Challenges in the Translation of Clinical Outcome Measures For Protein Replacement Therapy in Dystrophic Epidermolysis Bullosa

Lawrence Charnas, MD, PhD
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Disclosures

• Lawrence Charnas is a full time employee of Shire, plc.

• Lawrence Charnas holds stock in Shire, plc.
Objectives Of This Presentation

- Outline Challenges of Protein Therapeutic Development
- Clarify general challenges in translation of Clinical Outcome Measures in drug development
- Highlight some specific challenges of Clinical Outcome Measures in Dystrophic Epidermolysis Bullosa
Consider These Four Areas of Pharmaceutical Development

1) Pharmaceutical agent
   - Chemistry, Manufacturing and Controls (CMC)

2) Demonstration of Safety
   - Preclinical studies
   - Clinical Trials
   - Post Approval Safety Experience

3) Demonstration of Efficacy
   - Preclinical studies
   - Early clinical trials
   - Late (registration) clinical trials
   - Post approval outcomes

4) Post approval period
   - Country by country availability
   - Healthcare outcomes have influence
**Translational research** is concerned with moving basic discoveries from concept into clinical evaluation and is often focused on specific disease entities or therapeutic concepts.

**Clinical Outcomes** Impact The Entire Range Of Planned & Actual Human Experience

*Challenges and Opportunities Report - March 2004*

[Link](http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm)
Clinical Outcome Measures May Differ By Stage Of Development

### Phase 1
- **Safety- NHV**
- Pharmacokinetics (PK)
- Pharmacodynamics (PD)

### Phase 2
- **Safety-patients**
- PK/PD
- Dose finding
- Endpoints
- Efficacy

### Phase 3
- **Confirmatory efficacy**
- Clinical meaningfulness
  - Long term safety
  - Expanded PK/PD

### Phase 4
- Post Marketing Commitments (PMC)
- Additional trials
- Health Outcomes Research & information to consider
  - Safety-Pharmacovigilance

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**Clinical Outcomes**
Demonstration of Safety As A Clinical Outcome Measure

• Preclinical studies
  • Establish safety margins & dose selection
  • Permissive to proceed to clinical trials and inform known safety risks

• Clinical Trials
  • Sponsor control of exposure
  • Sponsor control of reporting and analysis (regulations in place)
  • Benefit:Risk ratio analyzed as presented
  • Sufficient information (size, duration) for confidence in human safety for trials to progress

• Real world experience after approval
  • Less control of exposure of pharmaceutical to individuals (physician control)
    – Potentially different eligibility criteria, concomitant medication use and compliance
  • Reporting to Agencies by sponsors is still highly regulated
    – Information to sponsors is less controlled
  • Longer term exposure than clinical trials
  • Disease modification which may allow expression of “silent” disease features
  • Potential for Investigator Sponsored Trials without sponsor oversight
  • Case reports - adverse findings, non-efficacy, unexpected benefit
Meeting Objectives Of “Efficacy” Is Stage Specific

- Pre-Clinical
  - Rationale for exposure of risk of New Molecular Entity (NME) to patients
  - Efficacy in animal models does not always translate to clinical benefit
- Early clinical trials
  - Phases I & II - clinical outcomes of safety, biomarkers for pharmacodynamic and dose finding effects for biological activity
    - Clinical outcome measures are not necessarily clinical efficacy
    - Clinically meaningful outcomes are desirable but not necessary
- Late (Phase III) clinical trials
  - 1º Outcome – Confirmatory trial, Clinically meaningful, accepted by agencies
  - 2º Outcomes – Biomarker or Clinically Meaningful endpoints
  - 3º Outcomes – exploratory
    - Biomarker or Clinically Meaningful endpoints
    - Development data in novel population for subsequent studies
- Post approval outcomes
  - Exposure of pharmaceutical to individuals with potentially different characteristics than in clinical trials
  - Longer term exposure than clinical trials for other benefits and disease modifying impact
  - Potential for disease modification may change disease trajectory
Endpoint Challenges In A DEB Trial

• Background-National Epidermolysis Bullosa Registry
  • NEBR (J.-D. Fine, P.I.) documents cumulative disability
  • Excellent description of long term complications
  • Categorical outcomes with Kaplan-Meier presentation
    • i.e. Pseudosyndactyly, malnourished, SCC (yes/no)

• General regulatory requirements for endpoints
  • Defined, measurable, reproducible, statistically significant
  • Documentation GCP compliant
  • Endpoints should be appropriate for stage of program

