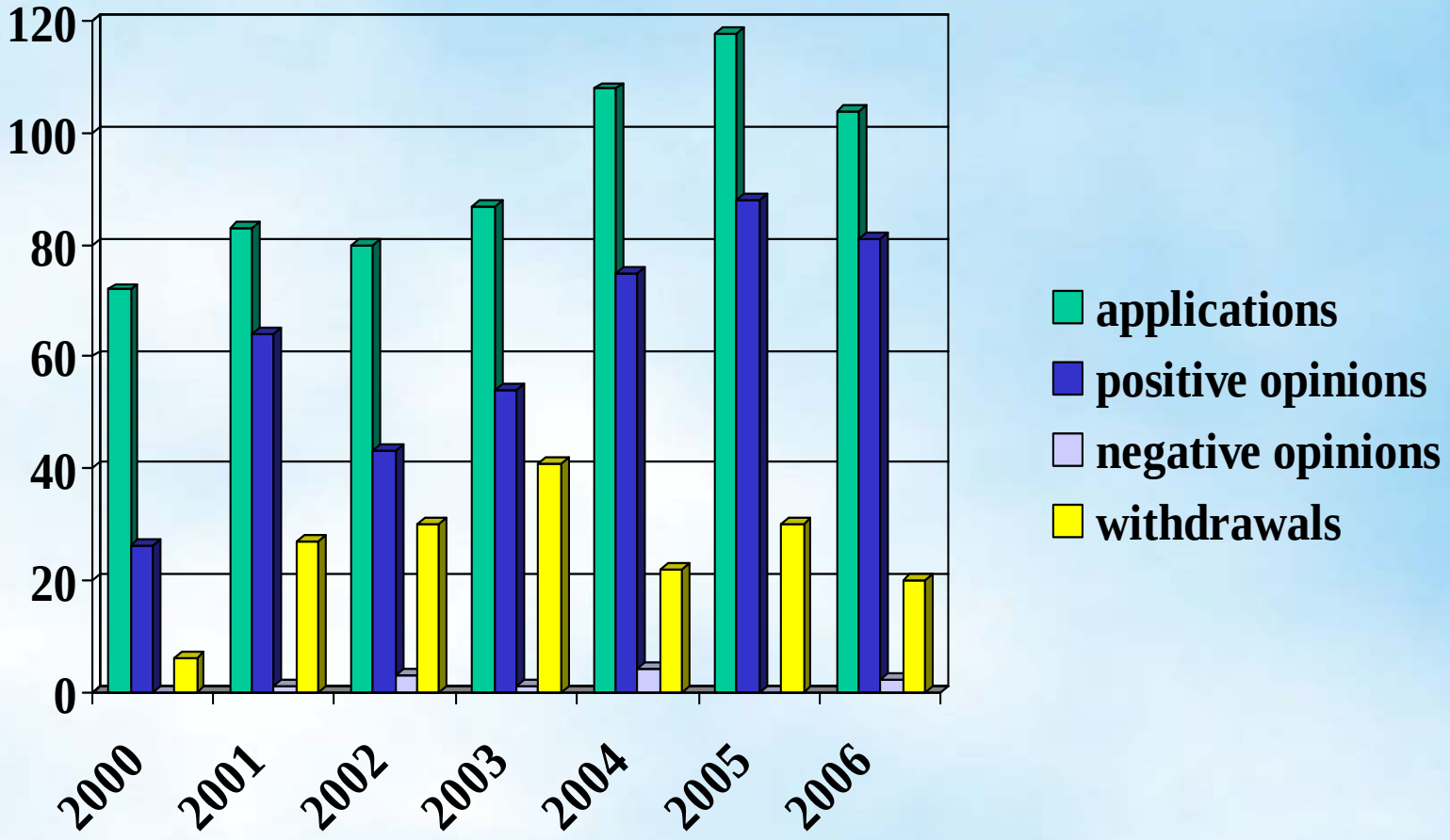
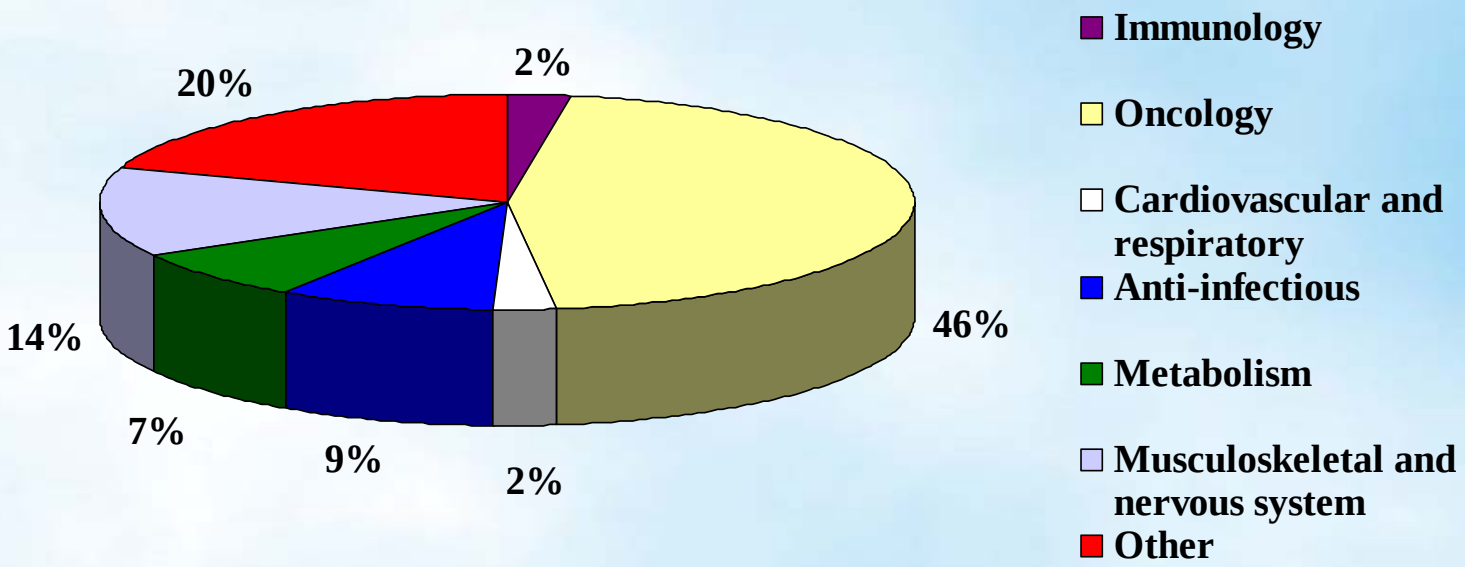
## Experience up to 2006



