Making Medicines Affordable

EUROPEAN GENERIC MEDICINES ASSOCIATION
EGA’s Perspective on Biosimilar Products

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On behalf of the European Generic medicines Association

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Definition

Basic concepts

Global biosimilar development

Status of biosimilar products in Europe

The next step - monoclonal antibodies

Conclusion
Definition
What is a biosimilar product?

- A biosimilar medicinal product is a successor to a biological medicinal product for which patent protection no longer applies.
- Manufactured by recombinant DNA technology (insertion of gene into the host cell to produce the protein).
- Comparable with the selected comparator biodrug(*) in terms of quality, safety and efficacy.
- The biosimilar product is usually approved for the same indications as the comparator biodrug given that they share the same mode of actions.

(*) EU Terminology: reference product
Basic Concepts
Development of a follow-on product following a target directed approach

Define development target

Development of biosimilar product, "Quality by Design"

Confirmation: Final comparability exercise

Analytical characterization

Analytics

Process development
Quality by Design

Manufacturing process is pro-actively designed to achieve a product equivalent to the comparator biodrug (quality, safety & efficacy)
- Extensive characterization of reference product (multiple batches)
- Broad set of orthogonal state-of-the-art analytical tools
- Accounting for formulation, packaging materials, etc.
- In vitro biological testing, in vivo PK/PD studies, clinical trial

Continuous feedback between process development and high performance analytical techniques result in the required specific selection of
- Cell line
- Raw materials, media
- Upstream and downstream process parameter
- Control of critical variables
- Formulation, primary packaging, delivery system
The development of a biosimilar medicine requires a complete product and process development
PLUS
comparative testing at all stages of in order to obtain approval by the European authorities (EMEA, CHMP, EC)
The Comparability Exercise - the core element in the Biosimilar Product development

The comparability with the comparator biodrug must be demonstrated at all levels of product development.

A biosimilar product is designed to meet the criteria of the comparator biodrug with regards to quality, safety and efficacy.

This rigorous comparability exercise qualifies Biosimilars for therapeutic interchange.
How close is close enough?

- The criteria for the comparison of the biosimilar candidate and the comparator biodrug are based on
  - Understanding batch-to-batch variability of the comparator biodrug
  - Classification of the product variants into product-related substances or impurities (ICH Q6B)
  - Level of understanding the relevance of subtle differences on safety/efficacy (ICH Q5E)

- The manufacturing process for the biosimilar is systematically designed to meet the required comparability criteria
Global development of Biosimilar Medicines
Global development of Biosimilars
What is the issue?

- The Japan draft guideline, the European and probably also future US legislation will require the use of a comparator biodrug authorized in their jurisdiction.

- This would require the performance of separate development programs for each country/region which is unnecessary, unethical (duplication of preclinical and clinical studies) and uneconomical.

- The development of Follow-on Protein Products is expensive.
• **Comparator biodrugs** are often the same or highly similar in different countries, even though licensed under different jurisdictions
  
  – Often, **documentation** is available in the public domain that the products are the same
  
  – **Comparability** of comparator biodrugs of one original manufacturer from different highly regulated countries (JP, US, EU) can be clearly established by stringent analytical and functional studies

• Under these premises it **should not be required to duplicate** preclinical and clinical **studies for each country/region**
Extrapolation of results and conclusions of clinical studies performed in one population to other populations

- Evaluate ethnic sensitivity of medicinal product - does it behave differently in different populations?
- In compliance with ICH E5(R1) “Ethnic Factors on the Acceptability of Foreign Clinical Data”
- In line with the spirit of the declaration of Helsinki which aims at avoiding duplication of tests and trials on animals and humans
Global clinical development

Points to consider

- Pharmacology and Mode of Action
- Diagnostic criteria and indications
- Posology and dose response
- Pharmacodynamics and pharmacokinetics
Global development: Stepwise approach to show comparability with comparator biodrugs

<table>
<thead>
<tr>
<th>JP</th>
<th>US</th>
<th>EU</th>
<th><strong>Requirements</strong></th>
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<tbody>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>rigorous physicochemical and biological comparison with comparator biodrug of both regions</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>appropriate comparative pre-clinical testing with comparator biodrug of both regions \textit{in case of physico-chemical differences} shown between drugs</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>rigorous comparative PK/PD clinical studies with comparator biodrug of both regions</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>comparative clinical studies with comparator biodrug from \textit{one} region only (\text{against either JP, US, or EP comparator biodrug})</td>
</tr>
</tbody>
</table>
Status of Biosimilar Products in Europe
EU Biosimilar Approvals

- Approved substances
  - Human Growth Hormone
  - Epoetin
  - Filgrastim

- 11 Marketing Authorisations
The next step
Monoclonal Antibodies
The logical next step
Monoclonal antibodies

Biological characteristics

Antigen binding

- VH
- CH1
- CH2
- CH3

Light chain

Heavy chain - S-S -

Fab

Effector functions
- Complement interaction
- Fc Receptor interaction

Fc

Physicochemical characteristics

N-terminal heterogeneity
- Pyroglutamate formation
- Other modifications

Amino acid modifications
- Deamidation, Oxidation, Glycation, Isomerization

Fragmentation
- Cleavage in hinge region, Asp-Pro

Oligosaccharides
- Fucosylation, Sialylation, Galactosylation,...

