
Gaining Regulatory Approval Establishing and Meeting regulatory Requirements

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The New European Pharmaceutical Legislation (Reg (EC) 7262004)

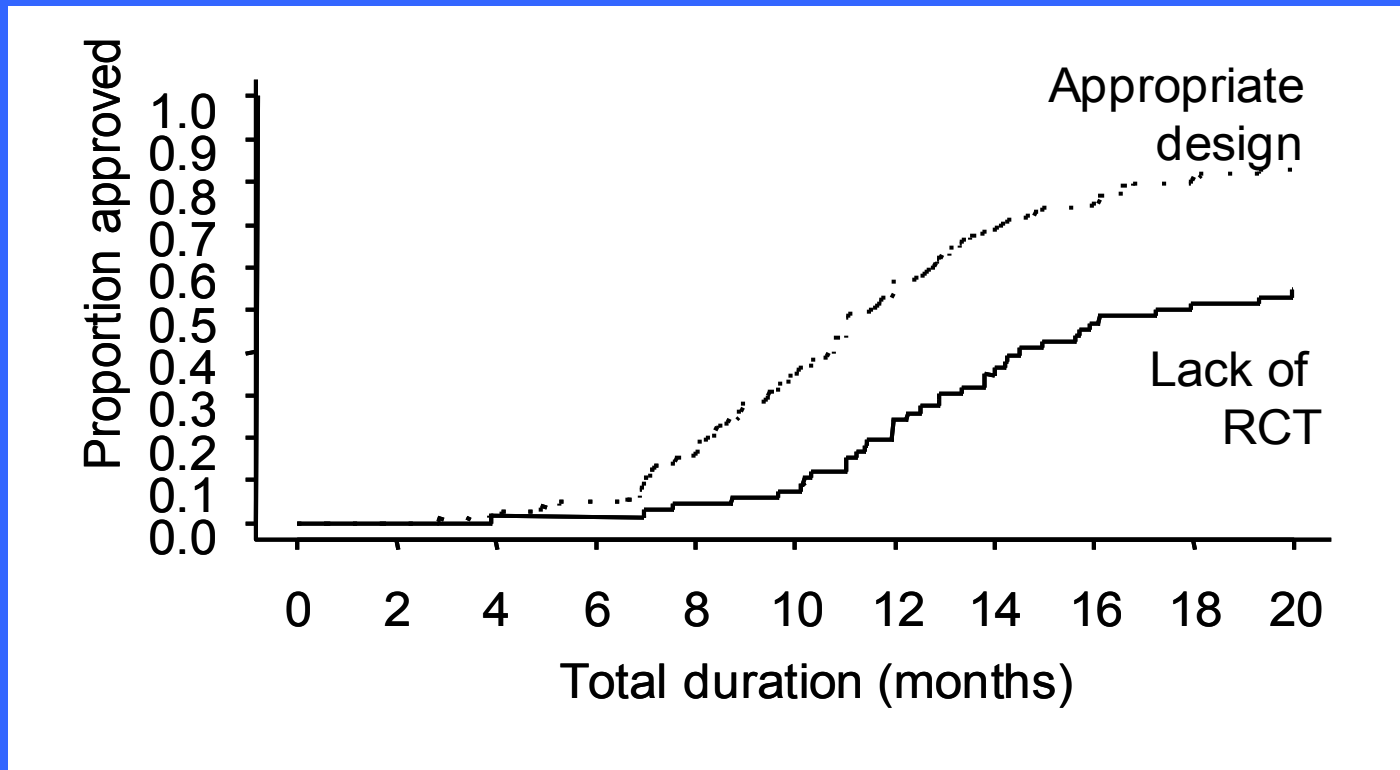
- Centralised route gives access to 27 (29) countries in Europe [25 (27) EU + Norway – Iceland]
- As of 20 November 2005 the Centralised route is mandatory for
 - ◆ Biotech Products
 - ◆ Orphan Products
 - ◆ Products indicated in 4 therapeutic fields of medical public health interest
 - AIDS, cancer, diabetes and neurodegenerative disorders
 - ◆ As of 2008 will be extended to all antiviral and immunologicals

