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GRX+BIOSIMS CONFERENCE

Considerations for Evaluating the Immunogenicity Risk of Biosimilars

October 27, 2025

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General Requirements—Section 351(k) PHS Act

(1) IN GENERAL.—Any person may submit an application for licensure of a biological product under this subsection.

(2) CONTENT.—

(A) IN GENERAL.—

(i) REQUIRED INFORMATION.—An application submitted under this subsection shall include information demonstrating that—

(I) the biological product is biosimilar to a reference product based upon data derived from—

(aa) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;

(bb) an assessment of toxicity (which may rely on, or consist of, a study or studies described in item (aa) or (cc)); and

(cc) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product;

Why an Immunogenicity Assessment?

Since biosimilars are derived from living organisms, there is a potential for the body to mount an unwanted immune response ("immunogenicity risk")

- The consequences of immune responses to therapeutic protein products can range from no apparent effect to serious adverse events (AEs), for example:
  - Although incidence is very rare, potential AEs could include life-threatening complications such as anaphylaxis or neutralization of endogenous proteins with nonredundant functions
  - Other potential immune-mediated AEs (hypersensitivity, other infusion reactions, injection site reactions)
  - Altered pharmacokinetics that impact efficacy

How to Evaluate Immunogenicity of Biosimilars?

Recognized that certain reference products may have inherent immunogenicity risk based on their mechanism of action, functional redundancy and degree of antigenicity ("non-self") and biosimilars to those reference products will carry same risk

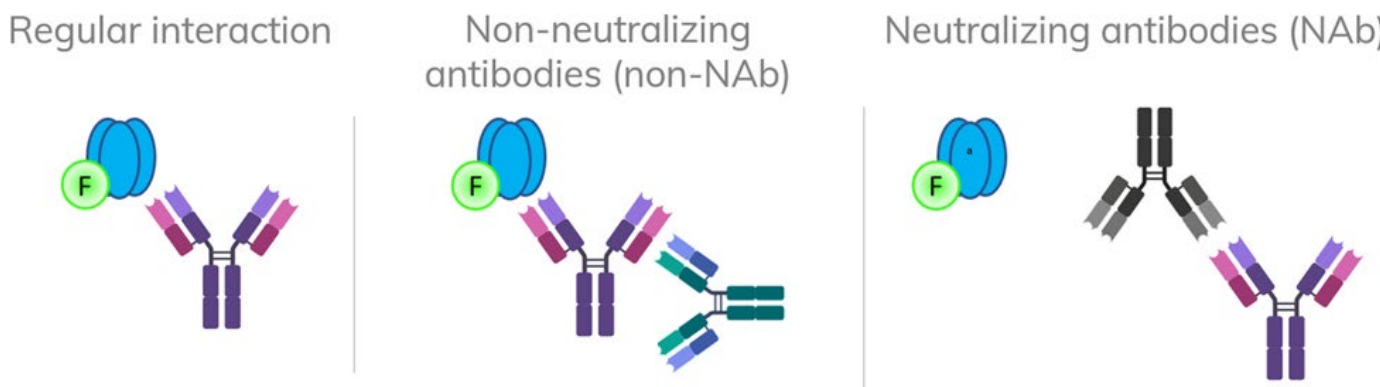
- In general, immunogenicity is assessed based on comparative clinical data
  - Insulin products being an exception*
- Because immune responses to a therapeutic protein commonly involve humoral mechanisms, circulating anti-drug antibodies (ADA) has been the chief criterion comparing immunogenicity:
  - Compare ADA Incidence and their neutralizing ability (nAb)
  - Conduct impact assessment of ADA/nAb positivity on PK or safety events

* See FDA draft guidance for industry, *Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products (2019)*

Anti-Drug Antibodies and Neutralizing Antibodies

Anti-Drug Antibodies (ADAs)
• Antibodies that develop in response to therapeutic protein • May or may not inactivate the therapeutic protein or otherwise cross-react with endogenous proteins.

Neutralizing Antibodies (nAbs)
• Specific type of ADA that binds to the drug (e.g., mAb) and inhibits its intended pharmacological function by preventing target binding.



ADAs can be either neutralizing or non-neutralizing; neutralizing antibodies (NAbs) interfere with the target binding of a therapeutic protein (e.g., another mAb as shown here).