• Which endpoints in the systemic disease of DEB are clinically meaningful
  • Wounds – which ones, measurements?
  • Enteric complications of DEB – how to measure?
  • Systemic effects in DEB – anemia, nutrition, well being?
Practical Challenges In Translational Outcomes In DEB

- Changes visible/measurable in time course of clinical trial
  - Typically 6 – 12 months
- Sample size calculation dependent upon documentation of short term variability (Standard deviation estimate) and expected treatment effect
- Trial design dependent upon current understanding of disease in standard medical practices - “Natural History”
- Venous access – IV delivery of rC7, routine safety monitoring in context of clinical trial
Challenges in Translation Of Endpoints In The Real World

• Successful Registration does not guarantee post approval availability
  • Availability determined by regulatory and reimbursement processes in country by country manner
  • Pre-approval sales and/or compassionate use in some countries
  • Influence of healthcare outcomes measures on reimbursement
    • UK-NICE (National Institute of Comparative Effectiveness)
    • US – shifting toward a European model
  • Differences remain between some countries/regions despite International Conference on Harmonization (ICH)
  • Different expectations of supply of pharmaceutical after clinical trial is complete
### Differences In US & EU Pediatric Regulations Create Challenges

<table>
<thead>
<tr>
<th>Development</th>
<th>USA *BPCA</th>
<th>USA *PREA</th>
<th>EU Paediatric Regulation EC No 1901/2006</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Voluntary</td>
<td>Mandatory if likely to be largely used and/or meaningful benefit</td>
<td>Mandatory (optional for off-patent), &amp; compliance check for MAA</td>
</tr>
<tr>
<td>Instrument</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>¹Pediatric Study Plan (PSP) (waivers/deferrals allowed)</td>
<td>¹Pediatric Study Plan (PSP) (waivers/deferrals allowed)</td>
<td>Paediatric Investigation Plan (PIP) (waivers/deferrals allowed)</td>
</tr>
<tr>
<td>Applicability</td>
<td>Ages likely to be studied</td>
<td>Ages likely to be studied</td>
<td>Pre-specified age groups</td>
</tr>
<tr>
<td>Timing</td>
<td>¹EoP2 thru post-marketing</td>
<td>¹Data with NDA submission</td>
<td>End of Phase 1</td>
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<tr>
<td>Reward</td>
<td>6-mo exclusivity</td>
<td>none</td>
<td>6-mo patent, or 2-yr exclusivity for Orphan</td>
</tr>
<tr>
<td>Orphan</td>
<td>Yes</td>
<td>Only exempted for designated indications</td>
<td>Yes</td>
</tr>
<tr>
<td>Coverage</td>
<td>Drugs only</td>
<td>Drugs and Biologics</td>
<td>Biologics and Drug</td>
</tr>
<tr>
<td>Decision</td>
<td>FDA/Review Division</td>
<td>FDA/Review Division</td>
<td>EMA/PDCO</td>
</tr>
</tbody>
</table>

¹FDA Draft Guidance on Pediatric Study Plans July 2013

*Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) became permanent as of 2012 FDASIA*
Limited Availability of Clinical Outcome Measure Data In Specific Populations Creates Challenges In PIP Design & Implementation

<table>
<thead>
<tr>
<th>Pediatric Subsets (ICH E11)</th>
<th>Which Clinical Outcome Measures in Future DEB Trials/PIP compliance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm newborn Infants</td>
<td></td>
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<tr>
<td>Infants and Toddlers (1 month to 23 months)</td>
<td></td>
</tr>
<tr>
<td>Children (24 months to 35 months)</td>
<td></td>
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<tr>
<td>Children (3-11 years 11 months)</td>
<td></td>
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<tr>
<td>Adolescents (12 -18 years)</td>
<td></td>
</tr>
</tbody>
</table>

- Pain measures, diet changes, functional normality are all age dependent
- Clinical trial will be needed to study if earlier age of therapy changes accumulated disability over time.
Conclusion

• Clinical Outcome Measures include safety data, pharmacodynamic and other biomarker data as well as clinically meaningful (primary endpoint) outcomes
• Collection and interpretation of these outcome measures changes with the stage of drug development and continues well beyond initial approval
• Country and Region specific differences have the potential for a significant influence on trial design and implementation of clinical outcome measures
• Improvement in data regarding each specific outcome measure in all relevant patient populations better inform the process