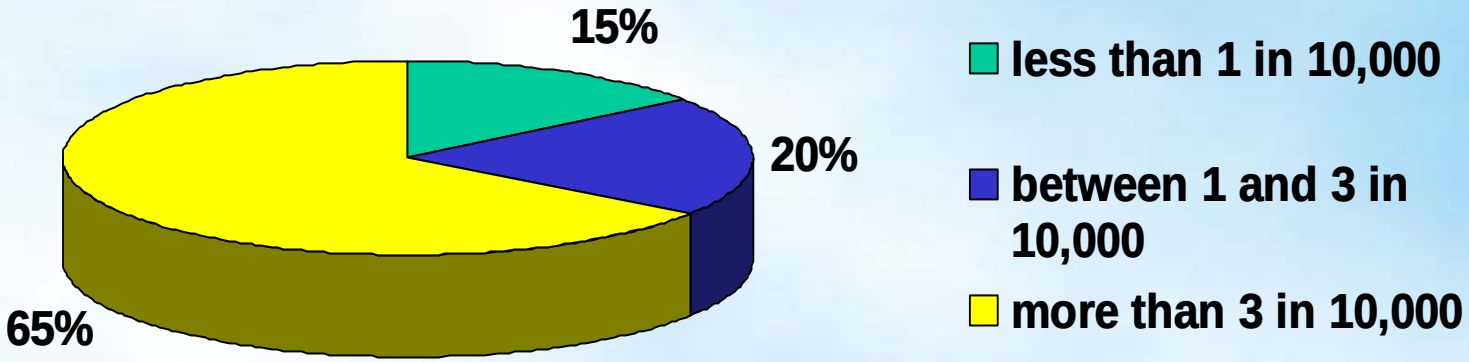

- In 2006: Application success ratio 77%
- Lowest withdrawal rate (19%) ever since 2000