Figure modified from Pedersen et al, 2022 (Scientific Reports); https://www.nature.com/articles/s41598-022-08682-3

For more information: Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection | FDA

Clinical Immunogencity Assessments

Typical Clinical Study Designs supporting Biosimilarity

Pharmacology studies

- Healthy subjects
- Single dose
- 1º endpoint(s):
  - PK or PK/PD parameters
- Safety/Immunogenicity

Comparative clinical studies

- Patients
- Multiple doses
- 1º endpoint:
  - Efficacy outcome
- Safety/Immunogenicity

Clinical Study Results Supporting Biosimilarity

Clinical Outcome	Endpoints (e.g.)	Data Analysis
Pharmacokinetics (PK)	$AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}	**Prespecified criteria** • 90% CI GMR within 80-125%
Pharmacodynamics (PD)	$AUEC_{0\text{-}t}$, $AUEC_{0\text{-}inf}$	
Efficacy	Clinical outcome or surrogate endpoint	**Prespecified criteria** • Statistical test; equivalence margin based on historical trials with reference product
Safety	Adverse events (n/N)	**Descriptive comparison** • Should also align with reference product experience
Immunogenicity	ADA and nAb incidence (n/N)	**Descriptive comparison** • Comparison within program only • Results are assay specific

Immunogenicity—What's the Risk?

Biosimilars are expected to have the same safety and effectiveness as the reference product, including incidence and severity of immunogenicity

Possible causes	Biosimilar Risk?	Risk Mitigation Strategy
Dose, frequency, route of administration	Same as reference product (RP)	n/a
Mechanism of Action	Same as RP	n/a
Patient population	Same as RP	n/a
Product-related "impurities"	Product specific	Comparative analytical assessment
Process-related "impurities"	Product specific	Appropriate manufacturing and process controls

Quality Attributes in the Comparative Analytical Assessment

Structure

Primary Structure
- Sequence
- Sequence Variant
- Deamidation
- Oxidation
- Phosphorylation
- Isoaspartate
- Conjugation Site

Higher Order Structure
- Free Thiols
- Disulfide Bonds
- Thioether
- Thermal Stability
- Secondary, Tertiary, and Quaternary Structure

Size Variants
- Monomer
- High MW – All
- High MW – Dimer
- Residual Homodimer
- Low MW – All
- Low MW – Individual

Linked Non-protein Polymer
- N-glycosylation
- O-glycosylation
- Conjugation

Active Ingredient

Charge
- Acidic Variants
- Basic Variants
- Neutral Main Peak
- Profile
- pI

Mass
- Intact MW
- Non-glycosylated MW

Absorbance
- Extinction Coefficient

Function

Cellular Evaluation
- ADCC
- ADCP
- Apoptosis
- Neutralization
- CDC
- Proliferation
- Inhibition
- Cytotoxicity

Binding
- FcRn
- C1q
- FcγRIa
- FcγRIIa
- FcγRIIIa
- Target Binding

Enzymatic Evaluation
- Kcat
- Km
- Activity

Material Properties

General Attributes
- Protein Concentration

Process-related impurities are evaluated to further establish biosimilar product quality and safety but are not assessed comparatively

Categories and subcategories adapted from Welch et al. Bulleted subcategories should not be considered exhaustive. For complete details of taxonomy see: Welch et. al., 2024 (AAPS Open). A controlled vocabulary and taxonomy for the submission of quality attributes for therapeutic proteins

Are Clinical Immunogenicity Data Always Needed?

- Our awareness and scientific understanding of immunogenicity concerns associated with biosimilars has increased since the time when recommendations for the clinical data needed to demonstrate biosimilarity and interchangeability were developed[1,2]
- The comparative analytical assessment that is part of every biosimilar application is recognized as a more sensitive evaluation than clinical data for potential differences between products that have the potential to impact clinical performance of biosimilars, including immunogenicity[3,4]
- Given the above, a refined approach for determining when clinical immunogenicity data are useful to support the demonstration of biosimilarity is needed

[1] FDA draft guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product: Update (June 2024)
[2] Cavazzoni P, Yim S. The Science of Biosimilars—Updating Interchangeability. *JAMA.* Published online September 18, 2024
[2] Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: a systematic review and meta-analysis. PLoS One. 2023;18(10):e0292231.
[3] Kurki P, Barry S, Bourges I, Tsantili P, Wolff-Holz E. Safety, immunogenicity and interchangeability of biosimilar monoclonal antibodies and fusion proteins: a regulatory perspective. Drugs. 2021;81(16):1881-1896.

Thank You!