Supporting orphan medicines development and addressing significant benefit requirements through protocol assistance

SME Info Day

Presented by Matthias Hofer on 17 November 2017
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Orphan environment after 16 years of EU orphan legislation

- Success of EU orphan legislation
- 128 orphan MAs until 2016 and rising
- ~ 75% require demonstration of SB
- Crowded areas, e.g. oncology, haematology, pulmonology
SMEs* develop a large proportion of orphan medicinal products

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<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Differences in characteristics between orphan and non-orphan medicines marketing authorisations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent variables</td>
<td>Non- orphan (n=475)</td>
</tr>
<tr>
<td>MAA outcome</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>101 (21%)</td>
</tr>
<tr>
<td>Positive</td>
<td>374 (79%)</td>
</tr>
<tr>
<td>Exceptional circumstances</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>457 (99%)</td>
</tr>
<tr>
<td>Yes</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Conditional approval</td>
<td></td>
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<tr>
<td>No</td>
<td>451 (97%)</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>Product type</td>
<td></td>
</tr>
<tr>
<td>Biologic</td>
<td>159 (33%)</td>
</tr>
<tr>
<td>Known substance</td>
<td>95 (20%)</td>
</tr>
<tr>
<td>New chemical entity (NCE)</td>
<td>221 (47%)</td>
</tr>
<tr>
<td>Therapeutic area</td>
<td></td>
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<tr>
<td>Endocrine and metabolic disorders</td>
<td>61 (13%)</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>150 (31%)</td>
</tr>
<tr>
<td>Neurologic and psychiatric disorders</td>
<td>65 (14%)</td>
</tr>
<tr>
<td>Oncology</td>
<td>55 (12%)</td>
</tr>
<tr>
<td>Other</td>
<td>193 (41%)</td>
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<tr>
<td>Company size</td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>234 (49%)</td>
</tr>
<tr>
<td>Medium</td>
<td>129 (27%)</td>
</tr>
<tr>
<td>Small</td>
<td>112 (23%)</td>
</tr>
</tbody>
</table>

* small, medium and large enterprises were categorised based on Scrips rankings

Study duration 2000-2013
Supporting orphan medicines development

Outline

- Protocol assistance with SB answer
- EMA support on orphan criteria
- Incentives
- Orphan legislation & EC Notice 2016
Legal background

   - COMP
   - Criteria for designation,
   - Incentives and procedure


Criteria for EMA orphan designation

1. Product intended for diagnosis, prevention or treatment
2. Serious condition (life threatening or chronically debilitating)
3. Affecting not more than 5 in 10,000 or insufficient return on investment
4. No satisfactory treatments or significant benefit over satisfactory methods
Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products

» Prevalence can equal 0

» Re-assessment of orphan criteria at time of variation may be requested

» Significant benefit discussion versus hospital preparations (magistral/officinal) of the same active substance
EMA and EU incentives

**Pre marketing authorisation**

- Fee reductions for regulatory procedures, extended for SMEs
- Access to centralised EU wide marketing authorisation
- Access to national and EU incentive programs (Horizon 2020)

**Post marketing authorisation**

- 10 (+2) year market exclusivity: protection against similar products
- Fee reductions for regulatory procedures
European regulatory input along drug life cycle

Clinical development:
- Pharm
- Non-clinical
- I
- II
- III
- MAA
- Post-mkt

ATMP Certification & Classification procedures

Scientific Advice/Protocol Assistance
- Orphan Drug Designation
- Review
- Variation

Paediatric Investigational Plan

Pharm

Supporting orphan medicines development
EMA support for orphan designation and maintenance

- EMA orphan designation website
- Pre-submission meetings (designation) and pre-validation meetings (review)
- COMP minutes (monthly on EMA website)
- OMAR – Orphan Maintenance Assessment Report (published with EPAR)
- Scientific publications
- Orphan designation queries via orphandrugs@ema.europa.eu / AskEMA system
- Protocol assistance queries via scientificadvice@ema.europa.eu / AskEMA system
Orphan condition

Use of biomarkers in the context of orphan medicines designation in the European Union

