Biosimilar Development Cost : Role of Analytics

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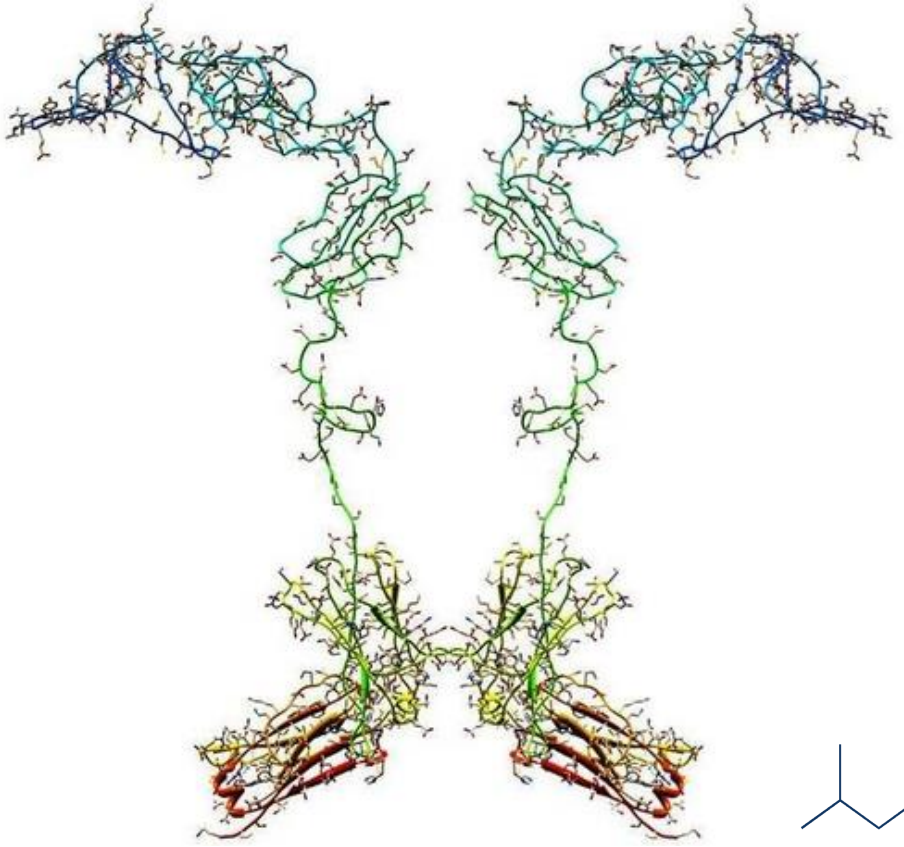
Agenda

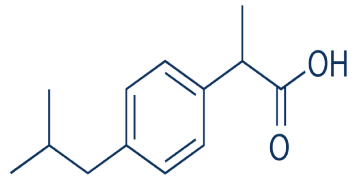
- Biosimilar
- Development Process
- Regulatory Requirements
- Role of Analytics
- Analytics and Development Cost
- Conclusions

Biosimilars

Biosimilars are a less expensive copy of Biological Products.

Biosimilars are complex heterogeneous molecules manufactured using living cells.





Approved Biosimilar

- EMA has approved 22 Biosimilar, 2 approvals have been withdrawn leaving 20 Biosimilar in Europe.

- On March 06, 2015, US FDA approved Zarxio, the first Biosimilar product in US. On April 2016, FDA approved Inflectra (infliximab-dyyb), administered as an intravenous infusion, for multiple indications. This is biosimilar to Janssen Biotech's Remicade (infliximab).

- Several approved in ROW (Japan, Korea, India, Canada, Australia Etc.).

Development Process

There are four stages in the Biosimilar development

- Product Development and Comparative Analysis.
- Process Development Scale-up and Validation.
- Clinical Trials.
- Regulatory Review and Approval.

Average Time: 8-10 Years

Average Cost: $ 100-300 Million

Product Development and Comparative Analysis

- Characterize Licensed Reference Product.
- Define Target product profile.
- Define critical Quality Attributes.
- Reverse Engineer the Biosimilar.
- Perform Analytical Comparability between proposed biosimilar and Reference product.

