Clinical Immunogenicity and the Biosimilar paradigm

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Access to safe and effective medicines is important to patients, to those who care for them and to AbbVie.

AbbVie fully supports the entry of Biosimilars that have been shown, with robust evidence, including clinical trials, to be as safe and efficacious as the innovator biologic medicines.
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Clinical immunogenicity
Immunogenicity- A Brief Introduction

What is Immunogenicity?

- Ability of antigen(s) to elicit an immune response
- Desired response to vaccination
- Undesired response to biopharmaceuticals

Almost every kind of foreign molecule can be antigenic, but usually only large macromolecules have the size and properties necessary to trigger a physiological immunogenic response.

Proteins are among the most powerful immunogens because they supply both T- and B- cells epitopes necessary to generate the immune response.
Classification of Anti-drug Antibodies

• Non-neutralizing (binding) antibodies
  – Binds to a non-functional site of the biologic, which can indirectly influence its ability to bind its target or impact its PK

• Neutralizing antibodies
  – Binds to a functional site of the biologic, which can directly reduce its ability to bind its target

• Circulating immune-complexes
  – Integral binding of an antibody to a soluble antigen

• Classification is based on in vitro assays
  – In vitro activity does not always correspond with activity in vivo
  – Both neutralizing and binding ADAs as well as circulating immune-complexes can impact clinical safety and efficacy in vivo

Bendtzen K. at Arthritis & Rheumatism, vol.63, nº4, April 2011: pag. 867-870
F. Atzeni et al. / Autoimmunity Reviews 12 (2013) 703-708
Schellekens H, Clinical Therapeutics, vol.24, nº 11, 2002: pag. 1720-
Many Product-Related Factors Contribute to the Immune Response

- Production Process: Contaminants, Impurities
- Modification: Glycosylation, Phosphorylation, Chemical Modifications
- Formulation and Dosage
- Route of Administration: s.c. >> i.v.
- Interaction With and Uptake by Immune Cells
- Function and “Target” of Proteins
- Protein Sequence

Human Immune System: Patient & Disease

Biologics are Highly Sensitive to Process Changes: 
Case studies of production process events with clinical impact

“...Despite such significant improvements in analytical techniques, however, current analytical methodology may not be able to detect all relevant structural and functional differences between two proteins. Thus, as set forth in the PHS Act, data derived from analytical studies, animal studies, and a clinical study or studies are required to demonstrate biosimilarity unless FDA determines an element unnecessary”¹ (emphasis added)

<table>
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<tr>
<th>Product</th>
<th>Event</th>
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<tr>
<td>Omnitrope®</td>
<td>• Added new manufacturing facility &lt;br&gt; • Spectrometric, sequence, and physicochemical data did not reveal significant differences &lt;br&gt; • Registration trials: Unexpected immunogenicity from host cell protein originating from new manufacturing source</td>
<td>• Up to 60% of study subjects developed anti-GH antibodies from new manufacturing site’s product &lt;br&gt; • No influence on growth rate detected &lt;br&gt; • Sponsor decided not to commercialize product from additional manufacturing facility</td>
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<td>Binocrit® (HX575)</td>
<td>• Analytically undetected tungsten contamination from pin used to manufacture syringe</td>
<td>• Denaturation and aggregation of epoetin alpha &lt;br&gt; • Neutralizing anti-epo antibodies &lt;br&gt; • Clinical trial discontinued</td>
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<tr>
<td>Eprex®</td>
<td>• Replaced HSA with sorbitol-80 stabilizer using un-coated stoppers in PFS</td>
<td>• 112 post-marketing case reports of neutralizing antibodies and PRCA &lt;br&gt; • Withdrawn marketing authorization of new product</td>
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¹.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 
Immunogenicity considerations for biosimilar development

- **Clinical immunogenicity** is a critical contributor to the totality of the evidence and is key to determining safety and efficacy of biosimilars.

- **Only clinical studies** are appropriate for detecting immunogenicity; there is no adequate analytical, in vitro or animal model to predict clinical immunogenicity.

