Orphan Drugs
Addressing Patients' Needs
Across Europe

2000 - 2005

1st Eastern European Conference on Rare Diseases and Orphan Drugs
Plovdiv, Bulgaria, 27 May 2005

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

EU 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

What are the EU incentives ?

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:

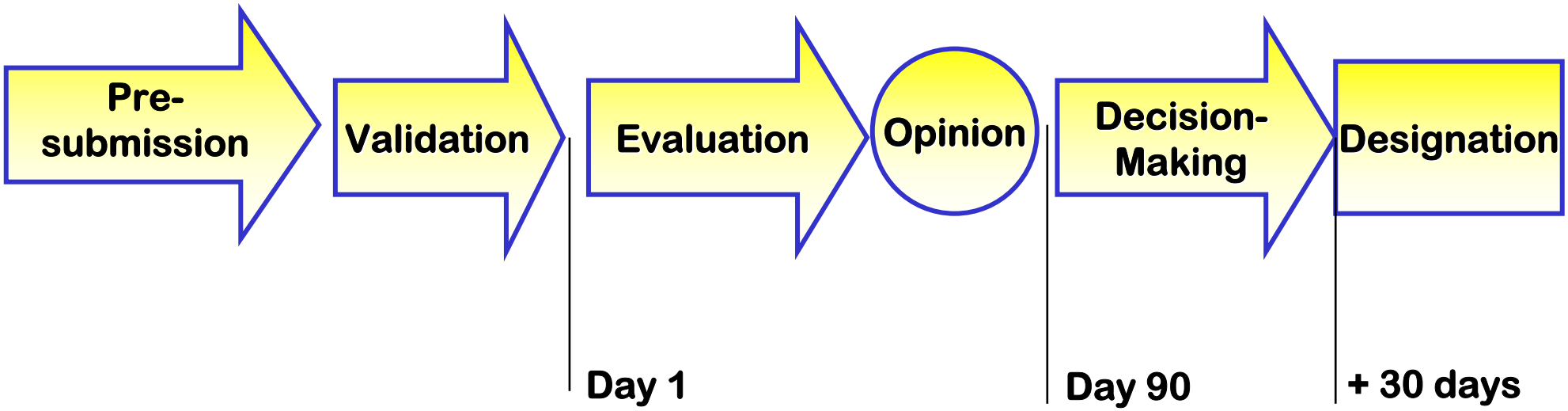
- opinions on designation
- advising on general EU policies
- international co-operation

