Regulatory perspectives on Duchenne muscular dystrophy (DMD) therapies

Presented by: Bruno Sepodes
Chairman of the Committee of Orphan Medicinal Products (COMP)
Member of the Committee of Human Medicinal Products (CHMP)
EU Charter of Fundamental Rights
Why an orphan regulation?

- Rare diseases → developing and marketing cost would not be recovered by the expected sales (products are called orphans, they do not have “developers”)
- Persons suffering from rare conditions deserve same quality of treatment as other patients
- Pharmaceutical industry does not develop medicines for rare diseases under normal market conditions
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)
Principles on orphan designation

Objective of Regulation (EC) No 141/2000

• provide incentives that stimulate research and development
• modify market conditions
• set up system of recognition for orphan medicines to be eligible for incentives:
  • Rarity (not more than 5 in 10,000)
  • Seriousness (life threatening / chronically debilitating)
  • Existence of alternative methods of treatment (significant benefit?)
Main characteristics orphan designation

- For medicinal products for human use
- 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
First lessons learned with the Orphan Regulation
Stakeholders & Development of orphan drugs in the EU

2000

Patients: few drugs

Industry: major ‘Big Pharma’ & development of *blockbusters*

Health care professionals/Academia: not involved

Regulators: at least 27 different procedures for MA

2010

Patients: 68 ‘active’ OD, > 800 products designations

Industry: major ‘small Pharma’ involvement – 2/3 of designations

Health care professionals/Academia: Sponsors of designations / some are MAH

Regulators: 1 procedure – centralised
Opportunities for patients

- Benefits for more than 30 millions of patients’ in the EU
- Potential benefits for neglected diseases
- Model of other geographic areas
- Study model for other more prevalent diseases
Stimulation of innovation

- Fusion proteins
- Monoclonal Antibodies
- Gene and cell therapy
- Oligonucleotides
- Tissue engineering
- etc.
Committee for Orphan Medicines (COMP)
Committee for Orphan Medicines (COMP)

- 1 elected Chair + EMA Scientific Secretariat
- 1 Representative per Member State
- 3 Patients’ Representatives appointed by Eur. Commission
- 3 Members appointed by European Commission on proposal from Agency
- 1 Member for Norway and 1 for Iceland

**Total**: 33 members + 2 non voting
COMP Mission

• Give opinions on designation
• Advise Commission on establishment and development of a policy on orphan medicinal products
• Assist Commission in international liaison
• Assist on guidelines
• Contribute to Protocol Assistance (esp. Significant Benefit)
COMP advisory role

Regular exchange of information with EC to identify high level research needs

Access to information on development

Regulators have direct contact experience with successes and failures

Direct access to a wealth of information

International collaboration between regulators (USA, Japan, Canada)
COMP responsibilities

“Dreamworks”

Idea

Hypothesis

Assumption or viable hypothesis

Proof / Evidence

COMP

CHMP
COMP

- Designates at any stage of development
- Resubmission is user friendly
- Occasionally might encourage dreams

“Gate opener”

CHMP

- Interrogative
- Adversarial
- If in doubt, negative
- Prudent and cautious
- Quality, Security and Efficacy

“Gate keeper”
Main characteristics orphan designation

For medicinal products for human use
Procedure free of charge
Can be requested at any stage of development
Sponsor can be either company or individual

• Established in the EEA (EU, Iceland, Liechtenstein, Norway)

European Commission Decision gives access to incentives
Designation criteria

RARITY (prevalence) / RETURN OF INVESTMENT
• Medical condition affecting not more than 5 in 10,000 in the EU (around 250,000 people)
• 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
**“Prevalence” criterion**

- Prevalence
  - \( \leq 5 / 10,000 \)
- Insufficient return on investment
  - (costs > expected revenues)

**“Seriousness” criterion**

- Life-threatening or chronically debilitating
- Life-threatening, seriously debilitating or serious and chronic

**“Existing methods” criterion**

- Available “methods” for diagnosis / prevention / treatment
  - **NO**
  - **YES**

- Significant benefit / non satisfactory
Prevalence of Designated Conditions

- 36% between 1 and 3 in 10,000
- 12% less than 1 in 10,000
- 52% more than 3 in 10,000
Incentives (I)

