Harmonizing clinical trials for Biogenerics

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What is Therapeutic Similarity?

Similarity is defined as:

- “the product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and,
- “there are no clinically meaningful differences between the test product and the reference product in terms of safety, purity, and potency of the product”
Biosimilarity Complexity: complete characterization: mission impossible

<table>
<thead>
<tr>
<th>(Analytical) techniques for monitoring protein structure</th>
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<tbody>
<tr>
<td>UV absorption</td>
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<tr>
<td>Circular dichroism spectroscopy</td>
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<tr>
<td>Fourier transform IR</td>
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<td>Fluorescence spectroscopy</td>
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<tr>
<td>NMR spectroscopy</td>
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<tr>
<td>Calorimetric approaches</td>
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</tbody>
</table>

Bio-Assays
- Immunochemical assays
  - ELISA
  - Immuno precipitation
  - Biosensor (SPR, QCM)
- Potency testing
  - In cell lines
  - In animals

Chromatographic techniques
- RP-HPLC
- SEC-HPLC
- Hydrophobic interaction HPLC
- Ion-exchange HPLC
- Peptide mapping

Electrophoretic techniques
- SDS-PAGE
- IEF
- CZE

Field flow fractionation
Ultracentrifugation
Static and dynamic light scattering
Electron microscopy
X-ray techniques
Mass spectrometry

The quality is in the process.
Biogenerics are like similar, not identical, to original product

*Biogenerics are similar……...*  
*...Not Identical*

Different cell lines  
Different mfg process

Small differences in substrate & mfg process may affect safety and clinical efficacy
Regulatory Framework

- No Harmonized Worldwide Regulatory Framework
- Small molecule generics model not appropriate
- In many regions limited or no regulatory process
- EU currently the most advanced region
- US legislation relatively new
- RoW evolving
Regulatory & Payers challenges

Interchangeability/substitution

- Interchangeable
  - Similarity to reference product
  - Will produce the same clinical result in any given patient
  - For a product administered more than once, the safety and reduced efficacy risks of alternating/switching are not greater than repeated use of reference product without alternating/switching

- Automatic substitution = switching products without the prescribing physician’s knowledge

- Interchangeability = switching between different products under physician supervision

- Automatic substitution and interchangeability will have a major impact on the market penetration of these medicines
  - Will require aggressive marketing strategies akin to those used with branded products are necessary for market penetration
• European Medicines agency (EMEA) guideline on how to obtain a licence for a biogeneric:
  – Main requirement for manufacturer is to prove ‘comparability’ for primary indication with a licensed product (which must already be licensed on the basis of a full registration dossier)
  
  – Comparability exercise includes non-clinical and clinical requirements
  
  – If a license is granted, efficacy for other indications may be extrapolated
A 351(k) application must include information demonstrating biosimilarity based on data derived from:

- Analytical studies demonstrating that the product is “highly similar” to the reference product notwithstanding minor differences in clinically inactive components;
- Animal studies (including the assessment of toxicity)
- A clinical study or studies (including the assessment of immunogenicity and PK or PD) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed.
- FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) application.
Regulatory approaches for biotherapeutics following licensing of the originator

- **Full licensing application**
  - Full dossier (no data reduction)
  - Stand alone product

- **Abbreviated licensing pathways**
  - **Biosimilar approach**
    1) Full quality dossier with a comparability exercise
    2) Reduced non-clinical and clinical data (comparative)
  - **Clinical comparability approach**
    1) Full Quality dossier
    2) Reduced nonclinical data
    3) Clinical data (head to head comparison with reference product)
  - Biosimilar product
  - Clinically comparable product
  - Extrapolation of indications possible on justification
  - No extrapolation of indication(s) To be considered
Biosimilar Broad Strategy

- Prioritize markets based on combination of regulatory approvability and commercial potential
- Each country is on its own maturity curve in terms of the biotherapeutic regulatory process
  - Engage with RA at earliest
- Clinical Strategies Must Focus on Patient Selection and Appropriate Clinical Endpoints
- Analytical and non-clinical functional similarity to the innovator biologic established in a stepwise process during development
  - **minimises need for extensive clinical evidence of similarity**
Similarity Comparability Exercise

Innovator Products
Step-wise testing based on:

- Molecular complexity
- Manufacturing process
- Degree of characterization
- Clinical indications
- Production history
- Availability of safety and clinical data

Quality Studies
- Physicochemical tests
- Bioactivity/Potency assays
- Stability

Non-clinical Studies
- PK/PD studies
- Toxicology

Clinical Studies
- Efficacy
- Immunogenicity

Biogeneric Products
Comprehensive studies due to:

- Complex structure
- Different cell line and production process
- Different characterization and release tests
- Extensive safety and clinical data not available

ICH Q5E: Quality attributes are highly similar (not necessary identical).
Demonstrating similarity - Basics

If there are *residual uncertainties* after:

- Conducting structural and functional studies
  - Animal toxicity studies
  - Human PK and PD studies, and
  - Immunogenicity assessment
- Then consider what comparative clinical safety and effectiveness data may be needed
- I suggest to encourages extensive consultation with agency
Clinical PK/PD Assessment