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

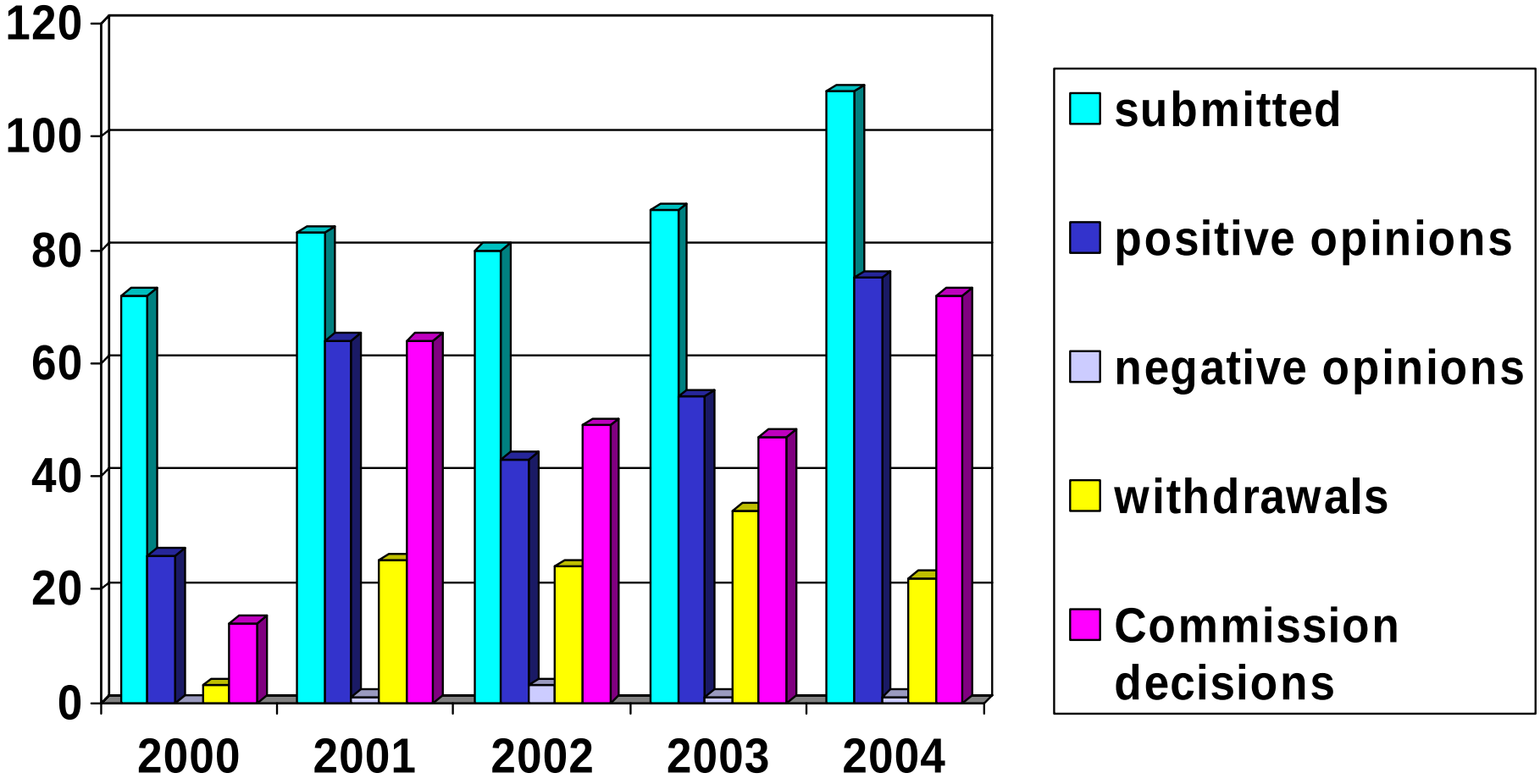
  be of significant benefit

All claims should be substantiated by references

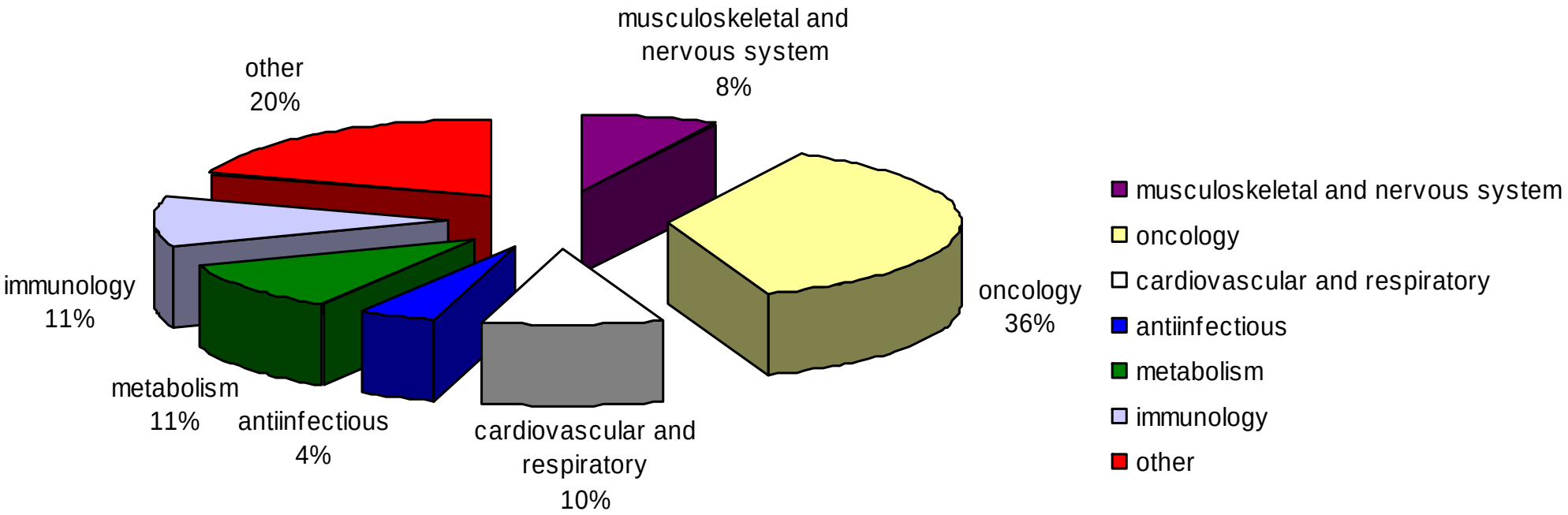
…Conditions for achieving orphan drug status…