- Fee reduction / exemption
  - Extended incentives for Small and Medium Sized Enterprises (SMEs)
- Market exclusivity (10 years)
- Protocol assistance
- Community marketing authorisation
- National incentives (inventory from European Commission)
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 responsible for 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: 29.4%
- Inspections: 3.9%
- Post-authorisation activities: 6.6%
Incentives (II)

10-year market exclusivity (+ 2 if paediatric indication – completion investigation plan)

• Protection against
  – similar products
    – Molecular structure
    – mechanism of action
    – for same indication
  – Three derogations (access to market even if similar)
    – Sponsor’s consent
    – Lack of supply
    – Clinical superiority
Fostering orphan drug development

Medicines development
- Orphan designation and protocol assistance

Economic incentives
- Fee reductions and market exclusivity

Support to research
- COMP advisory role to EC on policy for orphan medicines

Regulation (EC) No 141/2000
Fostering orphan drug development

**Medicines development**
- Orphan designation and protocol assistance
- Scientific validation / guided development

**Economic incentives**
- Fee reductions and market exclusivity
- Economic viability

**Support to research**
- COMP advisory role to EC on policy for orphan medicines
- Knowledge “repository” and target identification – public regulatory intelligence
The designation process in the EU

- **Submission**
- **Validation**
- **Evaluation**

**Day 1**

**Day 60**

**Day 90**

**COMP Meeting**

- **List of Questions / Oral Explanation**
- **Opinion**

**Decision by the European Commission**

**Publication of a Public Summary of Opinion at the EMA website**

# Status of Orphan Applications

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2006</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>Total</th>
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<tr>
<td>Applications submitted</td>
<td>548</td>
<td>686</td>
<td>166</td>
<td>197</td>
<td>4</td>
<td>1601</td>
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<tr>
<td>Positive COMP Opinions</td>
<td>348</td>
<td>500</td>
<td>111</td>
<td>139</td>
<td>8</td>
<td>1106</td>
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<td>Negative COMP Opinions</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>18</td>
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<tr>
<td>EC Designations</td>
<td>343</td>
<td>485</td>
<td>107</td>
<td>148</td>
<td>0</td>
<td>1083</td>
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<td>Withdrawals</td>
<td>156</td>
<td>144</td>
<td>45</td>
<td>52</td>
<td>4</td>
<td>401</td>
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</tbody>
</table>
Status of Orphan Applications

- submitted
- positive opinions
- negative opinions
- withdrawals
- Commission decisions
Oprhan drug designations for DMD

<table>
<thead>
<tr>
<th>Active Substance</th>
<th>Disease / condition</th>
<th>Date of decision</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>2’-O-methyl-phosphorothioate oligonucleotide</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>15/02/2006</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>2-(4-(Diethylamino) phenyl)-6-methyl-2H-benzo[d][1,2,3] triazol-5-amine</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>25/07/2006</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>27/05/2005</td>
<td>Positive</td>
</tr>
<tr>
<td>5-(Ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>04/12/2008</td>
<td>Positive</td>
</tr>
<tr>
<td>Adeno-associated viral vector containing a modified U7 snRNA gene</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>27/07/2005</td>
<td>Positive</td>
</tr>
<tr>
<td>Adeno-associated viral vector containing modified U1 snRNA</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>08/10/2009</td>
<td>Positive</td>
</tr>
<tr>
<td>3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>26/02/2009</td>
<td>Positive</td>
</tr>
<tr>
<td>5-(Ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>26/04/2012</td>
<td>Positive</td>
</tr>
<tr>
<td>2'-O-methyl-phosphorothioate oligonucleotide</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>26/04/2012</td>
<td>Positive</td>
</tr>
<tr>
<td>2-(4-(Diethylamino) phenyl)-6-methyl-2H-benzo[d][1,2,3] triazol-5-amine</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>06/12/2012</td>
<td>Positive</td>
</tr>
<tr>
<td>3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>06/12/2012</td>
<td>Positive</td>
</tr>
<tr>
<td>5-(Ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>06/07/2012</td>
<td>Positive</td>
</tr>
<tr>
<td>Adeno-associated viral vector containing a modified U7 snRNA gene</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>26/04/2012</td>
<td>Positive</td>
</tr>
<tr>
<td>Adeno-associated viral vector containing modified U1 snRNA</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>08/02/2013</td>
<td>Positive</td>
</tr>
<tr>
<td>3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>19/03/2007</td>
<td>Positive</td>
</tr>
<tr>
<td>Recombinant fusion protein consisting of the extracellular portion of human activin receptor IIB linked to the human IgG1 Fc domain</td>
<td>Treatment of Duchenne muscular dystrophy</td>
<td>02/02/2010</td>
<td>Positive</td>
</tr>
</tbody>
</table>
COMP and CHMP roles