• Human PK and PD studies fundamental components of similarity
• Establishing a similar human PK and PD profile may justify limiting subsequent clinical testing
• Import considerations:
  – Clinically relevant PK and PD parameters
  – Populations, dose(s), and route of administration that are the most sensitive to detect differences in PK and PD
  – Sensitive and relevant assays
Similarity – Global Clinical Challenges:

• Key challenges relevant to clinical development of biotherapeutics:
  – Maximizing patient recruitment while choosing the most sensitive patient population, most likely to respond to therapy
  – Expediting clinical trials and minimizing cost – sample size & geographic spread
Addressing Recruitment Challenges:

• **Patient recruitment –**
  – Accelerate by choosing (sites) countries in which to conduct clinical studies with greatest unmet need for the biotherapeutic
  – Engage with KOL’s to get their acceptance on end points and outcomes
  – Selecting markets where regulatory agencies are willing to work with companies to bring such products into market earlier - representative population
  – Investing in education of both investigators and their patients on potential benefit of participating in a bio-therapeutic trial
Key to Clinical Outcome-Right Patient Population

• Selecting an appropriate patient population and sample size -
  – Primary indication with which to demonstrate clinical similarity is critically important to obtain regulatory authority buy-in upfront
    • Further secure extrapolation to other indications for which the reference product is approved
  – Benefits of earlier commercialization may be realized if participation in clinical trials in such countries is a regulatory pre-requisite
Innovation in Clinical End-points

Incorporating the right clinical endpoints

- Including biomarkers or other surrogates predictive of clinical efficacy (obviates extensive and final end-point study)
- Establishing physicochemical, functional and nonclinical \textit{in vivo} comparability to decrease the amount of clinical data required

Disclaimer: incorporating all these requirements into a global clinical development plan is still challenging for integrated development
Addressing Challenges On Clinical Endpoints

- Agreement on endpoints with regulatory authorities early in development process
- Patient population sufficient to establish equivalence with innovator drug
- Optimised by use of surrogate biomarkers
- Encouraging investigators to participate in studies incorporating continued exploration of the use of such surrogate biomarkers and endpoints
Addressing Clinical Challenges On Design

• Integrated protocol designs:
  – Best applied when medical practices & Agency evaluators are sufficiently experienced and accept this approach
  – Allow data from multiple trial phases comparing the test drug to innovator product to be merged into one protocol
  – Does not necessarily reduce the cost of or the number of patients needed for the trials, but it can save some time

• These strategies may include effective KOL engagement, device improvements, and patient support programs
Immunogenicity Assessment

• Prospectively define clinical immune response criteria e.g., definitions of significant clinical events
• Consider the immunogenicity issues observed with the reference product

• Follow-up period based on time course:
  – Time course for generation of immune responses
    • e.g., development of neutralising antibodies, cell-mediated immune responses and expected clinical sequelae
  – Time course of disappearance of the immune responses and clinical sequelae following cessation of therapy
  – The length of administration
    • e.g., minimal follow-up period for chronically administered agents- expected is one year
## Immunogenicity for GH

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Cell Line</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humatrope</td>
<td><em>E. coli</em></td>
<td>481 patients, 2% with Ab &gt; 2mg/L</td>
</tr>
<tr>
<td>Nutropin</td>
<td><em>E. coli</em></td>
<td>0/232 with Ab &gt; 2mg/L</td>
</tr>
<tr>
<td>Protropin</td>
<td><em>E. coli</em></td>
<td>26,000 treated, 0.4% with Ab &gt; 2mg/L,</td>
</tr>
<tr>
<td>Norditropin</td>
<td><em>E. coli</em></td>
<td>0/358 with Ab &gt; 2mg/L, 12 months</td>
</tr>
<tr>
<td>Saizen</td>
<td><em>Mouse cells</em></td>
<td>1/280 with Ab &gt; 2mg/L</td>
</tr>
<tr>
<td>Genotropin*</td>
<td><em>E. coli</em></td>
<td>419, 1.9% with Ab; 0 &gt; 2mg/L</td>
</tr>
<tr>
<td>Omnitrope</td>
<td><em>E. coli</em></td>
<td>134, 1% with no effect on efficacy</td>
</tr>
<tr>
<td>Valtropin</td>
<td><em>Yeast</em></td>
<td>98, 3% with no effect on efficacy</td>
</tr>
</tbody>
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Efficacy & Safety Assessment

• Comparative safety and effectiveness data if there are ‘residual uncertainties’ about similarity

• Factors that may influence type and extent of clinical safety and effectiveness data:
  – Are non-clinical data predictive of clinical outcomes?
  – Is the MOA well understood?
  – Are human PK or PD predictive of clinical outcomes?
  – The extent of clinical experience with the reference product
    • Are there multiple versions on the market?
  – The extent of clinical experience with the proposed product
Totality of Evidence

• Key question
  – How similar does product need to be to be considered ‘similar’
  – (Generic question: Is it equivalent?)

• Given complexities of products question can only be answered on a case-by-case basis

• Start with physicochemical characterization and \textit{in vitro} activity
  Ensure characterization is maintained throughout development program to ensure data base build to support QbD approach

• Assess data to guide preclinical study requirements

• Assess preclinical data to guide clinical study requirements

• Well thought through & executed clinical plan!
Questions?