Average Time: 1-2 Years

Average Cost: 3.0 % of Total Cost

Process Development Scale-up and Validation

- Optimize the process until high analytical similarity between reference and biosimilar is achieved.
- Scale-up the manufacturing process.
- GMP are established.
- Process is Validated.

Average Time: 1-2 Years

Average Cost: 20% of Total Cost

Clinical Trials

- Non-clinical and Clinical studies are performed to demonstrate the Biosimilarity.
- Address the residual uncertainties with Analytical, non-clinical and clinical studies.

Average Time: 2-4 Years

Average Cost: 77% of total cost

Regulatory Review and Approval

- Average Time: 1-2 Years.

- Average Cost: Regulatory Fee as applicable.

Regulatory Requirements

- Biosimilar has the same mechanism of action, conditions of use, route of administration, dosage form and strength as reference product.

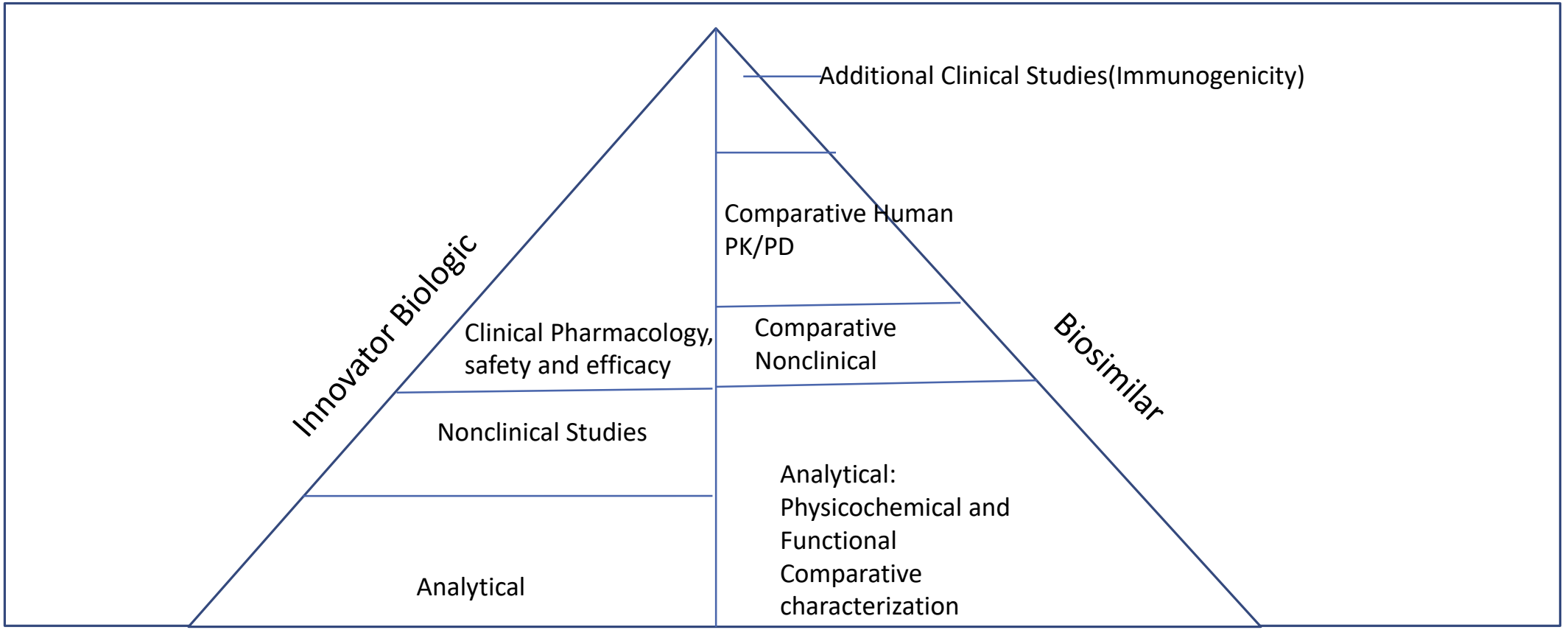
- Comprehensive characterization and comparison at quality level should provide a basis for reduction in the non-clinical and clinical data.