Judgement of Medical Plausibility

Evidence of positive Benefit-Risk

Prot. Assist

Knowledge

Evidence of Significant Benefit

COMP: Orphan Designation

Scientific Advice WP

CHMP: Marketing Authorisation

COMP: Orphan Designation
Protocol assistance

**Protocol assistance \(\cong\) scientific advice**

- Questions on quality-efficacy-safety
- Questions on significant benefit
- Company position required
- SAWP provides answers
  
  - CHMP adopts answers
  - COMP involved if issues on significant benefit arise
Protocol assistance

Provides Agency (EU Wide) advice on drug development

- clinical (90%; 51% exclusively)
- preclinical (44%)
- quality (27%)

Dedicated procedure for biomarker qualification

Following advice increases chances of marketing authorisation
  (RR 1.48; failure rate non compliant 70%; compliant 2%)
Significant benefit

Significant benefit: “A clinically relevant advantage or a major contribution to patient care”

- Based on **assumptions** at the time of orphan designation
- Significant benefit over “satisfactory methods”
- COMP to assess whether or not assumptions are 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

Clinically relevant advantage

- Drug has a new mechanism of action: clinically relevant advantage to be justified/demonstrated
- Opens possibilities for drug combination
- Alternative therapeutic option
- “complementary / better” safety profile

Major contribution to patient care

- Improvement quality of life (e.g. alternative to dietary restrictions)
- More “convenient” administration route
- Age adjusted formulation
Protocol Assistance - Procedure

40 or 70-day procedure (maximum)

- Pre-submission meeting highly recommended
- Discussion meetings with SAWP (in 50%)
  - Major disagreement
  - Need for additional information

Final advice letter adopted by CHMP

COMP involved if issues on significant benefit

Possibility of EMEA-FDA parallel advice
Type of requests

SA or PA requests can address different aspects (Quality, Safety, and/or Efficacy)

90% include clinical questions
- 51% related to clinical efficacy issues only
44% include pre clinical questions
27% include quality questions

Question on significant benefit almost always present if orphan drug and clinical questions
“Emerging” topics

Adaptive designs

• Modification of CT design at interim analysis, WITH control of type I error

Demonstration of positive benefit/risk with preliminary evidence (for a conditional marketing authorisation)

• Data necessary for authorisation
• Interim analysis, surrogate endpoints

Interim analyses

• Blinding
• Stopping rules
• Type I error control

Similarity issues

Biomarker qualification (!!!)
Critical issues about SA/PA

**Sponsor**

Ask question if
- Deviation from guidelines
- Uncertainty

Ask at the appropriate time
- Early
- Transition

Come back if necessary

Follow the advice!!

**Agency**

Involve experts if necessary (including patients) ...
conflicts of interest!

Feasibility

Flexibility (as much as possible)

Clear and comprehensive
Protocol assistance

<table>
<thead>
<tr>
<th>Year</th>
<th>Scientific Advice</th>
<th>Protocol Assistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>332</td>
<td>68</td>
</tr>
<tr>
<td>2011</td>
<td>347</td>
<td>79</td>
</tr>
<tr>
<td>2012</td>
<td>332</td>
<td>81</td>
</tr>
</tbody>
</table>
Authorisation of an orphan drug

Based on same standards as for non orphan products (quality / safety / efficacy)

Authorisation only centralised procedure

**CHMP responsible for assessment**

Authorisation within designated condition

More than one designation possible per product (independent incentives)
Specific requirements MAA (I)

