Orphan Medicinal Products

2000 - 2004

Drug Therapy in Rare Diseases

Persons suffering from rare diseases have the same rights as their fellow citizens to safe and effective therapies

What is an Orphan Medicinal Product

Orphan Medicinal Products

- for rare diseases
- development costs > expected return on investment
- life-threatening or very serious

Lack of sponsors developing orphan medicinal products

Orphan International Overview

- United States 'Orphan Drug Act' 1983
  - 1200 designations
  - 220 marketing authorisations
- Japan 'Orphan Drug Legislation' 1993
- Singapore 'Orphan Legislation' 1997
- Australia 'Orphan Legislation'
  - 1998

Orphan Regulations

- 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

Orphan Medicinal Products

Scope of EU Regulations

- For medicinal products for human use only
- Not for medical devices
- Not for food or food supplements
- Not for medicinal products for veterinary use

Orphan Medicinal Products

Main EU Incentives

- Ten years exclusivity from the date of marketing authorisation
- Protocol assistance from the EMEA
- Direct access to Centralised Procedure
- Fees reduction for centralised applications
- Priority access to EU research programs

National Incentives

- Inventory published on Commission Web-site

Committee for Orphan Medicinal Products (COMP)

EMEA Committee: 31 members + Chairman

- 1 Member per Member State
- 3 representatives from patients groups
- 3 members proposed by the EMEA

COMP Responsible for:

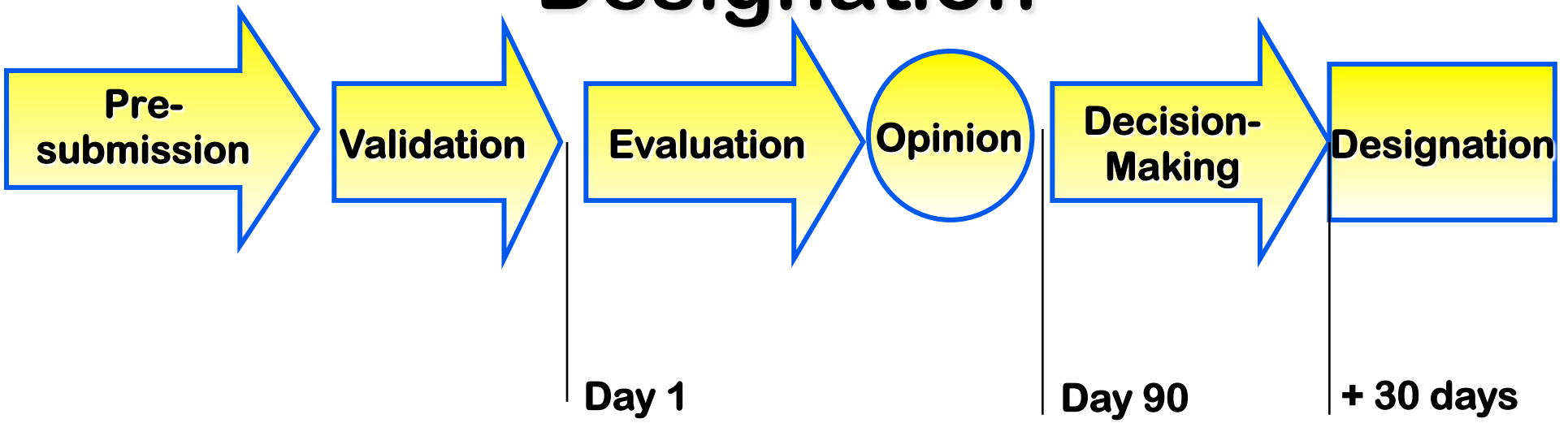
- opinions on designation
- advising on general EU policies
- international co-operation

Orphan Medicinal Products

Role of EMEA

- Administrative & technical secretariat of COMP
- Validation and assessment of requests for designation
- Protocol assistance: regulatory and scientific
- Fee reductions: any fee ⟶ EU special contribution
- EU Register on Orphan Drugs

