CLINICAL TRIALS AND RARE DISEASES

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DISCLOSURE

- I RECEIVE UNRESTRICTED GRANTS AND TRAVEL HONORARIA FROM ACTELION, BIOMARIN, GENZYME PTC, SHIRE, SYNAGEVA.

- I HAVE NO ECONOMICAL OR STOCK MARKET INTERESTS ON ANY RARE DISEASE PRODUCT
Clinical trials are research studies that test how well new medical approaches work in people. Each study answers scientific questions and tries to find better ways to prevent, screen for, diagnose, or treat a disease. Clinical trials may also compare a new treatment to a treatment that is already available.

- 50% of Rare Diseases affect children
- 95% of Rare Diseases have no single approved drug treatment
- 35% of the deaths in the first year of life are due to rare diseases
- 30% of children with a Rare Disease will not live up to the 5th year of age
BETTER MEDICINE FOR CHILDREN

• 21% of Europeans are children
• Children are not just small adults
• > 50% of medicines used for children were never or incompletely studied in this population!!! (unlicensed or off label use)

• Situation prior the pediatric legislation
  • Absence of age – and development-related research and lack of suitable products
  • Recurrent off-labe use
  • Economical/ ethical factors
  • Experience prevails evidence

The Pediatric Regulation Study of the ENVI Committee
June 16 2015
THE EU PAEDIATRIC DRUG REGULATION

  – (Paediatric Drug Regulation) has the objective to improve the health of European children by facilitating the development, accessibility and safe use of new drugs for children aged 0 to 17 years, through clinical studies

• 2009: The first marketing authorization based on a completed PIP
• 2011: the first Pediatrics Use Marketing Authorisation (PUMA)
• 2013: the first Commission Report
• 2014: Review of the Commission Guidelines
• 2017: the 2nd Commission Report
The 2013 report - conclusions

- Promising signs, but further experience needed:
  - More than 600 Paediatric Investigation Plans in 2013 (now more than 800)
  - Around 350-400 clinical trials per year including children (0-18 years)
  - Proportion of clinical trials including children has increased, to approximately 10%
  - Increase in the PIP studies of neonates and infants; currently, 30% of the paediatric investigation plans include studies with neonates
  - Enpr-EMA - Network of paediatric research networks has been created by the EMA (18 research networks)
  - Mixed picture in the field of paediatric oncology
# Paediatric clinical trials

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
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<tbody>
<tr>
<td>Preterm newborns</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>327</td>
<td>82</td>
<td>2522</td>
<td>1552</td>
<td>3724</td>
<td>4331</td>
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<tr>
<td>Newborns</td>
<td>0</td>
<td>98</td>
<td>5</td>
<td>184</td>
<td>169</td>
<td>1348</td>
<td>2283</td>
<td>1496</td>
<td>1948</td>
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<tr>
<td>Infants and toddlers</td>
<td>530</td>
<td>119</td>
<td>20</td>
<td>54715</td>
<td>2212</td>
<td>13313</td>
<td>62224</td>
<td>13414</td>
<td>39615</td>
</tr>
<tr>
<td>Children</td>
<td>2683</td>
<td>706</td>
<td>270</td>
<td>5783</td>
<td>2721</td>
<td>21654</td>
<td>30826</td>
<td>23230</td>
<td>62979</td>
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<tr>
<td>Adolescents</td>
<td>435</td>
<td>36458</td>
<td>285</td>
<td>5801</td>
<td>4831</td>
<td>20206</td>
<td>22680</td>
<td>17300</td>
<td>42353</td>
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<tr>
<td>Sum of above</td>
<td>3648</td>
<td>37381</td>
<td>580</td>
<td>66810</td>
<td>10015</td>
<td>59043</td>
<td>119565</td>
<td>59164</td>
<td>151226</td>
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<tr>
<td>Reference: number of paediatric trials</td>
<td>340</td>
<td>362</td>
<td>342</td>
<td>406</td>
<td>392</td>
<td>372</td>
<td>401</td>
<td>337</td>
<td>432</td>
</tr>
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</table>
NUMBER OF APPROVED ORPHAN DRUG BY YEAR

Data Source: FDA Orange Book
Source: FDA Law Blog
## EU ORPHAN DESIGNATION BY THERAPEUTIC AREA

<table>
<thead>
<tr>
<th></th>
<th>2000-2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
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<tbody>
<tr>
<td><strong>Applications received</strong></td>
<td>EMA/279601/2010</td>
<td>2012 Report on the State of the Art of Rare Disease Activities in Europe</td>
<td>2013 Report on the State of the Art of Rare Disease Activities in Europe</td>
<td>2014 Report on the State of the Art of Rare Disease Activities in Europe</td>
</tr>
<tr>
<td><strong>Applications which received positive opinions on orphan designations</strong></td>
<td>1113</td>
<td>166</td>
<td>197</td>
<td>201</td>
</tr>
<tr>
<td><strong>Number of application which received marketing authorisation per year</strong></td>
<td>/</td>
<td>5</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total number of application which received marketing authorisation</strong></td>
<td>63</td>
<td>68</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td><strong>Oncology</strong></td>
<td>45.2%</td>
<td>41%</td>
<td>39&amp;</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Musculoskeletal and nervous system</strong></td>
<td>12.4%</td>
<td>12%</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td>9.7%</td>
<td>7%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>9.7%</td>
<td>12%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Cardiovascular and respiratory</strong></td>
<td>9.4%</td>
<td>8%</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td><strong>Anti-infectious</strong></td>
<td>3.3%</td>
<td>4%</td>
<td>6</td>
<td>/</td>
</tr>
<tr>
<td><strong>haematology</strong></td>
<td>/</td>
<td>3%</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>10.3%</td>
<td>13%</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>
KEY CHALLENGES FOR STUDY DESIGN AND STATISTICAL ANALYSIS OF SMALL HETEROGENEOUS POPULATIONS

CT FOR RARE DISEASES INVOLVE VERY SMALL POPULATION OF PATIENTS. This implies the use of non homogenous groups for age and phenotypes which will be finally may negatively impact the understanding of the results of the trial itself.