Disulfide Bonds
- Free thiols, disulfide shuffling, thioether

C-terminal heterogeneity
- Lysine processing, Proline amidation
# Physicochemical characterization of mAbs: Structure, heterogeneity and degradation

<table>
<thead>
<tr>
<th>Molecular Parameter</th>
<th>Attribute</th>
<th>Methods for control and characterization</th>
</tr>
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<tr>
<td>Primary structure</td>
<td>Sum formula: Mass of light chain, heavy chain and of intact mAb</td>
<td>LC-ESI-MS</td>
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<tr>
<td></td>
<td>Amino acid sequence</td>
<td>Orthogonal peptide maps with high resolution MS and MS/MS sequencing</td>
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<td></td>
<td>Disulfide bridging</td>
<td>Non-reducing Peptide Map</td>
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<td></td>
<td>Free cysteines</td>
<td>Ellman's, Peptide Map</td>
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<tr>
<td></td>
<td>Thioether bridging</td>
<td>Peptide map, SDS-PAGE, CGE</td>
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<tr>
<td>Higher order structure</td>
<td>Secondary and tertiary structure</td>
<td>CD spectroscopy, DSC, H-D-Exchange, FT-IR</td>
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<tr>
<td>Glycosylation</td>
<td>Glycan isoforms</td>
<td>NP-HPLC-ESI-MS of 2AB-labeled glycans, exoglycosidase digestion, MALDI TOF/TOF</td>
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<tr>
<td></td>
<td>Sialic Acids incl. NGNA</td>
<td>NP-HPLC, WAX, HPAEC; RP-HPLC (DMB-label)</td>
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<tr>
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<td>Aglycosylated mAb</td>
<td>CGE, Peptide map</td>
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<tr>
<td>Heterogeneity</td>
<td>C- and N-terminal: ±Lys, pyroGlu</td>
<td>CEX; Papain-IEX; Peptide Map, RP-HPLC</td>
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<tr>
<td></td>
<td>Glycation of Lys</td>
<td>Boronate affinity; LCMS; Peptide map</td>
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<tr>
<td></td>
<td>Oxidation</td>
<td>RP-HPLC; Papain-HIC; Peptide map</td>
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<tr>
<td></td>
<td>Deamidation</td>
<td>CEX; Papain-IEX; Peptide map</td>
</tr>
<tr>
<td></td>
<td>Aggregation</td>
<td>SEC, FFF, MALLS, DLS, AUC; imaging, particle char.</td>
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<tr>
<td></td>
<td>Fragmentation at disulfides (HL, H₂L, H, L) and in amino acid chain (p100, p50)</td>
<td>CGE, SDS-PAGE, SEC, RP-HPLC</td>
</tr>
</tbody>
</table>
A toolbox of bioanalytical methods addresses possible mechanisms of action for a mAb

- **CDC**
  - complement dependent cytotoxicity
  - CDC assay
  - C1q binding
  - Membrane attack complex

- **ADCC**
  - Antibody dependent cellular cytotoxicity
  - Binding assay
  - ADCC assay
  - FcγR binding

- **PCD**
  - Programmed cell death (apoptosis)
  - Binding assay
  - Apoptosis assay

Target cell

Effector cell (NK cells)
Conclusion
Conclusions

- Biosimilar Medicines are a reality in the EU
- Multiple biosimilars are being used safely and providing access to competitively priced products to numerous patients
- Thorough demonstration of comparability provides the scientific basis for interchangeability
- Current science allows development of a diverse portfolio of biosimilar products, including monoclonal antibodies
- Global biosimilar development is possible based on sound scientific principles and should be enforced by regulatory pathways
Thank you for your attention
Main Acronyms Used

- EGA European Generic medicines Association
- EMEA European Medicines Agency
- CHMP Committee for Medicinal Products for Human Use
- EC European Commission
- EU European Union
- RMP Risk Management Plan
- ICH International Conference on Harmonisation
- JP Japan
- US United States of America