Procedure for Orphan Designation



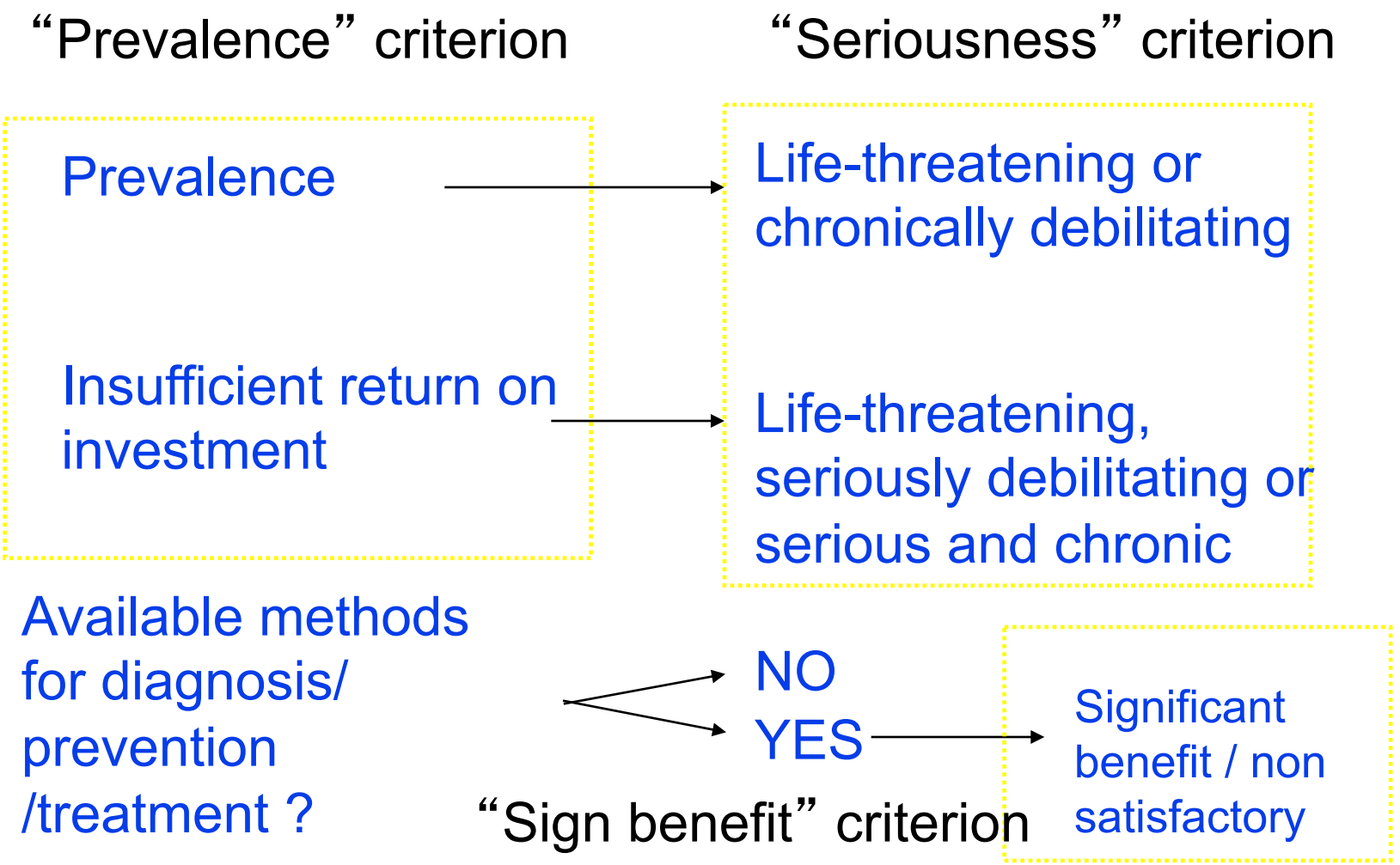
Application for Orphan Designation

Application should demonstrate orphan criteria have been met:

- life-threatening or debilitating nature of condition
- medical plausibility
- prevalence < 5 in 10,000 or unlikely to generate sufficient return on investment
- no satisfactory methods exist or medicinal product will be of significant benefit

All claims should be substantiated by references

Criteria for Orphan designation



...Conditions for achieving orphan drug status...