- **Studies** should be sufficiently powered and designed as comparative, parallel, head-to-head studies of at least one year duration for chronically administered products.

- **Clinical immunogenicity** study design should be informed by the analytical and pre-clinical data available for the biosimilar as well as the experience with the reference product.

- **Among and within indications**, the most **immuno-competent** patient population would generally be preferred over immuno-suppressed patients if indication extrapolation is being sought.

- **Repeated switches** between the biosimilar(s) and an originator’s product may increase immunogenicity with potentially negative clinical effects.

- **Post-marketing assessment safety studies** and/or in participation in already existing registries are necessary to detect long-term and/or rare immunogenicity responses.
EMEA guidance on higher vs. lower immunogenicity:

- A higher immunogenicity as compared to the reference mAb may become an issue for the benefit/risk analysis and would question biosimilarity.
- A lower immunogenicity for the biosimilar mAb would not preclude biosimilarity.
  - Efficacy analysis of the entire patient population could suggest that the biosimilar is more efficacious, so it is recommended to pre-specify an exploratory subgroup analysis in patients that did not mount an anti-drug antibody response.
  - Subgroup analysis could establish that the efficacy of the biosimilar and the reference mAb are similar if not impacted by an immune response.

FDA guidance on higher vs. lower immunogenicity*

Generally only important to demonstrate that the immunogenicity of the biosimilar is not increased, so a one-sided design will ordinarily be adequate to compare clinical immunogenicity.
Perspectives on Lower Immunogenicity

• Immunogenicity study should follow a comparative, parallel, two-sided design

• Acceptance of lower immunogenicity of biosimilars is not unreasonable

• However, immunogenicity may act as a sensitive biomarker and high similarity in immunogenicity contributes to the "totality of the evidence" approach

• Lower immunogenicity of the biosimilar compared to the reference product should be interpreted as a different outcome in a clinically relevant biomarker

• In case of lower immunogenicity, it would be recommended to do a thorough experimental investigation and a scientific rationale as to why that is the case
Regulatory Guidance on Extrapolation of Immunogenicity Data

- **WHO**: If the manufacturer intends to extrapolate efficacy and safety data to other approved indications of the RBP, care should be taken to ensure that *immunogenicity is investigated in the patient population that carries the highest risk of an immune response and immune-related adverse events*.

- **FDA**: With regard to *extrapolation to other indications*, the study population and treatment regimen that are the most sensitive for detecting a difference in immune responses should be selected.

- **EMA**: Immunogenicity could differ among indications and *absence of immunogenicity assessment in a particular indication may have to be justified*.

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Draft FDA Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Feb 2012

EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006)
Current analytical methods or animal models cannot accurately predict human immunogenicity

- Only clinical studies are appropriate for detecting immunogenicity
- Current analytical methods or animal models cannot accurately predict human immunogenicity
- Lack of international standardization of assays and references makes it impossible to compare results from different test laboratories
- Comparison of immunogenicity can only be performed via comparative clinical studies and not by comparison of or to historical data
- It would be preferable to use a single assay that measures binding of ADAs, using inhibition by the biosimilar and reference product to detect ADAs that recognize novel epitopes on the biosimilar
- Assays should ideally be capable of detecting immune responses even in the presence of free circulating drug product
- The biosimilar product and reference product should be assessed in the same assay with the same patient sera whenever possible

Which Clinical Model is the Most Sensitive for the Detection of Immunogenicity Differences?