Type of Approvals

- Normal
 - ◆ Comprehensive data to assess risk-benefit balance
 - ◆ RCT to show clinical benefit
- Exceptional circumstances
 - ◆ Comprehensive data can normally never be provided because
 - e.g. indication too rare
- Conditional approval (*new*)
 - ◆ “early approval”
 - ◆ Comprehensive clinical data not yet available but...
 - Positive benefit-risk balance
 - It is likely that comprehensive data can be provided
 - Unmet medical needs will be fulfilled
 - Valid for 1 year, renewable

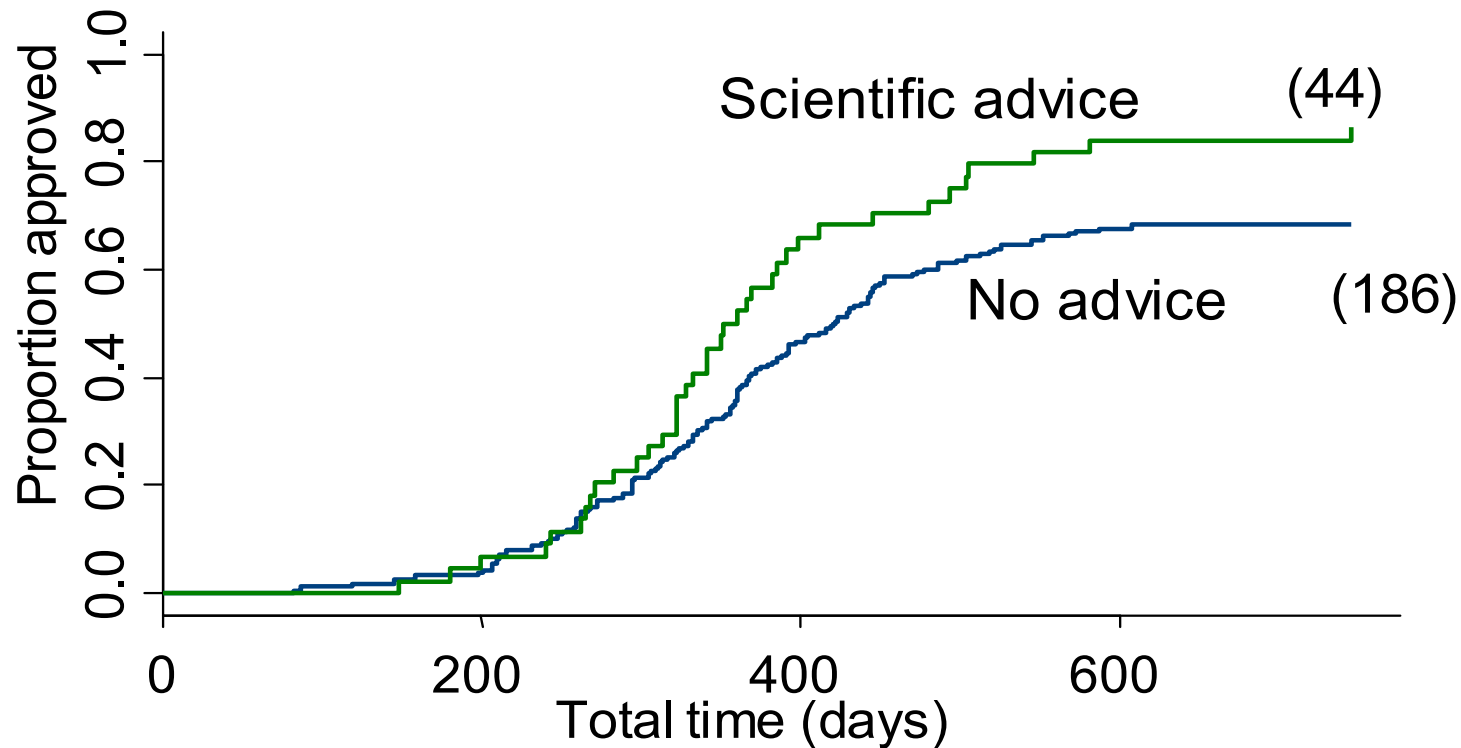
Important Reasons for Rejection

- Objection on **lack of adequate RCT** most important factor associated with rejection



CPMP opinions September 1997 to July 2002 (N=170). Competing risks analysis.
Aronsson, *DIA*, 2003

Requirements for Registration



CPMP opinions September 1997 to March 2003 (N=230)
Competing risks analysis. Aronsson, *DIA*, 2003 (updated)