- The sponsor's hypothesis should be biologically plausible
- The indication should be a genuine one not 'manufactured' by sub-setting a common condition

…the level of evidence…

CHMP

COMP

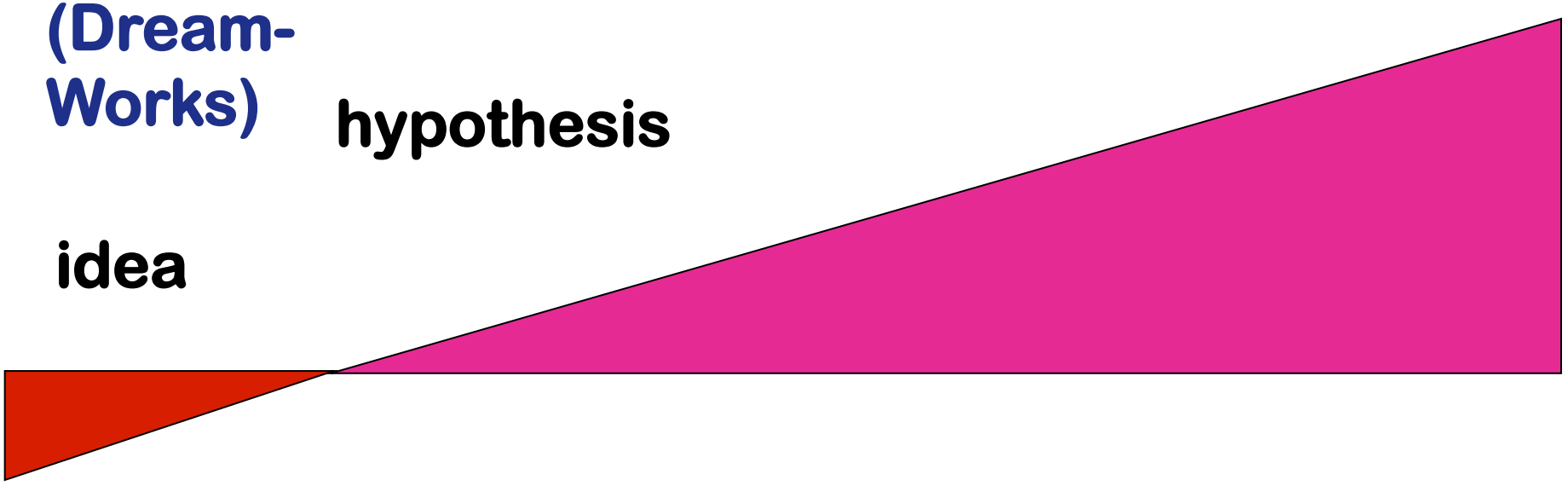
evidence

plausible
assumption

(Dream-
Works)