- Patient populations may vary in their response to biologics:
  - Overall incidence and time course for generation of anti-drug antibodies
  - Occurrence of neutralizing antibodies and effects of ADA on safety or efficacy, incl. PK/PD
  - Confounding by concomitant medication (eg, immunosuppressants)
- Among and within indications, the most immuno-competent patient population would generally be preferred over immuno-suppressed patients

Infliximab: Anti-Drug Antibody Formation Rate in Various Indications

1. REMICADE SmPC Information; accessed on 04/10/2014
Immunogenicity: Switching Challenges

- Repeated switches between the biosimilar(s) and an originator’s product may increase immunogenicity with potentially negative clinical effects.
  - Drug neutralization with ensuing loss of efficacy is one of the major risks associated with switching.
  - The choice of biologic treatments is often limited for many diseases/patients – lost ground may be lost forever.
  - In clinical switching studies, immunogenicity should always be assessed, as it can cause serious adverse events as well as drug neutralization and loss of efficacy.
  - Some immunogenic reactions, such as pure red cell aplasia (PRCA), may develop or be detected only after several months of treatment.

“We report on a patient treated with the originator drugs such as epoetin theta, epoetin β and darbepoitin α, who developed ESA-induced PRCA. The repetitive switching of agents hampered our ability to attribute PRCA to the appropriate agent.”

“The detection of the neutralizing antibodies was a challenge in our case. …. Only the control tests months later (RIP and TF-1 bioassay) were positive. By this time, however, two more ESAs (epoetin beta and darbepoitin alfa) had been administered.”

Biosimilars and Pharmacovigilance
Pharmacovigilance - A Brief Introduction

- World Health Organization (WHO) defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem”

- Proper labeling, product tracking and a standardized operational system of pharmacovigilance, and attributing adverse events are all components of a well-functioning pharmacovigilance program

- The main issues involved in monitoring the safety and effectiveness of a commercial pharmaceutical are as follows:
  - Identifying the patient receiving the drug
  - Monitoring the patient over time for adverse reactions and the effectiveness of the product
  - Substitution or interchangeability
  - Extrapolation of indications
  - Data collection
  - Data analysis
  - Data reporting
Pharmacovigilance is a key pillar in the concept of Biosimilarity

Based on science, the Concept of Biosimilarity is built on five indispensable pillars:

- Analytical Similarity
- Pre-clinical Similarity
- Clinical Similarity
- Proper Quality System
- Pharmacovigilance

IFPMA
Importance of Pharmacovigilance

- At the moment of regulatory approval of a biosimilar there is already extensive real world safety/efficacy related evidence/information available on the reference biologic.
- For the biosimilar, specific data is limited to the comparability exercise.
- It is known that (small) changes in the production and purification process of biologicals can have (major) implications on their safety profile, which will mainly be reflected in an altered immunogenicity profile.
- It is highly expected that adverse events based on the pharmacology of the biological are similar between biosimilar and reference product.
- Since the manufacturing process of the reference product is proprietary knowledge, the manufacturer of the biosimilar will not be able to precisely replicate the protein product, which may influence the benefit-risk profile.
- Additionally, the effect of such Biosimilars on diverse patient populations with respect to the dosage and duration of therapy needs to be closely monitored.
Routine Pharmacovigilance & Spontaneously Reported AEs

Routine pharmacovigilance/spontaneous monitoring

- Routine pharmacovigilance includes the collection of spontaneously reported adverse events by healthcare professionals and patients.

- Limitations of spontaneous reports of adverse events have been widely acknowledged and described and include under-reporting and a difficult to establish causality assessment between the adverse events and the drug of interest.

- In the case of biologicals and biosimilars, some additional challenges related to traceability and naming might occur in the assessment of spontaneous reports.

Ref: Sabine MJM Straus, MD, PhD, Medicines Evaluation Board, Utrecht, The Netherlands; Erasmus University Medical Centre, Department of Medical Informatics, Rotterdam, The Netherlands.
RMPs Play a Key Role In Proactive Pharmacovigilance

Proactive Pharmacovigilance

• In geographies like Europe, regulators require biosimilar companies to submit a risk management plan (RMP) along with the marketing application and to provide regular safety update reports after the product is in the market.

• The RMP includes the safety profile of the drug and proposes the prospective pharmacovigilance studies.
  
  • In the RMP, the safety profile of the medicine has to be described and pharmacovigilance activities should be proposed to further study safety concerns during use of the drug in the real-world setting and, if considered necessary, additional risk minimization activities should be described.