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Abstract
The use of biomarkers within the procedures of the Committee of Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) is discussed herein. The applications for Orphan Medicinal Product designation in the EU are evaluated at two stages. At the time of orphan designation application, the file undergoes an assessment to establish whether the proposed condition is a distinct and serious condition affecting not more than 5 in 10,000 people in the EU, and whether the product is plausible as a therapy for that condition. In cases where therapies already exist, the
Medical plausibility

- Nonclinical or preliminary clinical data
- Relevant models
- Data with the proposed product
- Relevant outcomes
Prevalence

- Clear case definition and consideration of duration

- Treatment indications: full point prevalence unless duration <12m

- Diagnosis and Prevention: annual number of eligible population
Significant benefit I

• DATA to support a comparative discussion

• Discuss your orphan product vis a vis the satisfactory products to show improved effects, add-on effects, targeting different aspects or populations, major contribution to patient care
Significant benefit II

**Clinically Relevant Advantage**

- Improved Efficacy
  - Use in Combination
  - Efficacy in Sub-populations
  - Better Clinical Effect

- Improved Safety
  - Less serious ADRs
  - Less severe ADRs
  - Less frequent ADRs
  - Treatment-sparing

**Major Contribution to Patient Care**

<table>
<thead>
<tr>
<th>Ease of use</th>
<th>Availability*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation/administration route</td>
<td>Shortage of supply</td>
</tr>
<tr>
<td>Dosing schedule</td>
<td>Centralized MA</td>
</tr>
<tr>
<td>Compliance</td>
<td>Other</td>
</tr>
</tbody>
</table>
Maintenance of orphan designation with significant benefit

• Observations on orphan MAAs in 2016
  • Products that received previous PA+SB kept orphan status
  • More important role for PA+SB
• The number of PA+ SB not rising
COMP priority is to foster early dialogue on SB via EMA PA procedure

Kind invitation for SME sponsors to use the tool of PA+SB
When should SB question be asked?

Clinical development

<table>
<thead>
<tr>
<th>Pharm</th>
<th>Non-clinical</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>MAA</th>
<th>Post-mkt</th>
</tr>
</thead>
</table>

Orphan Drug Designation | Review | Variation

SA | PA | PA+SB (initial and subsequent variations)
Iterative PA

- Cumulative body of evidence over time
- Updates to clinical development
- Changes in regulatory environment, e.g. EC notice 2016/C 424/03
- Changes in authorised competitors

- PA with SME fee reductions allow for iterative PA process
- SB question has to be part of PA procedure with other questions
- Combination with other initiatives, e.g. PRIME, HTA parallel advice
Does the COMP agree with the proposed strategy to demonstrate significant benefit of XYZ over currently authorised products?

- Link to clinical development plan discussed with SAWP/CHMP -> endpoints, comparators
- "Clinically relevant advantage" or "major contribution to patient care"
- Target population/proposed therapeutic indication -> best standard of care outlining authorised products of relevance
- Planned methodology (direct/indirect/bibliographical etc)
- Major contribution to patient care: specify and discuss patient-centric measurements
- Mechanism of action/ nonclinical evidence/improved PK profile/ "self-evidence"
Does the COMP agree with the proposed strategy to demonstrate significant benefit of xyz over currently authorised products?

- Link to clinical development plan discussed with SAWP/CHMP -> endpoints, comparators
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Who provides COMP SB answer?

COMP-SAWP coordinator as link to EU network

COMP peer review

COMP PA working group

COMP

more expertise, better peer-review and more time for critical discussion
Take home messages

✓ Orphan designation can be requested for free at any stage of development
✓ Orphan legislation sets out criteria and incentives
✓ European Commission Decision gives access to incentives
✓ Concept of “significant benefit”
✓ Significant benefit must be demonstrated by data
✓ Invitation to seek early regulatory dialogue with COMP via protocol assistance procedure

Supporting orphan medicines development
References (in order of appearance)


- EMA Sponsor’s guide to orphan designation (EMA orphan designation homepage: “How to apply for orphan designation”)


- Establishing medical plausibility in the context of orphan medicines designation in the European Union, Tsigkos S et al, Orphanet J Rare Dis. 2014 Dec 5;9:175


Any questions?

Further information

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