Marketing Authorisations for OMP

(October 17, 06)

- Number of Orphan Medicinal Products authorised
 - ◆ 30 OMP centrally authorised
 - ◆ 2 OMP in decision-making
 - ◆ 27 different orphan conditions
 - ◆ 18 / 27 (67%) conditions have prevalence $< 1 / 10,000$
- Orphan Medicinal Products withdrawn / negative at MA
 - ◆ 16 OMP withdrawn
 - ◆ 2 OMP negative decisions/refusals

Orphan Cancer-related Conditions

Centrally Authorised (October 17, 06)

- Acute lymphoblastic leukaemia (3), *Prevalence 0.4*
- Chronic myeloid leukaemia (2), *Prevalence 0.9*
- Malignant gastrointestinal stromal tumour (2), *Prevalence 0.06*
- Renal cell carcinoma (2), *Prevalence 3.5*
- Acute promyelocytic leukaemia, *Prevalence 0.8*
- Hairy cell leukaemia, *Prevalence 3.65 (indolent non-Hodgkin lymphoma's)*
- Adrenal cortical carcinoma, *Prevalence 0.1*
- High-grade dysplasia in Barrett's Esophagus, *Prevalence 3.6*
- Treatment of anthracycline extravasations, *Prevalence 0.03*
- Conditioning treatment prior to hematopoietic progenitor cell transplantation, *Prevalence 0.7*
- Dermatofibrosarcoma protuberans, *Prevalence < 1*

Other Orphan Conditions Centrally Authorised (1)

- Cardiovascular / respiratory diseases
 - ◆ PAH and CTEPH (4), *Prevalence < 2*
 - ◆ Patent ductus arteriosus, *Prevalence 1.7*
- Metabolic diseases
 - ◆ Fabry disease (2), *Prevalence 0.013 – 0.027*
 - ◆ Gaucher disease, *Prevalence < 0.6*
 - ◆ N-acetylglutamate synthetase (NSAGS) deficiency, *Prevalence 0.00125*
 - ◆ Mucopolysaccharidosis type I, *Prevalence 0.025*
 - ◆ Mucopolysaccharidosis VI, *Prevalence 0.024*
 - ◆ Glycogen storage disease type II (Pompe's disease), *Prevalence 0.137*
 - ◆ Tyrosinaemia type 1, *Prevalence 0.1*

Other Orphan Conditions Centrally Authorised (2)

- Musculoskeletal and nervous system diseases
 - ◆ Wilson's disease, *Prevalence 0.6*
 - ◆ Chronic pain requiring intraspinal analgesia, *Prevalence 1.55*
 - ◆ Narcolepsy, *Prevalence 4.9*
- Other
 - ◆ Acromegaly, *Prevalence 0.6*
 - ◆ Familial Adenomatous Polyposis (FAP), *Prevalence < 1*
 - ◆ Essential thrombocythaemia, *Prevalence 3*
 - ◆ Chronic iron overload requiring chelation therapy, *Prevalence 2.7*

Evidence at Time of Centralised MA

(Pivotal trial design)

- Double blind randomized (placebo / active controlled)
 - ◆ 16 / 36 orphan conditions (44%)
 - ◆ 7 / 16 (44%) in conditions with prevalence $< 1 / 10,000$
- Open label, non-randomized (or 2 doses R)
 - ◆ 15 / 36 orphan conditions (42%)
- Bibliographic applications / meta-analysis
 - ◆ 3 / 36 orphan conditions (8%)
 - Adrenal cortical carcinoma and Wilson's disease, patent ductus arteriosus (meta-analysis)
- Case reports / compassionate use
 - ◆ 2 / 36 orphan condition (6%)
 - N-acetylglutamate synthetase deficiency (case reports), and tyrosinaemia type I (compassionate use)

Summary

- New legislation obliges OMP to be centrally authorised
 - ◆ One procedure providing access to 27 countries (population 460,000,000)
 - ◆ Incentives
- In general, RCT increases chance of approval
- Scientific advice / protocol assistance increases chance of success (if followed)
- In five years, 32 OMP authorised in 27 different conditions
 - ◆ 67% of the conditions have population less than 46,000 patients in the EU
 - ◆ 44% of the pivotal trials are based on RCT
 - Almost 50% of them performed in conditions < 1/10,000

Development of MP in orphan conditions is feasible