hypothesis

idea

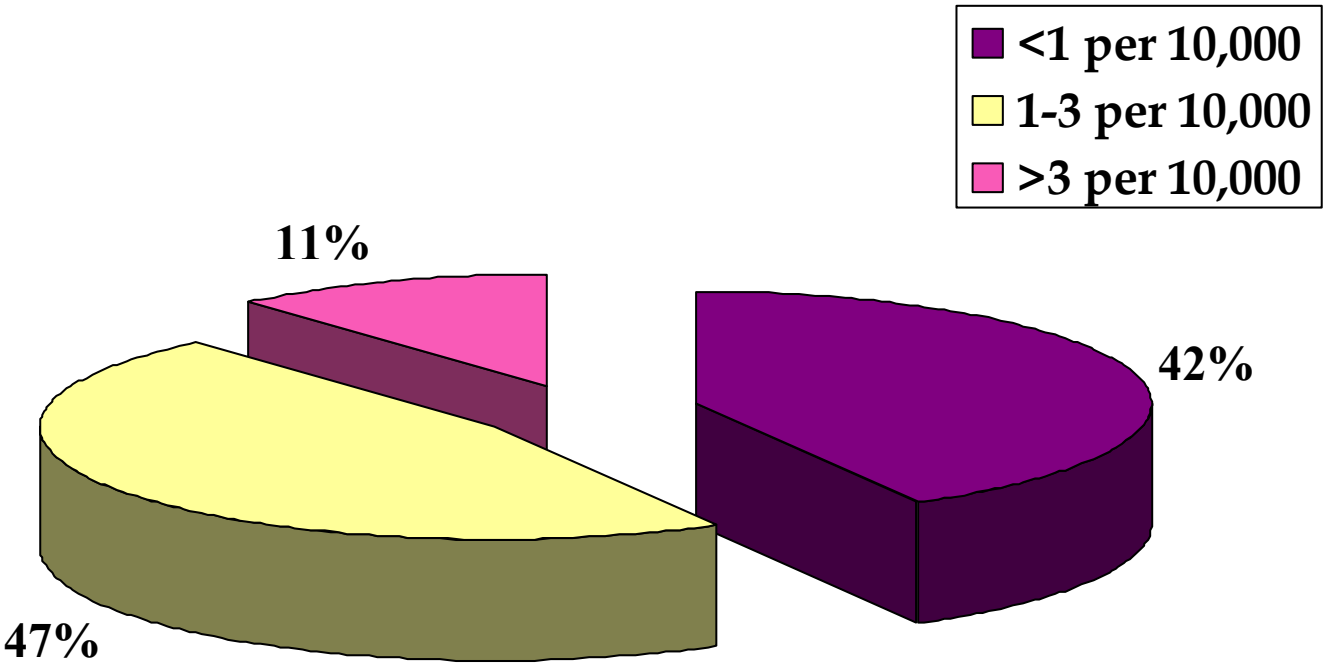


Prevalence

- Applications may seek to obtain designation based on a subset of a condition which otherwise would exceed the prevalence limit of 5 per 10,000

- What is considered a valid condition and what is considered “invalid” subset within a condition

Prevalence



Up to October 2004

Other methods

- Details of any existing diagnosis, prevention or treatment methods, e.g. authorised medicinal products medical devices and other approaches, such as surgical interventions, radiological techniques, diet, physical means, etc
- Justification
  - as to why methods are not satisfactory

  or
  - of significant benefit

Other methods

- **Justification as to why methods are not satisfactory**
  - The sponsor should provide justification as to why the existing methods are not considered satisfactory. This should be substantiated by scientific literature and/or clinical information.

Justification of significant benefit

- With reference to authorised methods, sponsor should provide justification for the assumption that the medicinal product for which designation is sought will be of 'significant benefit' to those affected by the condition

- Substantiated by scientific literature or the results of comparative studies (definitive or preliminary nature)

- Significant benefit defined as:

