Orphan designation in the EU

Orphan drugs and rare diseases seminar

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Outline

Overview orphan designation

Procedure and criteria

- Definition of a medical entity
- Significant benefit

Outcomes

Other activities
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Other activities
Objective of the Regulation

- Provide incentives that stimulate research and development (push)
- Modify market conditions (pull)
- Set up system of recognition orphan drugs entitled for incentives
Legal references in the EU


- Criteria for designation
- Committee (COMP)
- Procedure
- Incentives

Commission communication July 2003 (2003/C 178/02)
Commission communication on Art 8(1) and (3) (C(2008) 4077)
Main characteristics orphan designation

- For medicinal products for human use
- For treatment, prevention or diagnosis of a rare disease
- 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
Incentives

- Protocol assistance: Scientific Advice with significant fee reductions
- Priority Access to Parallel Scientific Advice with FDA
- Fee reduction / exemption at Marketing Authorisation Stage (annually reviewed)
- Extended incentives for small and medium sized enterprises (SMEs)
- Automatic access to EU wide marketing authorisation
- Market exclusivity (10 years)
- (+2 if paediatric indication – completion investigation plan)
Protocol assistance
(scientific advice for orphan medicines)

Procedure: max 70 days including face to face meeting

Forum to agree the methodological approach in quality, non-clinical and clinical (+ questions on significant benefit)

Quality: comparability and potency assays

Non-clinical: relevance of animal models for pharmacology and toxicology

Clinical: milestones of study design, including e.g. non-feasibility to conduct a comparative trial

**Qualification of biomarkers and early dialogue with Health Technology Assessment**
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Designation criteria

RARITY (prevalence) / RETURN OF INVESTMENT

Medical condition affecting not more than 5 in 10,000 persons in the Community (around 250,000)

Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment.

SERIOUSNESS

Life –threatening or chronically debilitating

ALTERNATIVE METHODS AUTHORISED

If satisfactory method exist the sponsor should establish that the product will be of significant benefit.
The designation process in the EU

Intent to file letter
Application submission
Validation
JOINT FDA/EMA?
Evaluation
Decision (European Commission)
Opinion

DAY 1
DAY 60 (COMP meeting)
DAY 90 (COMP meeting)
List of questions
Oral discussion

Orphan designation, Oct 2013
Committee for Orphan Medicines (COMP)

1 elected Chair (Prof Bruno Sepodes)

Vice chair: Lesley Greene (Patient Rep)

1 Representative per Member State

3 Patients’ Representatives appointed by Eur Commission

3 Members appointed by Eur Commission on proposal from Agency

1 Member for Norway, and 1 for Iceland
COMP responsibilities

- Give opinions on designation
- Advise Commission on establishment and development of a policy on orphan medicinal products
- Contribute to Protocol Assistance for Significant Benefit
- Assist on guidelines
- Assist Commission in international liaison
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Medical condition

EC Guideline (ENTR/6283/00)

- **Definition:**
  - Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome)

- Development plausible based on pathogenesis and pharmacodynamics

- Distinct pathophysiology, histology, clinical presentation

- *E.g.* *Mucopolysaccharidosis II*

- Different severities- stages *not acceptable*

- *E.g.* *active ulcerative colitis*
Accepting subsets?

Medically plausible subset:

Usually defined by characteristics of the drug that limit the use of the investigational medicinal product in only the subset of the patients with the disease:

- Subset is medically recognizable
- To restrict the use of the medicinal product in the population subset → scientific-based justification should be provided
- It is expected that the drug will not be effective/safe for the rest of patients population not included in the subset
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Definition: “A clinically relevant advantage or a major contribution to patient care”

- Significant benefit over authorised products (=satisfactory methods)
- Based on assumptions at the time of orphan designation
- Assumptions supported by available data/evidence supplied by applicant
- Sign benefit to be confirmed prior to marketing authorisation to maintain orphan status

Recommendation document on data for SB and plausibility
Examples assumption for significant benefit

Claims of better efficacy

Drug has a new mechanism of action

- Efficacy will have to be demonstrated
- Opens possibilities for drug combination

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?)
More on significant benefit

- Higher level of evidence required at time of marketing authorisation compared to time of designation (in line with stage of development)
- Comparative data **may be** necessary
- Claim on different mechanism of action should be accompanied by data on benefit
- Safety profile is usually characterised after the product is placed on the market
- Recommendation document on data for SB and plausibility
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Evolution orphan designations in the EU

- Approx 70% success rate
- Re-submission possible and common
Designations per prevalence

- less than 1 in 10,000: 12%
- between 1 and 3 in 10,000: 36%
- more than 3 in 10,000: 52%
Fee reductions

• Annually EU allocated special fund to cover fee reductions (approx. 6 million Euro)
• EMA has consistently kept maximum coverage for SMEs
• Academia and SME in 79% development of advanced therapies
• Policy reviewed annually, needed revision in 2013 according to current budget
Allocation funds for fee reductions (2012)

Use EU fund

- Marketing authorisation (60%)
- Protocol assistance (29%)
- Inspections (6.6%)
- Post-authorisation activities (3.9%)
Marketing authorisations

- **Positive opinions:**
  - 82 granted to date

- **Ongoing applications in review process:**
  - Approx. 24 applications in review process

- **Variations / line extensions in review process:**
  - Approx. 2 applications in review process

- **Negative outcomes for orphan MAA:**
  - More than 55 applications withdrawn
  - 10 negative decisions/refusals
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What information is public today?

Orphan designation

- COMP monthly report (after opinion)
- EU Commission Register of orphan designated medicinal products (after decision)
- Public summary of positive/negative opinion for orphan designation (after decision)
- Position on the removal of a designated orphan medicinal product from the community register (COMP monthly report)
- Position on review of criteria for orphan designation at time of MA (from 2010)
Information about review orphan status at time of authorisation

Summary of COMP position on the review on web
Includes information on
• prevalence
• seriousness
• and significant benefit if applicable
Link to EPAR and viceversa
Publication since 2010
Early dialogue regulators – health technology assessment bodies

- Increasing dialogue
- Joint EMA-HTA scientific advice / protocol assistance

International support to research in rare diseases

- Next EU research program (Horizon 2020)
- International Rare Diseases Research Consortium: Prioritisation of Research Funds, research policies; check www.irdirc.org
Orphan designation, Oct 2013
Many thanks

any questions?

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