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

Status of Orphan Applications 2000-2004



Distribution of opinions



Up to April 2005

Protocol Assistance

Article 6 of Regulation (EC) No 141/2000

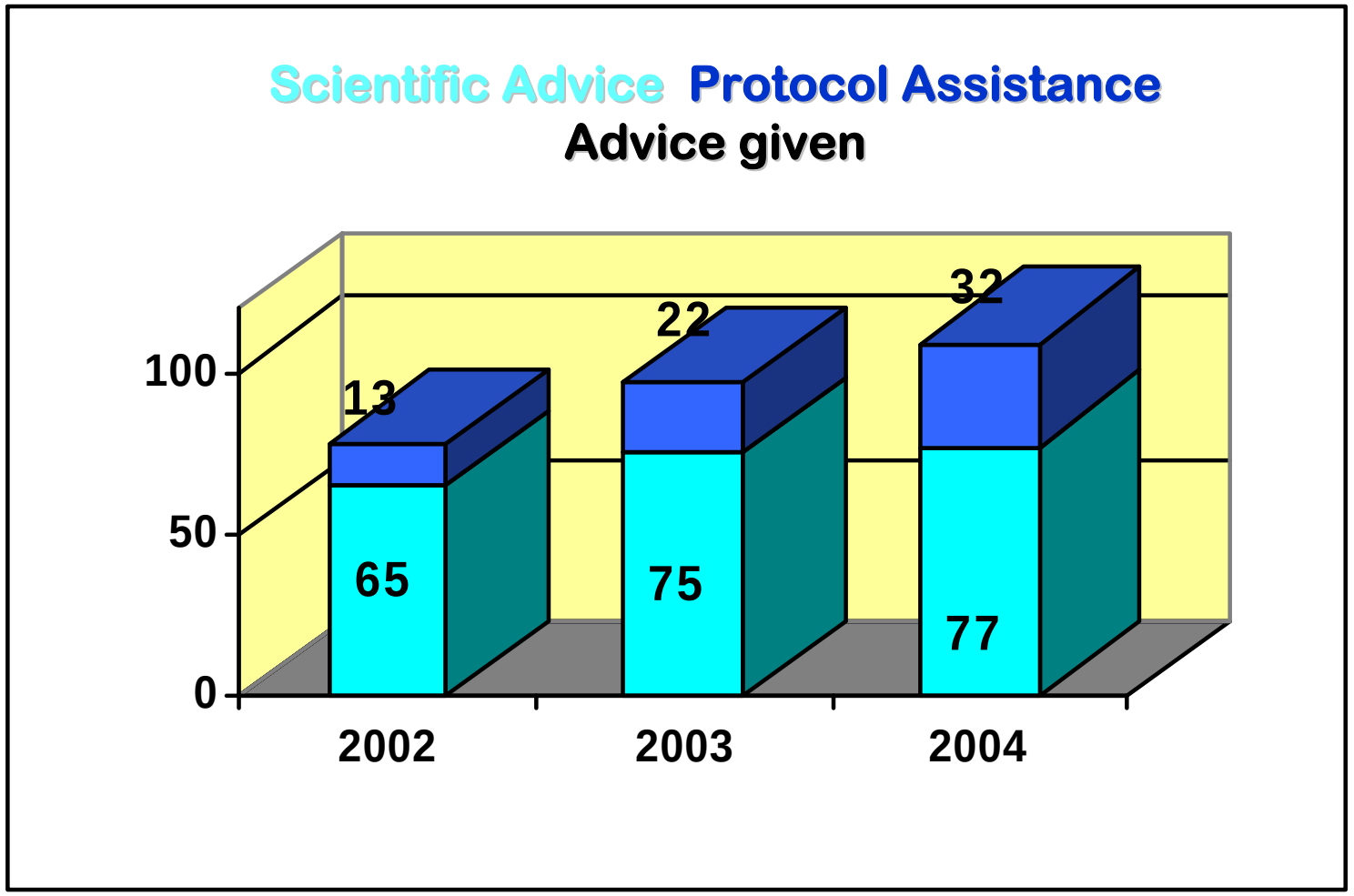
- Protocol Assistance = Scientific Advice for companies developing Orphan Medicinal Products

- Revised procedure adopted by the CHMP 2003
- Implementation of changes from new Pharmaceutical Regulation by end 2005

Protocol Assistance – Key Features

- Systematic pre-submission meeting with the EMEA
- Oral explanations in the majority of cases
- Additional and specific expertise to participate in SAWP
- Involvement of 2 representatives of the Committee for Orphan Medicinal Products in SAWP (Significant Benefit issues)
- Fee reduction (currently 100% = free)