  clinically relevant advantage or a major contribution to patient care

Justification of significant benefit

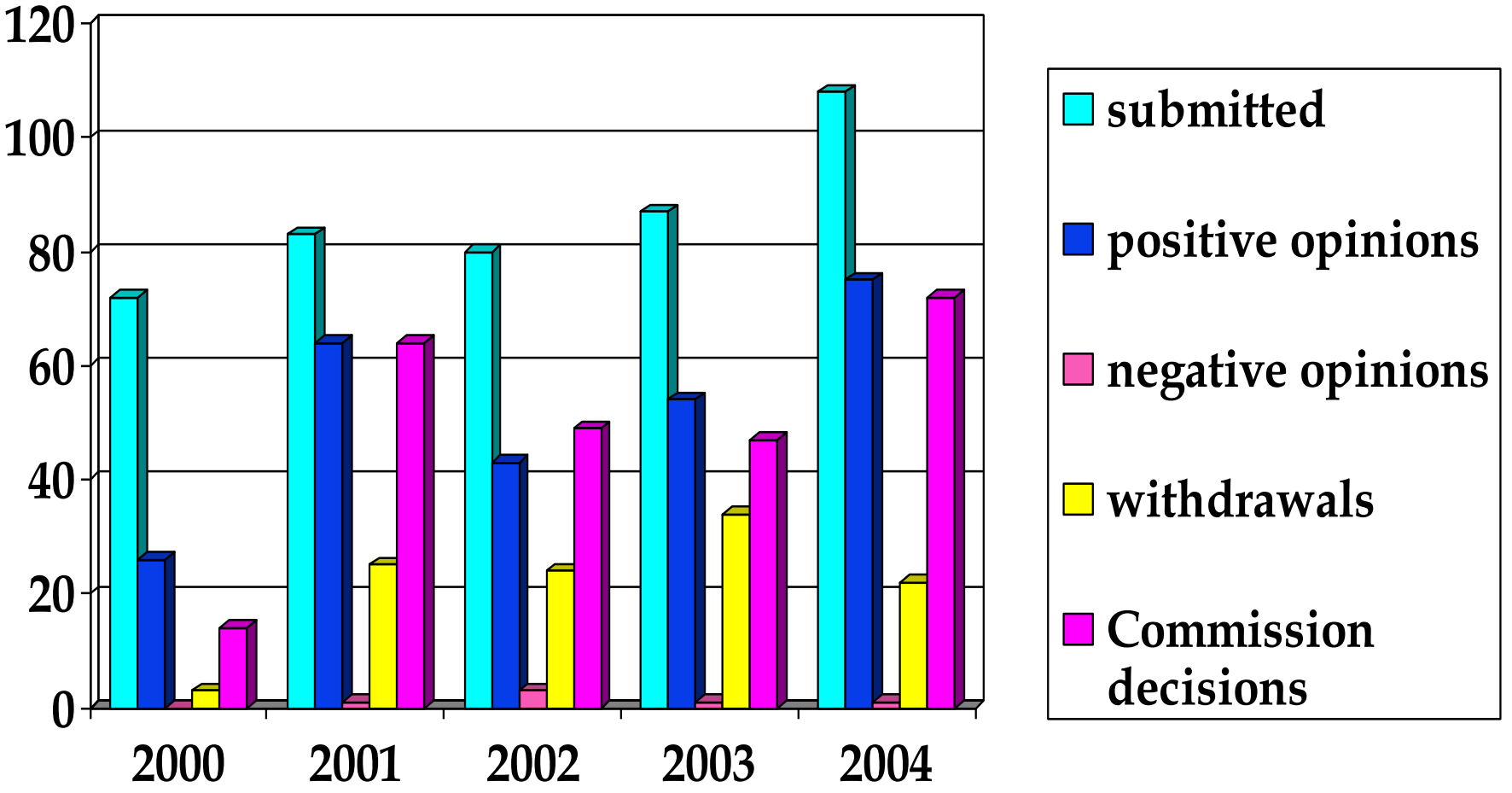
Examples:

- expected benefits to a particular population sub-set
- expectations of clinically relevant improved safety profile
- availability - authorisation in all EU member states may constitute benefit vs product authorised in limited number of MS only
