Scientific Challenges for Development of Biosimilar Monoclonal Antibodies

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Presentation outline

- Biosimilars – Definitions and Concepts
- Regulatory Framework
- Bioanalytical assay development considerations
  - PK and Immunogenicity assay development
- Summary
What does Biosimilar or Biosimilarity means?

- The biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and
- There is **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity and potency of the product.
- Neither the EU legislation nor the EMEA CHMP guidelines provides a definition of a biosimilar other than it is a product comparable in **quality, safety and efficacy** to a reference product.
- The **acceptable differences** between biosimilar and reference products in these three major attributes are not stated.
A 351(k) application must include information demonstrating biosimilarity based on data derived from:

- **Analytical studies** demonstrating that the biological product is “highly similar” to the reference product notwithstanding minor differences in clinically inactive components;

- **Animal studies** (including the assessment of toxicity); and

- A **clinical study or studies** (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 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.*
No “one size fits all” assessment:

FDA scientists will evaluate the applicant’s integration of various types of information to provide advice on scope and extent of develop plan and, ultimately, an overall assessment that a biological product is (or is not) biosimilar to an approved reference product.
Accurate and precise bioanalytical data is critical to establishing comparability between biosimilar and innovator products.
Monoclonal Antibodies

Monoclonal antibodies have been established as a major product class of biotechnology-derived medicinal products.

Different mAb products share some properties, e.g. being cytotoxic to their target, or neutralizing a cytokine, but differ in aspects like the mechanism of action.

They are structurally complex, and may have several functional domains within a single molecule, depending on the Isotype (antigen-binding region, complement-binding region, constant part interacting with Fc receptors).
Monoclonal Antibodies

Enbrel®
Etanercept

Remicade®
Infliximab

Infliximab is efficacious in Crohn’s disease\(^1\), but etanercept is not\(^2\)


Source: Sherman, R. Biosimilar Guidance Webinar
Bioanalytical Testing (PK/TK and Immunogenicity testing) – Scientific and Regulatory Gap

- Comparability Studies
  - EMA Bioanalytical Guidance
  - EMA Immunogenicity Guidance
  - FDA Bioanalytical Guidance
  - FDA Immunogenicity Guidance
  - White papers
Bioanalytical Testing (PK/TK Assay)
Design of Bioanalytical Testing (One PK/TK Assay)

- Standard curve: Innovator or Biosimilar
- QCs: Innovator and Biosimilar
- Custom reagents: Capture and detection antibodies generated against both innovator and biosimilar. Reagents should be well characterized and cross-verified. Celerion has observed greater than >30% differences between innovator and biosimilar due to differences in reagents.
- Assay parameters to be investigated during method development:
  - Accuracy and precision
  - Sensitivity
  - Selectivity
  - Specificity
  - Stability

*State of the art technology should be utilized for PK/TK assays*
PK/TK Assay (Pre-study validation)

Accuracy
- Innovator and Biosimilar QCs at same level
- +/- 20% RE and 20%CV (25% at LLOQ); Total error 30% (40% at LLOQ)

Precision

Selectivity
- Innovator and Biosimilar
- 80% of the matrices within 20% RE

Sensitivity
- Innovator and Biosimilar
- 25% recovery at LLOQ

Stability
- Innovator and Biosimilar
- 20% RE
PK/TK Assay (In-study validation)

- **QCs**
  - Innovator and Biosimilar QCs
  - 4-6-20 rule

- **Sample analysis**
  - Ideally should be set up for simultaneous analysis of Biosimilar and Innovator

- **ISR**
  - Perform ISR for both Innovator and Biosimilar

- **Stability**
  - Samples (both Innovator and Biosimilar) should be within their respective stability period
If two assays are used (one for Biosimilar and one for Innovator):

- Same platform?
- Same sets of reagents?
- Same assay conditions?
- Cross-validation – use of correction factor

Results:

- Challenges in interpreting the results
- Investigations - source of the differences
  - Reagents?
  - Platform?
  - Biosimilar is NOT similar?
Bioanalytical Testing (PK/TK and Immunogenicity Assays) – Scientific and Regulatory GAP

Comparability Studies

- EMA Bioanalytical Guidance
- EMA Immunogenicity Guidance
- FDA Bioanalytical Guidance
- FDA Immunogenicity Guidance
- White papers
Bioanalytical Testing (Immunogenicity Assay)

ONE

TWO
Design of Bioanalytical Testing (Immunogenicity Assay)

- Blocked ELISA well

**Detection Innovator**
- Label
- Color / Light
- Substrate

**Innovator**

**Detection Biosimilar**
- Label
- Color / Light
- Substrate

**Biosimilar**

**Blocked ELISA well**
Typical Work Flow

Screening Assay

Confirmation (Specificity)

Screen Positive? Yes

Specificity? Yes

Characterize Ab Response
(Titer Determination)
(Ab Isotype, Ig Subclass)

Neutralizing Ab Testing
(Cell Based Assay)

No

Report as Negative

Specificity? No

Report as Negative

Yes

Screen Positive? No

Report as Negative
Immunogenicity Assay (Pre-study validation)

- **Cut Point**
  - Innovator and Biosimilar Independent cut points
  - If the cut points are significantly different it needs to be investigated

- **Positive Controls**
  - Multiple controls against Innovator and Biosimilar
  - Positive controls should

- **Sensitivity**
  - Innovator and Biosimilar
  - Expectation: Equivalent

- **Drug tolerance**
  - Innovator and Biosimilar
  - Expectation: Equivalent

*State of the art technology should be utilized for Immunogenicity assays*
Immunogenicity Assay (In-study validation)

- **Drug**: Lot of drug used for dosing should be used for both capture and detection.

- **Sample analysis**: Ideally should be set up for simultaneous analysis of biosimilar and innovator.

- **Specificity**: Specificity should be performed only using relevant drug (biosimilar or innovator).

- **Additional**: Additional specificity and characterization of positive samples may be necessary if significantly different antibody responses are observed.
Post-marketing surveillance of immunogenicity

- Post-marketing surveillance of immunogenicity key requirement all biosimilars
- Pre-market clinical testing of immunogenicity is limited and cannot reliably detect rare, but serious immunogenic responses
- Immunogenicity may be predictive of clinical consequences. It is important to understand potential mechanism(s) causing change and determine relevance
- Potential for conflict and confusion if patient treated with both reference and biosimilar products – which product elicited immunogenic response?
- Reference product sponsor and biosimilar firm will have different analytical methods for measuring immunogenicity and may report different results for the same patient samples
Monoclonal antibodies are complex molecules
PK assay – one assay should be used to measure both innovator and biosimilar drug.
Immunogenicity assay – two assays should be used to measure anti-drug (innovator and biosimilar) antibodies.
A robust assay is required to monitor long term immunogenicity assessment.
Interpretation of results (establishment of biosimilarity) is challenging; specifically when working with a qualitative immunogenicity assays
State of the art technologies should be used for both PK and Immunogenicity assays
The Celerion Solution

The bridge between manufacturing and clinical efficacy

- Manufacture of Biosimilar Product
- Biological Manufacturer
- Early assessment to ensure comparability to reference product
- Non-clinical Safety and Efficacy
- Immuno-toxicology
- Human PK Safety
- Bioanalysis and Immunogenicity Testing
- Functional Cell Based Assays
- Comparable efficacy and long term patient safety
- Multi-site Patient Study
- Regulatory Strategy and Support