# Opinions in 2006 per organ / system




- More than 20 % of designated products are biotechnology products
- More than 50% are innovative products

# Prevalence designated conditions



## Authorisations

- 31 orphan medicinal products had been granted a centralised marketing authorisation (four products in decision making process)
- Two authorisations non centralised
- Benefit to 1.6 million European patients suffering from 25 (+2) rare conditions

- Negative outcomes and withdrawals
  - 17 withdrawals
  - Three negative opinions

## Evidence at Time of Centralised MA (Pivotal trial design)

- 44% double blind randomized (placebo / active controlled)
- 42% Open label, non-randomized (or 2 doses R)
- 8% Bibliographic applications / meta-analysis
  - Adrenal cortical carcinoma and Wilson's disease, patent ductus arteriosus (meta-analysis)
- 6% Case reports / compassionate use
  - N-acetylglutamate synthetase deficiency (case reports), and tyrosinaemia type I (compassionate use)

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## Conclusions

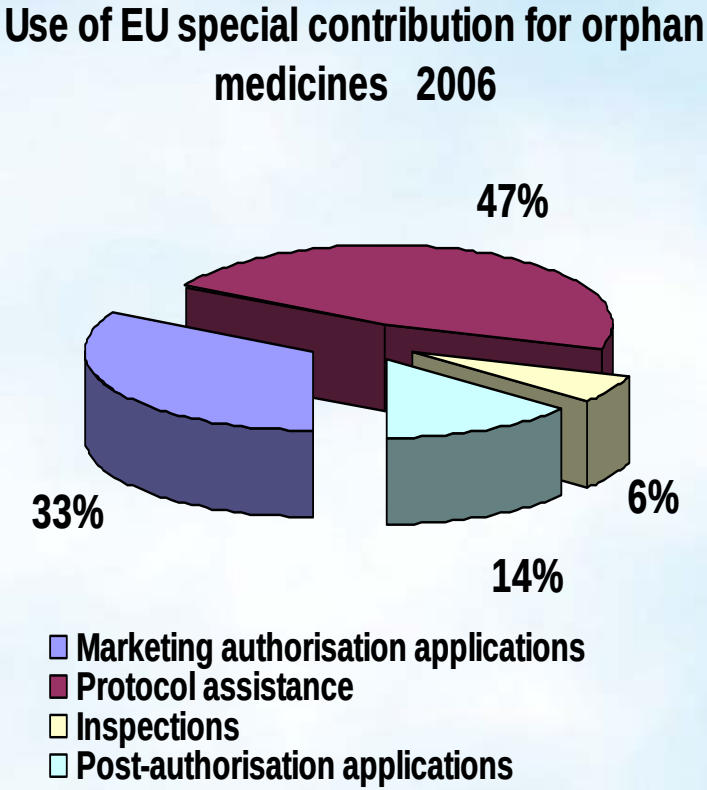
- Orphan regulation offers important incentives for development and marketing of medicinal products for rare diseases
- Exclusive incentives applicable to SMEs
- Rare diseases offer “natural environment” for SMEs
  - Biotechnology products and innovative products
  - Orphan conditions offer attractive opportunities for drug development
- Designation procedure has minimal regulatory burden for sponsors
- So far positive experience resulting in more than 400 designations and more than 30 authorised products

# Back-up slides

## Economic incentives

- Fee reductions (50% market authorisation aplication, 100% protocol assistance, post authorisation)
- 10-year market exclusivity
  - protection against
    - similar products (structure/mech of action) for
    - same indication
    - Three derogations
      - Sponsor's consent
      - Lack of supply
      - Clinical superiority

# Use of EU special contribution 2006




## 2006

- More than € 5.7 million (86%)
- pre-authorisation activities
- More than € 0.95 million (14 %)
- post-authorisation activities

## 2007

- 6,0 € million granted

## Incentives for development

- **Protocol assistance**
  - **Protocol assistance ≅ scientific advice**
    - **Questions on quality-efficacy-safety**
    - **Questions on significant benefit**
    - **Company position required**
    - **SAWP provides answers**

    - **CHMP adopts answers**
    - **COMP involved if issues on benefit**

# Designated orphan medicinal products for the treatment of children and adults 2004-2006