Clinical Challenges with Biosimilar Drug Development

Frank A. Scappaticci, MD, PhD

Clinical Science Leader
Genentech, Inc. / F. Hoffmann-La Roche Ltd.
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Outline

• Distinguishing between Biosimilars and Generics
• Complexities with Biologic Agents and their Manufacturing
• Substitution / Interchangeability
• Pharmacovigilance
Monoclonal Antibody Programs at Roche - Decades of Development

- Monoclonal antibodies have been developed at Roche for a variety of indications including oncologic and non-oncologic indications

- Examples of approved antibodies include:
  - Bevacizumab for CRC, NSCLC, BC, RCC, GBM, OC
  - Trastuzumab for Her2+ BC (metastatic and adjuvant) and GC
  - Pertuzumab for BC (Her2+ metastatic in combination with Herceptin)
  - Rituximab for NHL, CLL, and RA
  - Tolcilizumab for RA
  - Omalizumab for allergy

- Newer monoclonal antibody platforms being developed (ex., humanization, ADC, glycoengineering, single chain, bispecific antibodies)
Biosimilars | Biologics manufacturing

The proprietary process is the product

### Generics

Follow-on products of traditional chemical pharmaceuticals are exact chemical copies

Relatively easy to reproduce exactly

### Biosimilars

Similarity has been shown in terms of quality, safety and efficacy to the originator.

Manufacturing based on unique cell lines

Processes are very complex and difficult to reproduce

There are no ‘bio-generics’, there are only similar products

Changes may lead to different clinical efficacy and safety
Complexity of Biologics
Protein Complexity: Structure

Biopharmaceuticals are structurally diverse

Chemical pharmaceutical
- Simple structure of elements

Biopharmaceutical
- Multiple levels of structural complexity

Aspirin = C$_9$H$_8$O$_4$

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>Tertiary</th>
<th>Quaternary</th>
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<tbody>
<tr>
<td>Amino acid sequence</td>
<td>Alpha, beta sheets</td>
<td>Folding</td>
<td>Polypeptide arrangement</td>
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Biological Product Complexity:

Examples of modifications: inherent or due to the manufacturing process

- Pyroglutamyl peptides
- Deamidation
- Methionine oxidation
- Glycation
- High mannose, G0, G1, G1, G2
- Sialylation
- C-terminal Lysine

Modifications may result in approximately $10^8$ potential variants

Adapted from: Steven Kozlowski; FDA
The Mode of Action of mAbs is Complex and May Involve Contributions from Multiple Mechanisms

- Inhibition of Signal Transduction or Receptor Activation
  - Inhibition of Ligand Binding (Example: Cetuximab)
  - Induction of Receptor Internalization (Example: IGF-1R-Abs)
  - Inhibition of Receptor Dimerization (Example: Pertuzumab)
  - Inhibition of Receptor Shedding (Example: Trastuzumab)

- Induction of Apoptosis (Example: Rituximab)

- Activation of Effector Mechanisms
  - Complement Activation (CDC) (Example: Rituximab)

- Antibody-dependent cellular Cytotoxicity (ADCC) (Examples: Rituximab, Trastuzumab)

- Targeting of Toxins (Example: T-DM1)

- Blocking Ligand Binding (Example: Bevacizumab)

- activation of T-Cells (Example: Catumaxomab)

- Induction of Apoptosis (Example: Rituximab)

The in-vivo mode(s) of action are often incompletely understood and may differ between indications

Challenges with Manufacturing of Biologics
Protein Microheterogeneity

Small Molecule Drug

Protein Drug
Biotech Products Manufacturing

- MCB, WCB
(establishment of unique master and working cell banks suitable for large scale fermentation)
Biotech Products Manufacturing

- Working cell bank
- Spinner flasks
- 20 L Bioreactor
- 80 L Bioreactor
- 400 L Bioreactor
- 2,000 L Bioreactor
- 10,000 L Bioreactor
Biotech Products Manufacturing

• Downstream processing (Purification) (Includes cell removal-, removal of HCP and HCDNA, viruses, medium components, removal of related substances (oxidized-, aggregated-, deamidated- and other truncated forms), concentration-steps, buffer-exchange)

Ultrafiltration -> Depth Filtration -> Column1 -> Column2 -> Column3 -> Bulk Filling -> Drug Product Manufacturing

Cell free supernatant
Intended Copies/Biosimilars of Biotech Products

a different manufacturer uses...

- Human Gene Sequence
- DNA Vector
- Host Cell Expression
- Fermentation
- Purification

Maybe the same gene sequence
Probably a different DNA vector
A different recombinant production cell
A different fermentation process
A different downstreaming protocol
Substitution / Interchangeability
Key Concern: Immunogenicity

• Neutralizing antibodies → impact on therapeutic effect
  – coagulation factor concentrates (eg, Factor VIII and Factor IX),
  – enzyme replacement therapies (eg, acid-α-glucosidase and glucocerebrosidase),
  – hormones (eg, GH)
  – cytokines (eg, GM-CSF and IFNβ)

• Hypersensitivity reactions

• Cross-reactivity with an endogenous protein that has a vital, non-redundant biological function
  – PEGylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF),
  – PRCA with epoetin alfa

Wadhwa, Idrugs, 2009
Substitution & its Challenges

- Substitution of a biological medicinal product, including biosimilars, can impact patient safety
- Substitution makes product post-marketing surveillance / traceability more difficult
- Substitution should involve the physician
- Patients have a right to be informed
- Need for pharmacovigilance
Interchangeability

  - Biosimilars cannot be considered identical to their biological reference products
  - Decision to treat a patient with either should be made by a qualified healthcare professional

- ‘Switching’ and ‘interchanging’ of medicines that contain a given mAb might occur. Thus, applicants are recommended to follow further development in the field and consider these aspects as part of the risk management plan. (Final EMA MoAb Guidance June 2012)

- Fifteen countries across Europe have brought in new rules to prevent automatic substitution of biological medicines by biosimilars (Source: APM Health Europe, 21 February 2008).
An interchangeable product must be shown to be biosimilar to the reference product and meet the other standards described in section 351(k)(4) of the PHS Act.

At this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment.

FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product.
What is the role of Pharmacovigilance (PV)? Are products interchangeable?

- Safety in the post-authorization setting must be investigated => may exceed routine PV (e.g. participation in registries)

- Biosimilar antibody products should have unique identity or name and prescriptions be made by brand name, allowing traceability to the patient level

- Labelling for biosimilar antibodies must clearly identify the sources of the specific clinical safety and efficacy data obtained during its development (e.g. extrapolation, originator’s data, data of the biosimilar)

- The marketing and utilization of biosimilar antibodies must not enable substitution with a reference product without the consent and supervision of a qualified physician
Conclusions

- Biologics are complex in structure and function as they are manufactured using biologic systems compared with small molecule drugs that can be synthesized and to which identical copies can be made.

- Biosimilar agents can never be identical to innovator products because of differences in structure/post-translational modification and manufacturing.

- Biosimilars should not be automatically substituted but rather substitution should require the approval of a physician.

- Interchangeability will require additional clinical data to ensure patient safety and efficacy of the biologic product.

- Biosimilar medications will require extensive follow-up for safety and immunogenicity in the post-marketing setting.