Assessment of similarity **(WHEN ORPHAN IS ON MARKET)**

- Applies if other orphan medicines authorised for same designated condition
- Need to submit report in module 1.7
  - Molecular structure
  - Mechanism of action
  - Similarity of indication (“significant overlap of populations”?)
- Assessment by CHMP competent working party
- Final opinion by CHMP
- Similarity can be triggered any time before EC decision
- Proactive publication on ongoing procedures
Specific requirements MAA (II)

Maintenance designation criteria

• Report to orphan medicines section
  – At time of submission MA
  – Possible to update
• Need to address all designation criteria
• Standard set at time of authorisation
• Assessment by COMP; opinion after MA opinion by CHMP
Level of evidence

Of the granted marketing authorisations:

- 30 (45%) MAAs included double blinded randomised studies
- 27 (41%) MAAs included open label studies
- 8 (12%) MAAs were based on bibliographical data
- 1 (2%) MAAs were based on case reports

Of the rejected marketing authorisations:

- 15 (37%) MAAs included double blinded randomised studies
- 23 (56%) MAAs included open label studies
- 3 (7%) MAAs were based on bibliographical data
Significant benefit

- 49 (74%) of the granted MAs had to show significant benefit
- 27 (66%) of the rejected MAs would have had to show significant benefit
Protocol assistance and scientific advice

Granted MA n=71

Initial MAA n=112

Rejected MAA n=41

PA or SA?

Yes n=39
No n=32

OD n=38

OD n=28

PA or SA?

Yes n=22
No n=19
## Authorised products not showing SB

<table>
<thead>
<tr>
<th>Product</th>
<th>SB at orphan designation</th>
<th>At marketing authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ruconest</strong> (R. Human C1 inhibitor) MA 28/10/2010 Treatment of angioedema</td>
<td>Availability</td>
<td>Berinert (plasma derived C1 inhibitor) approved in 22 member states through mutual recognition</td>
</tr>
<tr>
<td><strong>Votrient</strong> (Pazopanib) MA 14/06/2010 Treatment of renal cell carcinoma</td>
<td>New mechanism of action and improved efficacy (preclinical data)</td>
<td>Pazopanib was unable to show a relevant clinical advantage compared to sunitinib or sorafenib</td>
</tr>
<tr>
<td><strong>Teysuno</strong> (Tegafur, gimeracil, oteracil) MA 14/03/2011 Treatment of gastric cancer</td>
<td>Improved effect</td>
<td>Teysuno+cisplatin not shown to be superior to 5-FU+cisplatin. Improved safety claimed could not be supported by data</td>
</tr>
<tr>
<td><strong>Cinryze</strong> (Human C1 inhibitor) MA 15/06/2011 Treatment of angioedema</td>
<td>Availability and longer duration</td>
<td>Availability; Berinert see above. The pharmacokinetic characteristics has not been translated to a relevant clinical advantage</td>
</tr>
<tr>
<td><strong>Ixario</strong></td>
<td></td>
<td>Prevalence criteria re-evaluated at marketing authorisation</td>
</tr>
</tbody>
</table>
Status of Orphan Marketing Authorisation Applications: 78 granted to date

**Adopted positive opinion**
- 1 awaiting decision

**On-going applications in review process**
- 27 applications in review process

**Variations / Line Extensions in review process**
- 3 applications in review process

**Negative outcomes for orphan MAA**
- 56 applications withdrawn
- 10 negative decisions/refusals
Where to have more information
Where to have more information

Rare disease (orphan) designations

This search allows you to find information on rare disease (orphan) designations. A designation from the European Medicines Agency's Committee on Orphan Medicinal Products (COMP) permits a pharmaceutical company to benefit from incentives from the European Union to develop a medicine for a rare disease such as a genetic disorder or a rare cancer. A large number of these diseases affect children and newborn babies. Once orphan designation is granted a medicine may be developed by the pharmaceutical company.

