Gaining Regulatory Approval
Establishing and Meeting regulatory Requirements

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

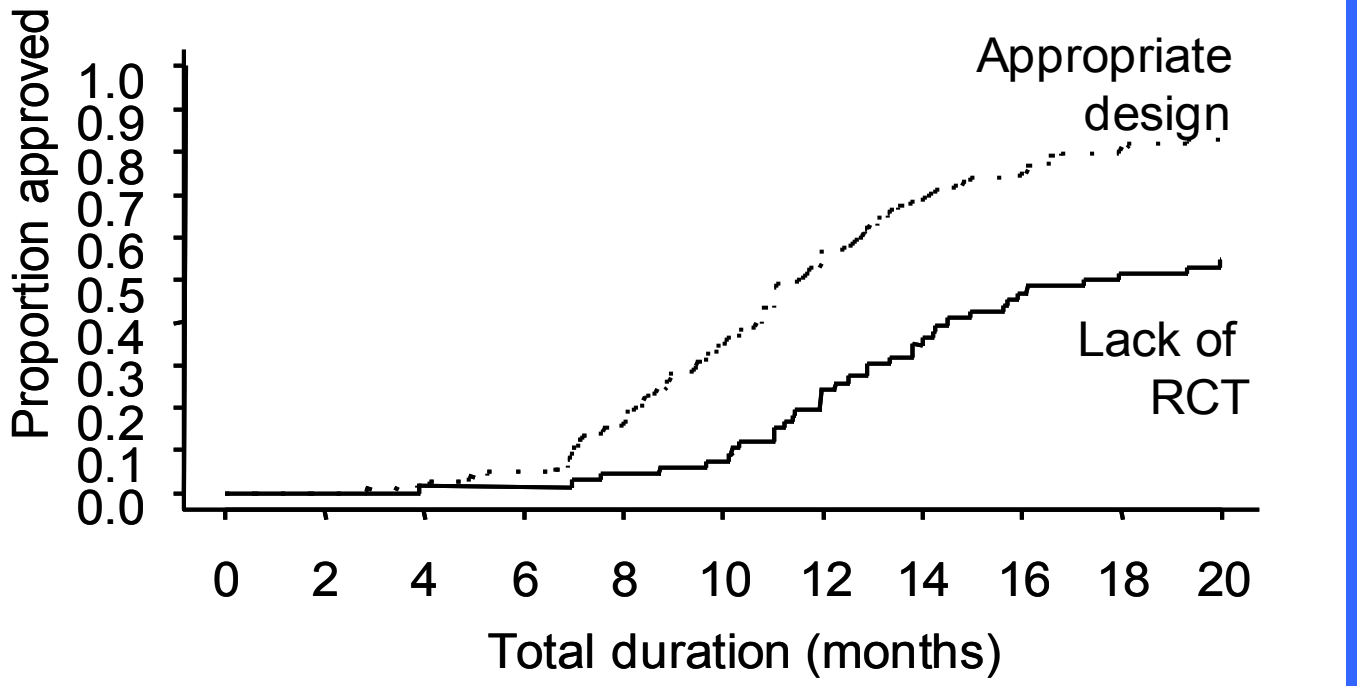
- Centralised route gives access to 27 (*29*) countries in Europe [25 (*27*) EU + Norway – Iceland]
- As of 20 November 2005 the Centralised route is mandatory for
  - Biotech Products
  - Orphan Products
  - Products indicated in 4 therapeutic fields of medical public health interest
    - AIDS, cancer, 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

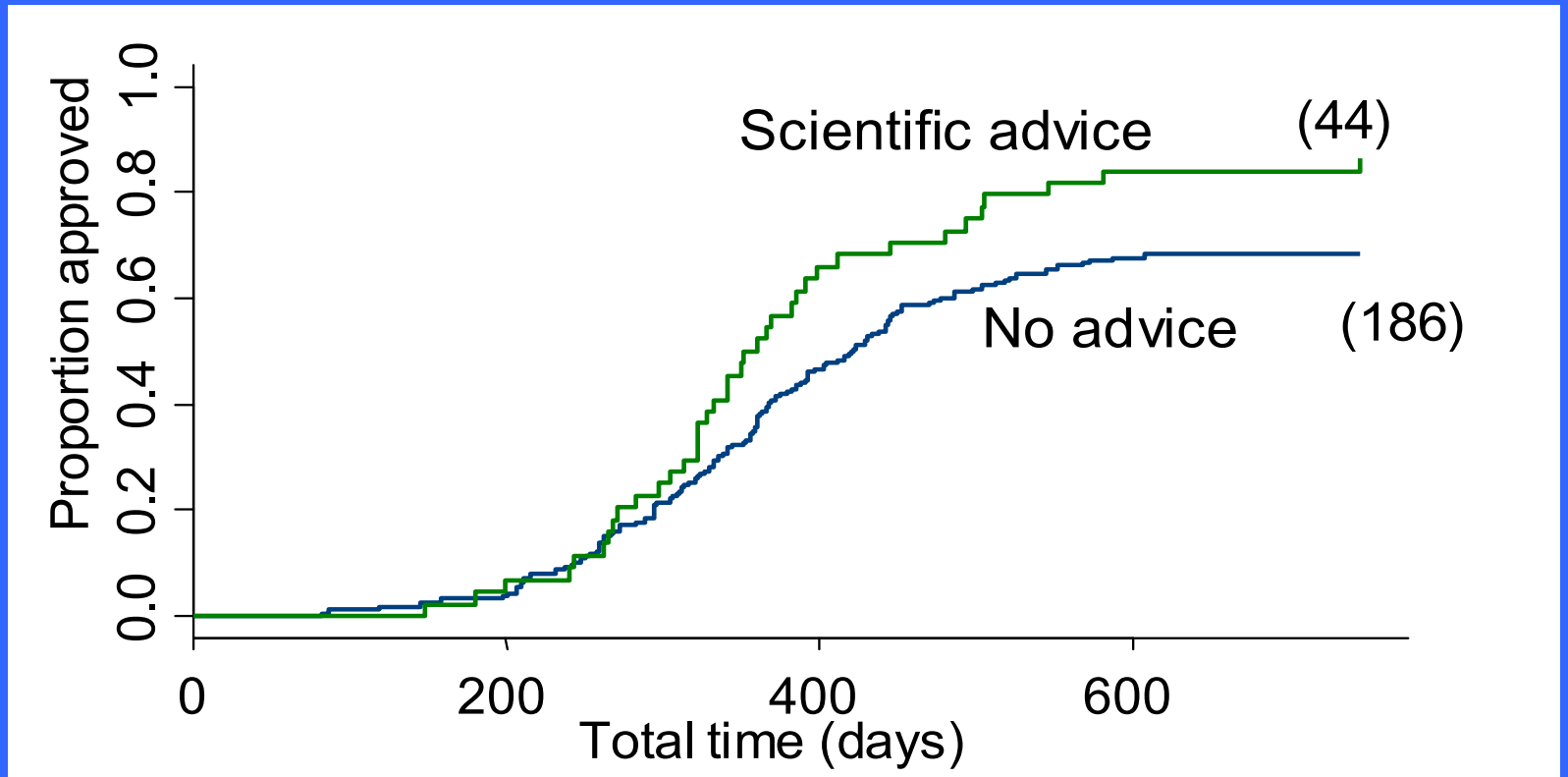
Important Reasons for Rejection

- 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- Orphan Medicinal Products withdrawn / negative at MA
  - 16 OMP withdrawn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