- more favourable and clinically relevant pharmacokinetic properties
- more convenient formulation/route of administration

Status of Orphan Applications – 2000 - 2004

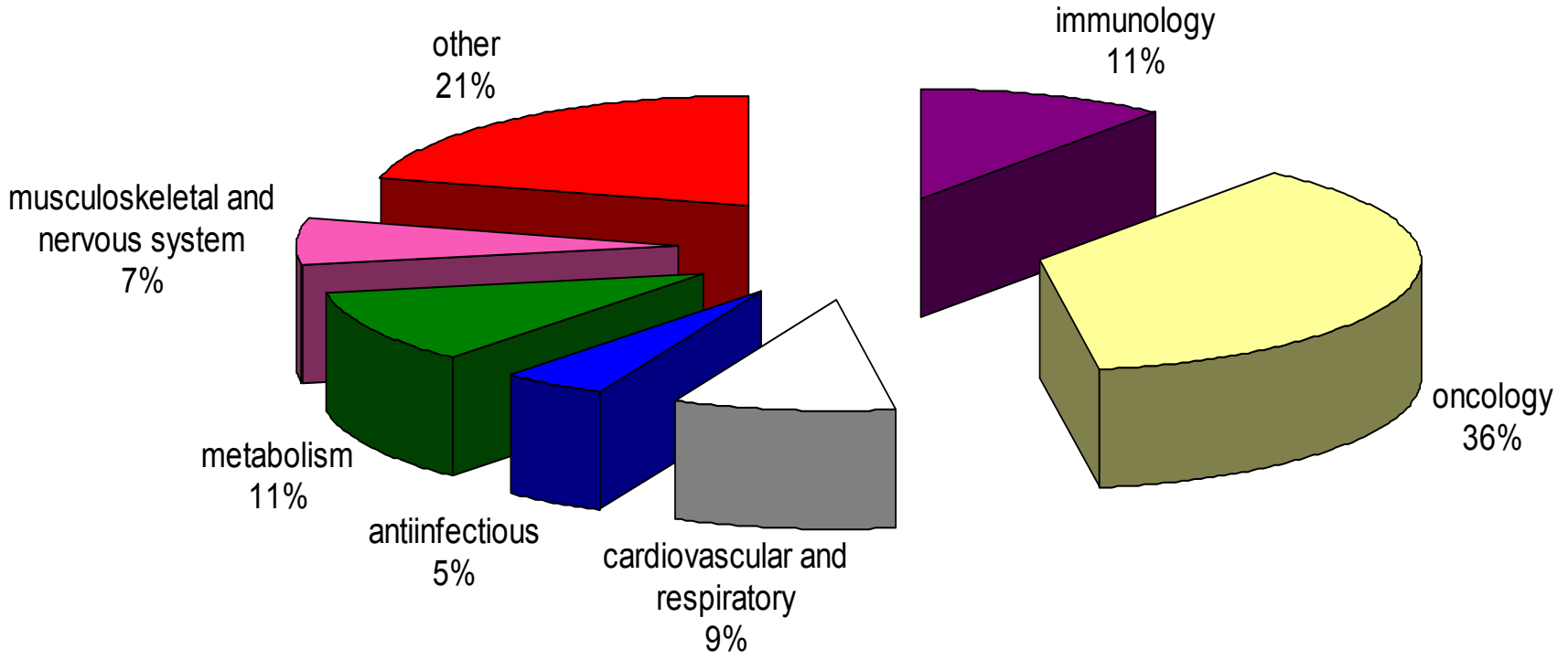
	2000	2001	2002	2003	2004	Total
No. of applications submitted	72	83	80	87	108	430
Positive COMP Opinions	26	64	43	54	75	262
Commission Designations	14	64	49	55	72	254
Final Negative COMP Opinions	0	1	3	1	1	6
Withdrawals after Submission	6	27	30	41	22	126