• In addition, the need for additional efficacy and safety studies in indications in which the biosimilar has not been studied pre-approval, but that are based on extrapolation, should be evaluated on a case-by-case basis.

• Immunogenicity, including lack of efficacy, is a safety concern that should specifically be addressed in the RMP and the need for additional pharmacovigilance activities should be clearly evaluated.
  
  • Immunogenicity studies conducted post-approval should be done on a product specific basis and are especially important in case no long-term immunogenicity data has been obtained pre-approval.

• Drug and disease-based registries have shown to be important tools for the post-marketing collection of safety data for biologicals in general.
  
  • Biosimilar companies are therefore recommended to participate in already existing registries; this will, for example, improve our knowledge on very rare adverse events like progressive multi-focal leukoencephalopathy, PRCA etc.

Ref: Sabine MJM Straus, MD, PhD, Medicines Evaluation Board, Utrecht, The Netherlands; Erasmus University Medical Centre, Department of Medical Informatics, Rotterdam, The Netherlands.
Biological Qualifier (BQ)
Biological Qualifier (BQ) – A Useful Tool For Effective PV

Biological Qualifier – a unique and valuable link for PV

- PV requires accurate and shared monitoring of signals
- Variety of reporting requirements for ADR globally
  - Only one region specifically addresses biotherapeutics
- Within countries and regions, excellence in PV
- Critical goal is to link these systems globally
- BQ provides this unique global link, enhancing oversight of patient safety
Biological Qualifier’s Design Considerations

- The proposed BQ consists of a randomly generated 4 letter code
- The 4-letter code is acceptable, but WHO should consider whether a shorter code would facilitate adoption by DRAs and be more memorable for users
- Use of BQ in conjunction with the INN (e.g. “epoetinalfabbbbb”)  
  Not part of the INN
- Could be used to identify a product’s drug substance in lieu of trade names for drug compendia and for prescribing and dispensing (e.g. “epoetinalfabbbbb4,000 IU/0.4 mL injection”)
- Can be adapted by drug regulatory authorities (DRAs) for local nomenclature and labelling standards could facilitate product identification and PV
- Consistent and durable
- Given to all biotherapeutics’ active substances
- Globally consistent and durable
- Linked to the parent company/entity responsible for the licensure globally
- Non-discriminatory in its application
- Independent of a regulatory pathway
Biological Qualifier’s Application Considerations

BQ application

• Applicable prospectively and retrospectively
• Issued to the sponsor in advance of submission of the product’s marketing authorization application
• For inclusion in labelling information
• Communicated to the “pertinent” DRA for validation in database
• Careful implementation where applied retrospectively to marketed products to avoid confusion for stakeholders
• Avoiding restriction of import/export of medicinal products or substances unnecessarily
• Further details needed on process for retrospective assignment of BQ
• Applicable to all biological substances assigned or registered INNs
• Opportunity for the applicant to review prior to BQ assignment
Closing Thoughts

- **Clinical immunogenicity** is a critical contributor to the totality of the evidence and is key to determining safety and efficacy of biosimilars.

- Only clinical studies are appropriate for detecting immunogenicity; there is no adequate analytical, in vitro or animal model to predict clinical immunogenicity.

- **Repeated switches** between the biosimilar(s) and an originator’s product may increase immunogenicity with potentially negative clinical effects.

- **Risk Management Plans (RMP)** Are a Key Component Of Proactive Pharmacovigilance.

  - The RMP includes the safety profile of the drug and proposes prospective pharmacovigilance studies.

  - The WHO proposed **Biological Qualifier** (BQ) is an useful tool for effective pharmacovigilance.

  - Some of the Ideal characteristics of the BQ would consist of the following:
    - Given to all bio therapeutics’ active substances
    - Globally consistent and durable
    - Linked to the parent company/entity responsible for the licensure globally
    - Applicable prospectively and retrospectively
    - Issued to the sponsor in advance of submission of the product’s marketing