- A final determination of Biosimilarity is based on totality of the evidence: combination of quality, non-clinical & clinical evaluation.

Dossier Requirements

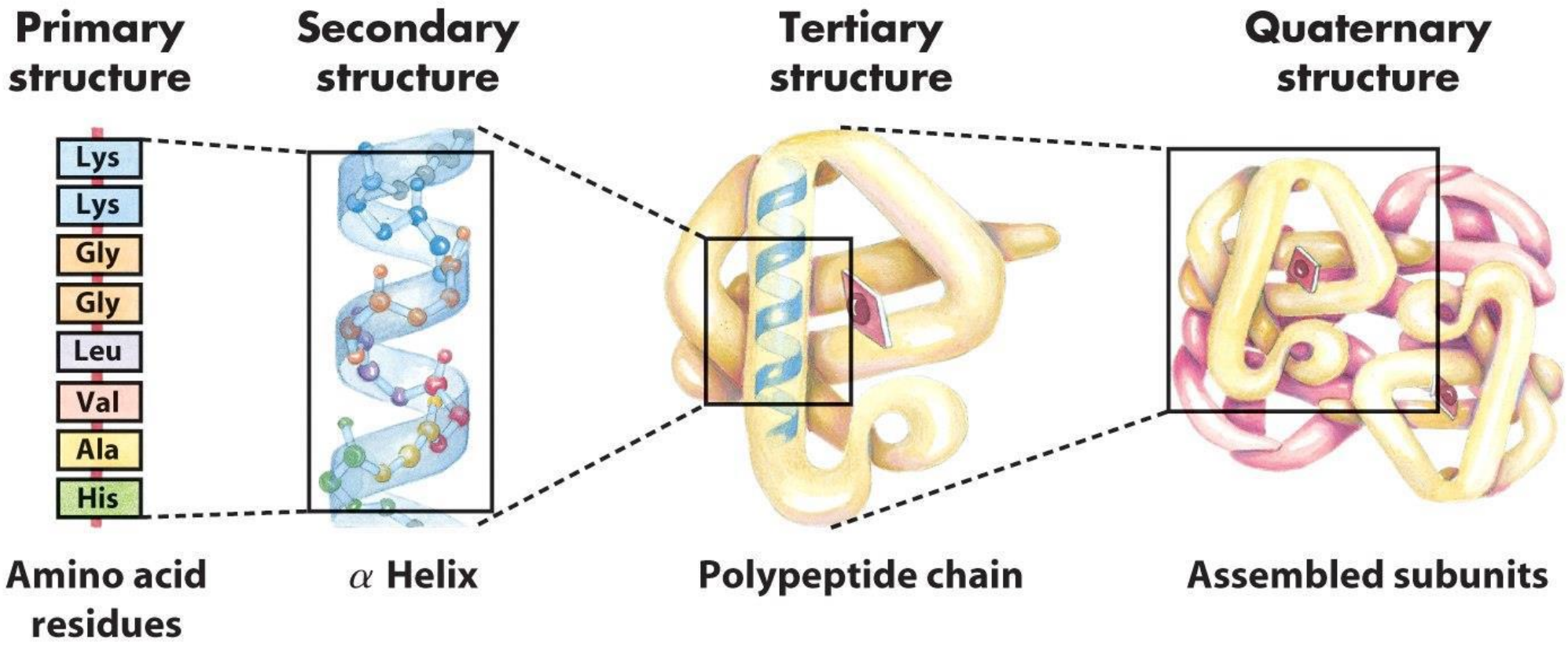
New Biologics	Biosimilar
Full Quality Data	Full Quality Data + Comparability
Full Non-clinical Data	Reduced Non-Clinical Data + Comparability
Full Clinical Data	Reduced Clinical Data + Comparability

Development Process of Biosimilar vs Biologics



Analytical data is the foundation of Biosimilar Approval.