Scientific Advice / Protocol Assistance
Procedures



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

Therapeutic Indication

- Therapeutic indication at the time of the marketing authorisation will be the result of the assessment of the quality, safety and efficacy data in a certain population
- It may be more limited than the orphan condition

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

Status of Orphan Marketing Authorisation Applications

20 centralised marketing 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
↓ Aldurazyme for Mucopolysaccharidosis
↓ Busilvex for haematopoietic progenitor cell transplantation

Up to April 2005

Status of Orphan Marketing Authorisation Applications cont'd

- ↓ 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
- ↓ Orfadin for Hereditary tyrosinemia type 1
- ↓ Prialt for chronic pain requiring intraspinal analgesia

Up to April 2005

Status of Orphan Marketing Authorisation Applications cont'd

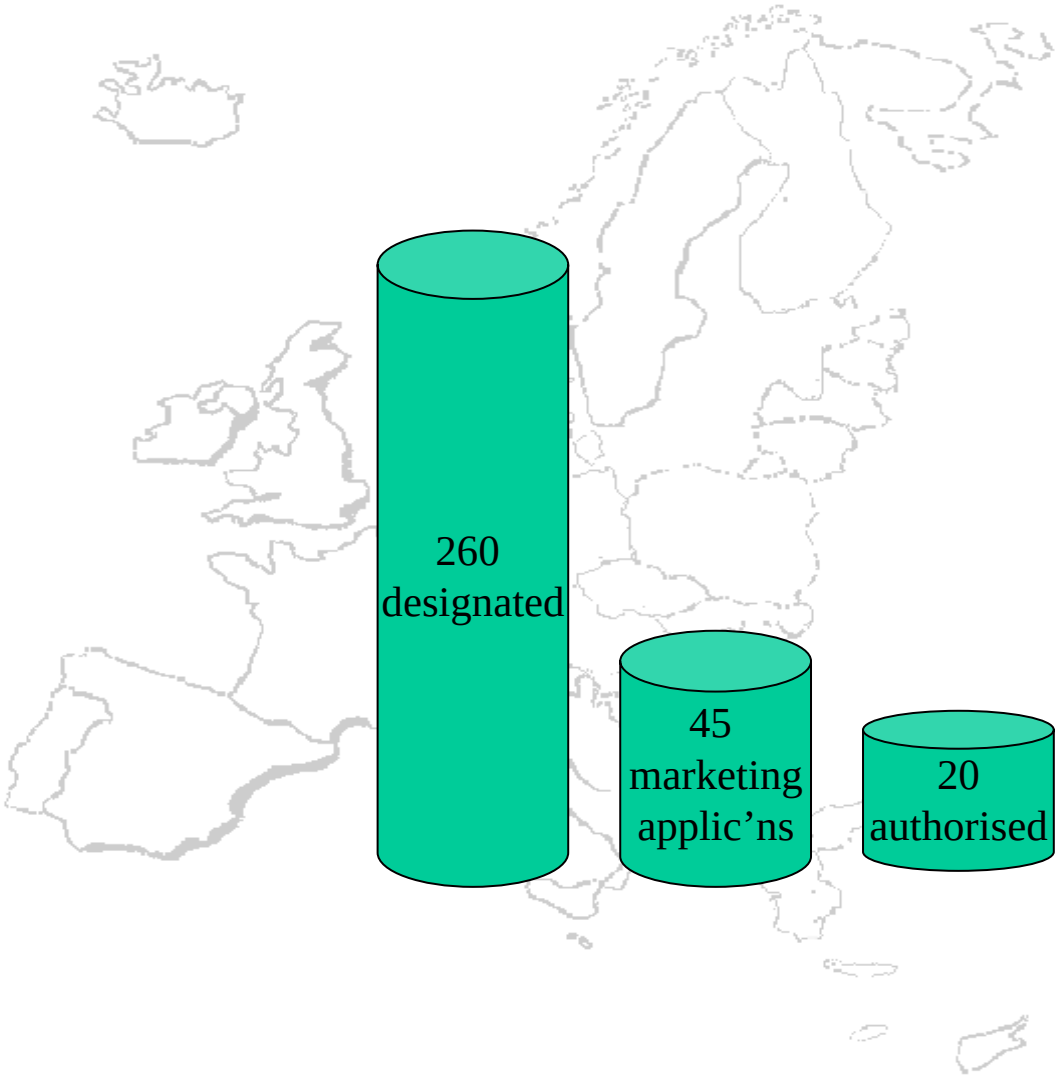
Three extensions of indication

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

Fifteen centralised applications in review process

Two marketing authorisations granted through Mutual Recognition

Orphan EU Marketing Authorisations



1,043,000 patients