Status of Orphan Applications



Up to January 2005

Distribution of opinions



Up to December 2004

Orphan Medicinal Products Application for Marketing Authorisation (MAA)

At the stage of MAA:

- **Filing can currently be through Mutual Recognition Procedure or Centralised Procedure**

  In November 2005, Centralised filing obligatory

- **To obtain Market Exclusivity MA must be granted by all Member States**
- **Fee reductions are granted by some MS's and by EMEA for centralised applications**

Orphan Medicinal Products Application for Marketing Authorisation (MAA)

At the stage of MAA:

- **Designation shall be removed if it is established prior to grant of the marketing authorisation that the designation criteria are no longer met (Art 5.12 Reg 141/2000)**
- **COMP will review 'significant benefit' criterion prior to grant of MA**

Orphan Medicinal Products Market Exclusivity

Period of 10 years exclusivity from MA grant in all MS

Reduction in period of exclusivity:

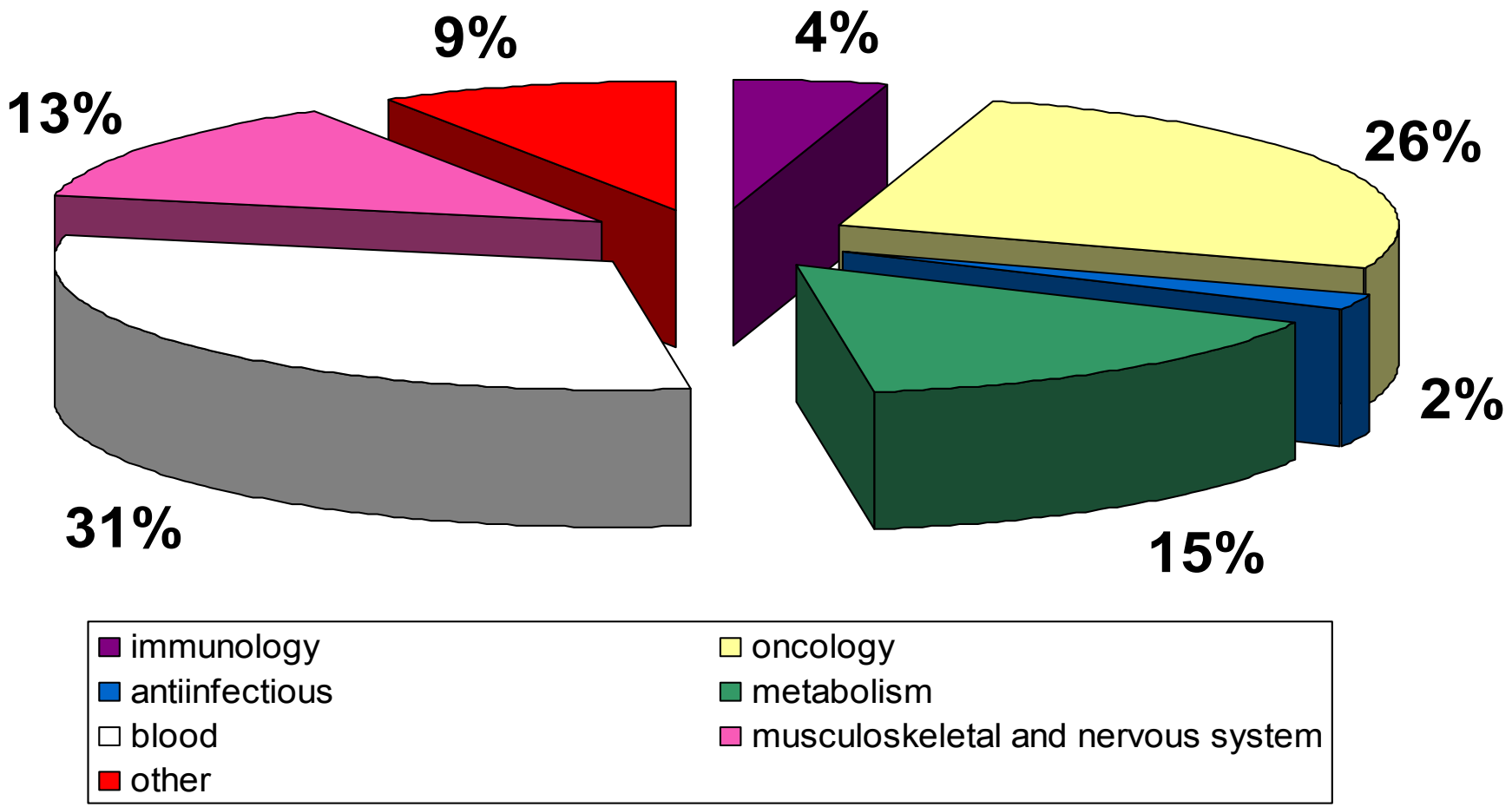
- May be reduced to 6 years if
  - » medicinal product is sufficiently profitable

Criteria for breaking the exclusivity:

- if MAH consents or,
- MAH is unable to supply sufficient quantities of product, or
- if the similar product is clinically superior

Distribution of orphan MAAs

41 orphan centralised MAAs, 4 through MR



Up to January 2005

Status of Orphan Marketing Authorisation Applications

18 authorisations granted to date

- Fabrazyme for Fabry disease
- Replagal for Fabry disease
- Glivec for chronic myeloid leukaemia
- Tracleer for pulmonary arterial hypertension
- Trisenox for acute promyelocytic leukaemia
- Somavert for acromegaly
- Zavesca for Gaucher disease
- Carbaglu for hyperammonaemia

Up to January 2005

Status of Orphan Marketing Authorisation Applications cont' d

- Aldurazyme for Mucopolysaccharidosis
- Busilvex for haematopoietic progenitor cell transplantation
- Ventavis for pulmonary arterial hypertension
- Onsenal for Familial Adenomatous Polyposis
- Litak for Hairy cell leukaemia
- Lysodren for adrenal cortical carcinoma
- Pedea for Patent Ductus Arteriosus
- Photobarr for Barret' s oesophagus
- Wilzin for Wilson's disease
- Xagrid for Thrombocythaemia

Up to January 2005

Status of Orphan Marketing Authorisation Applications

Two CHMP Opinions in decision-making

- **Orfadin for Hereditary tyrosinemia type 1**
- **Prialt for chronic pain**

Three extensions of indication

- **Glivec for GIST**
- **Glivec for first line use in CML**
- **Glivec for paediatric use in CML**

Twelve centralised applications in review process

Four applications filed through Mutual Recognition

Up to January 2005

Negative outcomes for orphan MAA

Eight applications for MA withdrawn

Two negative decisions/refusals

One variation type II withdrawn (extension of indication)