Role of Analytics



Role of Analytics

- A deep understanding of primary and 3-D molecular structure, biological function & critical quality attributes (CQA) of Reference and Biosimilar is critical step for establishing the Analytical Similarity.
- Biosimilar may not be exact match but if Molecular structure/biological function and CQA of Reference and Biosimilar are highly similar, there is a great possibility that clinical performance (efficacy & safety) will be highly similar to reference product.
- It is also important to understand how CQA link to the manufacturing process (Material Quality Attributes and Critical Process Parameters), so that process can be adequately controlled to obtained desired CQA.

Role of Analytics

Understanding the relationship between CQA and Clinical Performance (safety, PK/PD, activity and immunogenicity) of the product is critical.

- Helps to predict clinical similarity from quality data.
- CQA can be controlled to obtain desired/similar clinical performance.

All CQA Need to match.

Thanks to power of Analytics

- Deep and Comprehensive evaluation of Biosimilar and Reference Product structure & function can be obtained by using modern analytical methods.

- Complexity of the protein products can be addressed using large array of powerful tests.

- Relationship between CQA, CPP and Clinical performance can be understood with advanced analytical technologies.

Sensitive and State of the Art Analytical Tools

- Molecule can be analyzed and characterized using State of the art analytical technology.
- Sensitive biological tests can be used to understand the relationship between functional CQA (potency, activity etc.) and clinical performance.

Higher Analytical Capability and State of the Art Analytical techniques are key to demonstrating analytical similarity between reference and biosimilar product.

Role of Analytics

Analytical technology/Tools can be classified into 3 major categories:

- Biochemical/Chemical Tools: To study the structure of protein.
- Biological/ functional Tools: To study the activity/immunogenicity of protein.
- Biophysical tools: To study the 3-Dimentinal structure/folding of proteins.

Role of Analytics: Chemical Analysis

How to tell if Reference and Biosimilar product are similar

- Thorough understanding of CQA of molecule can be achieved by Analytical Characterization and increased Testing.
- Powerful analytical tools can detect the smaller differences in primary structure or carbohydrate structure of molecule due to change in process.
- Analytical methods can even detect minor differences on Glyco-protein structure, which may impact clinical performance of the product.
- Analytical tools can also detect minor non-product related residual impurities which may impact clinical performance.

Role of Analytics: Chemical Analysis

Examples of Chemical Analytical Tools to evaluate Biosimilar

- Amino acid analysis
- Mass Spectroscopy
- Size exclusion chromatography
- HPLC (Reverse Phase)
- Ion-Exchange Chromatography
- Capillary electrophoresis and SDS-PAGE
- Analytical Ultracentrifugation

Role of Analytics: Biophysical Analysis

How to tell if Reference and Biosimilar product fold similarly and has similar 3-dimentional structure

- X-Ray Crystallography can be used to understand the molecule, how it folds and what is the 3-dimentional structure of the molecule.
- Crystallography can demonstrate if reference and biosimilar are similar in 3-dimentional structure.
- Two molecules with similar amino acid sequence/glycosylation structure and three dimensional structure will probably have similar functional PK/PD profile and clinical performance.

Role of Analytics: Biophysical Analysis

Examples of Biophysical analytical tools

- X-Ray Crystallography
- Micro-Calorimetry
- Circular Dichroism
- Fluorescence Spectroscopy
- NMR
- Raman Spectroscopy
- Mass Spectroscopy
- Size Exclusion Chromatography

Role of Analytics: Biological Analysis

How to tell if reference and biosimilar molecule is functionally equivalent?

There are a whole array of biological assays available, which can detect:

- Differences in functional attributes of the Reference and Biosimilar product.
- Help in determination if differences will be clinically meaning full or not.
- To demonstrate the Clinical Comparability of the product.

Role of Analytics: Biological Analysis

Examples of Bioactivity or Bioassay for Biological Analysis

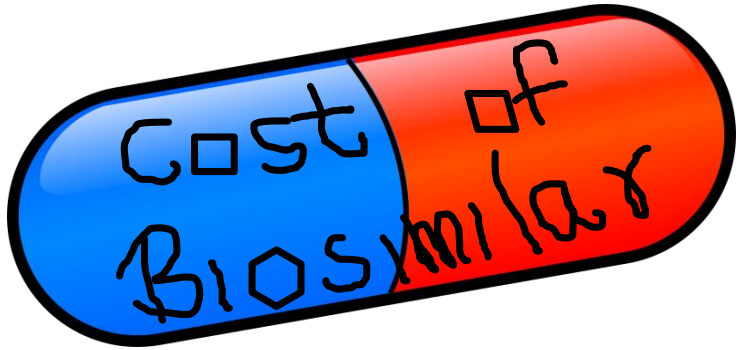
- Cellular Bioassay
- Animal Bioassay
- Ligand and Receptor Binding assay (ELISA, surface Plasmon resonance)
- Signal transduction
- Immunoassay
- Flow Cytometry