Browse A-Z

Search for active substance by letter and/or number:

ABCDEFGLMNOPQRSTUVWXYZ

View all

Download results to spreadsheet

Active substance | Disease / condition | Date of decision | Decision | Medicine name
--- | --- | --- | --- | ---
(1-Methyl)-2-nitro-1H-imidazole-5-y)methyl N,N'-bis(2-bromomethyl) diaminophosphate | Treatment of soft tissue sarcoma | 05/03/2012 | Positive | 
(-)-(2R)-(2-hydroxymethyl)14-4x-oxy)pheryl-4,4,4-trifluorobutane-1-sulfonate | Treatment of moderate and severe closed traumatic brain injury | 05/09/2008 | Positive | 

Include:
- Positive opinions
- Negative opinions
- Withdrawn
- Expired
EU/3/05/267

Orphan designation

Please note that this product was withdrawn from the Community Register of designated orphan medicinal products in July 2008 on request of the sponsor.

On 10 March 2005, orphan designation (EU/3/05/267) was granted by the European Commission to Pfizer Limited, United Kingdom, for (2)-N-[2-(diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidine)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxy succinate for the treatment of malignant gastrointestinal stromal tumours.

What are malignant gastrointestinal stromal tumours?

What is the estimated number of patients affected by the condition?

What treatments are available?

How is this medicine expected to work?

What is the stage of development of this medicine?

Opinions on orphan medicinal product designations are based on the following three criteria:

- EU/3/05/267: Public summary of positive opinion for orphan designation of (2)-N-[2-(Diethylamino)ethyl]-5-
Draft guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy

Document details

Reference number    EMA/CHMP/236981/2011
Status              draft: consultation open
First published     01/03/2013
Last updated        01/03/2013
Consultation start date 01/03/2013
Consultation end date    31/08/2013

Email address for submissions    cnswpsecretariat@ema.europa.eu

Summary
Recent advances in basic and clinical research have opened new perspectives for future therapeutic options in Duchenne and Becker muscular dystrophy. This guideline is intended to provide guidance for the evaluation of medicinal products in the treatment of these diseases, including study design, the choice of appropriate efficacy endpoints and the definition of reliable surrogate outcome measures.
Therapeutic approaches

- Limited to symptomatic treatment
- Medical and physical therapies to improve cardiac and respiratory functions
- Corticosteroids to improve muscle strength and function
- Other standards of care apply (multi-disciplinary teams)
- Therapies exist for orthopedic corrections

Currently no curative treatments for DMD exist.
<table>
<thead>
<tr>
<th>Other therapies <em>(none registered)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
</tr>
<tr>
<td><strong>Myostatin inhibition</strong></td>
</tr>
<tr>
<td><strong>Exon skipping</strong></td>
</tr>
<tr>
<td><strong>AON</strong></td>
</tr>
<tr>
<td><strong>Gene therapy</strong></td>
</tr>
<tr>
<td><strong>Stem cell : myoblast mesoangioblast transplantation</strong></td>
</tr>
<tr>
<td><strong>Utrophin upregulation</strong></td>
</tr>
<tr>
<td><strong>Myostatin inhibition</strong></td>
</tr>
</tbody>
</table>
Therapeutic advances in DMD

- **Gene therapy**

  *Introduction of a transgene coding for full-length or a truncated version of dystrophin complementary DNA (cDNA) in muscles*

- **Pharmacological therapy**

  *With the objective of restoring dystrophin expression or alleviate the DMD phenotype*

  - the stop codon read-through approach
  - the exon skipping approach
Specific considerations when developing products for the treatment of DMD

- Improvement of symptoms and improvement of disability in affected patients

- Modification of the natural course of the disease or increasing survival
Conclusions

- Orphan designation is centralised in the EU → EMA Committee (COMP); Applications to be submitted to EMA and assessed by COMP; designations by European Commission
- Free of charge; requirement: Sponsor is established in EU
- 99% agreement FDA-EMA regarding conditions
- Significant benefit exclusive to EU: justifications to support claims (even at early stage)
- Orphan drugs for DMD have been designated
- The review process for MA has started for some on the pipeline but still not concluded
- After first DMD orphan drug approval, significant benefit will take this into account
There is no disease so rare, that it does not deserve attention

Committee of Orphan Medicinal Products
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