THE LARGE VARIATION IN SEVERITY, STAGE, IRREVERSIBILITY AND AGE leads to a very large range at baseline for many measures of efficacy, making it hard to detect clinical important efficacy changes.

THE LACK OF QUANTITATIVE NATURAL HISTORY INFORMATION and difficulty using this information in analyzing clinical trial data,
The complexity of disease multitorgan manifestations requires more than one clinical endpoint for one domain to assess an effective treatment,

the accurate analysis of safety data due to the fragmented approach to safety reporting that will miss lower frequency safety events in small populations.

the interpretation or calibration of the relative magnitude and clinical meaningfulness of endpoint changes in terms of established minimal important clinical differences to understand what effective really means.

KEY CHALLENGES FOR STUDY DESIGN AND STATISTICAL ANALYSIS OF SMALL HETEROGENEOUS POPULATIONS
WHAT DO WE NEED TO IMPROVE CLINICAL TRIALS IN RARE DISEASES

**BETTER CONTROLLED STUDY DESIGNS ALLOW BETTER ANALYSES:** The traditional randomized controlled studies are not suited for small populations. It is difficult to create comparable groups and to adequately assess change between variable groups. Controlled rigorous designs that allow within-patient comparisons and treat all subjects will assess therapies more accurately.

**IMPROVED NATURAL HISTORY STUDY DESIGNS AND ANALYSES** would allow more efficient interpretation of clinical studies: The lack of natural history information provides little insight regarding how to choose endpoints or how to design and power a clinical study. An improved paradigm for conducting a cost-efficient natural history study and to allow the integrating natural history observational data into clinical trial analyses can enhance the data set value.

**BETTER STATISTICAL ANALYSES WILL DEPEND ON MORE EFFICIENT AND EFFECTIVE ENDPOINT DESIGNS FOR EVALUATION OF THE BROADER BASIS FOR CLINICAL EFFICACY:** Single clinical endpoints do not adequately cover the breadth of disease. Novel approaches to combine independent multi-domain analysis to better assess efficacy are necessary.
Key challenges for study design and statistical analysis of small heterogeneous populations

**INTERPRETATION AND COMBINATION OF CLINICALLY IMPORTANT CHANGES IN ENDPOINTS REQUIRES BETTER USE OF MINIMALLY IMPORTANT DIFFERENCES (MID’S) OR RESPONDER ANALYSES:** A systematic approach using natural history and comparable disease information should be developed to an efficient method for translating MID’s from common diseases to rare diseases. The MID’s may allow the interpretable combination analysis of clinically important changes in multiple domains.

**SAFETY EVALUATION IN SMALL POPULATION STUDIES NEEDS TO INTEGRATE KNOWN ADVERSE PHYSIOLOGIES IN DATA COLLECTION AND ANALYSIS:** Adverse events are the key tools for safety assessment. Individual symptoms often obscures and fails to capture underlying pathophysiology. In contrast with big numbers study, A small study cannot readily detect recurrent patterns of adverse event responses based existing methods of safety reporting and analysis which could be dramatically improved.
AIMS OF A COORDINATED CLINICAL TRIAL SETTING INSIDE THE ERN (TECHNICAL POINTS)

- Development of cost-efficient novel, rigorous controlled STUDY DESIGNS and relevant analyses that are effective in studying efficacy in heterogeneous, small populations.

- Design of NATURAL HISTORY STUDIES to capture clinical information more cost-efficiently and to help inform on the optimal approach to treatment development.

- Establishment and use of strategies to more efficiently analyze a broader array of CLINICAL ENDPOINTS for a more comprehensive set of affected clinical domains, set up strategies to identify VALUABLE BIOMARKERS.

- Development and evaluation of novel more efficient TOOLS FOR SAFETY evaluation using adverse physiology-related groups and allow the integration of known medical physiology into analyses of safety information to detect recurrent adverse physiologies.
AIMS OF A COORDINATED CLINICAL TRIAL SETTING INSIDE THE ERN (POLITICAL POINTS)

To collaborate with Regulatory Agencies (EMA) and EU (i.e. reg. EU 536/2014, directive 2001/83/EC etc.) to determine a guideline for the setting of Clinical Trial in Rare Diseases.

To collaborate to identify a policy for the scientific independency of the Clinical Trial setting and favour a cosponsorship of Academia in the field of Rare Diseases.

To favour interaction with Member States to uniform the Clinical Trial policy for Rare Diseases.

To collaborate with Member States Agencies to speed up the availability of products to patients affected by Rare Diseases.

To collaborate with Family Association to empower patients in participating and counselling the Clinical Trial.

To collaborate with pharmaceutical industries and networks to achieve better results.
Thanks for your attention

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