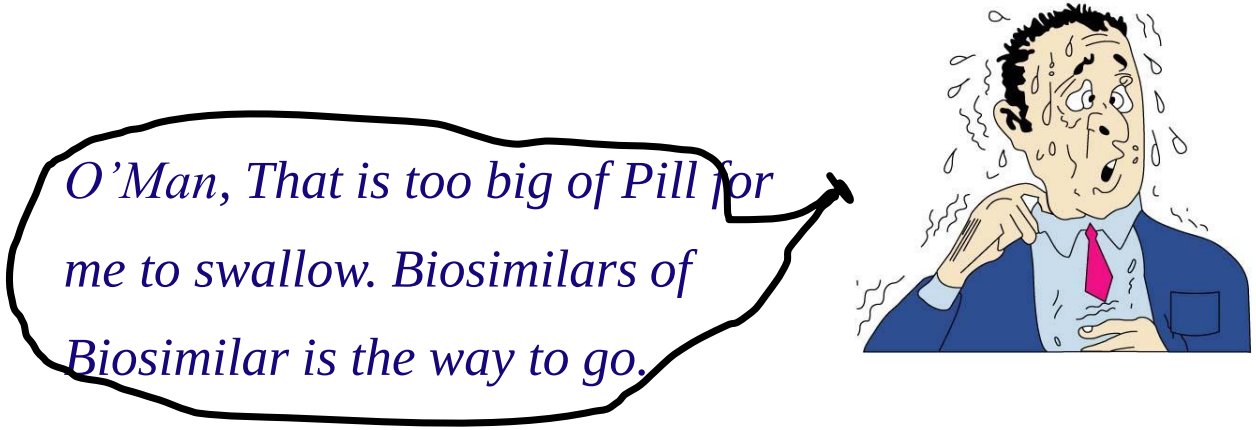
Analytical data makes foundation for Biosimilar Approval.

Modern analytical technology/tools can help to generate extensive analytical characterization and functional data.

Development Cost

How Powerful Analytics can help to reduce cost of Biosimilar Development??





Analytics and Development Cost

- Prices of Biosimilar are only 30% lower than innovator drugs as compared to Generics which are about 80-90% lower than innovator drugs.

- Biosimilar manufacturing is more time consuming and costlier than the generic drug development due to complex manufacturing process and higher Pre-clinical/ Clinical Cost.

- Generic Development Cost: 1-2 years and $ 5-10 million.
- Biosimilar Development Cost: 8-10 years and $ 100-300 million.

Analytics and Development Cost

- Cost of Analytical characterization: 2-3% of total cost.
- Cost of Process optimization: 20% of total cost.
- Cost of Clinical Trials: 77% of total cost.

- Demonstrating that Biosimilar is highly similar to reference product using extensive analytics data can reduce Clinical Trials requirements and high Clinical Trial cost because analytical data serves as surrogate for large clinical data.

Analytics and Development Cost

Extensive analytical characterization and analytical similarity demonstration not only reduces cost of clinical trials but also reduces approval time, thus resulting in total cost of development.

Understanding potential impact of CQA on activity, PK/PD, safety and immunogenicity at early development stage can also result in reduction of pre-clinical and Clinical study cost.

Conclusions

- State of the Art Analytics are key to reducing Biosimilar development time and Cost of development because analytical data develops the basis of reduced clinical testing.
- Analytics can be used to demonstrate high level of structural similarity.
- Analytics can used to understanding the relationship between CQA and Clinical Performance.
- Performing extensive Analytical Characterization using State of the Art Techniques may increase the cost of product comparative analysis from 3% to 6% but it creates an opportunity for reduction in high percentage of clinical trial cost.