# IMMUNOGENICITY AND BIOSIMILARS: MOVING FROM SMALL TO LARGE MOLECULES

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All data in this presentation are modified, and were crafted specifically as example scenarios

# LEARNING OBJECTIVES

- What Are Biosimilars?
- What Regulatory Pathways Apply to Biosimilars?
- What Types of Clinical Studies are Required for Biosimilar Applications?
  - PK Assays
  - Immunogenicity Assays – Anti-Drug Antibodies
  - Parallel vs. Crossover Design
  - The Tiered Assay System

# WHAT ARE BIOSIMILARS?

- **The FDA defines a biosimilar as:** ***a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product***
  - ***Why "similar"? Why not "equivalent"?***
  - ***Small molecules are made by chemical synthesis – the active ingredient is exactly the same as the reference product***
  - ***Large molecules are produced by recombinant technology; minor changes in things like post-translational modifications can occur during production***

- ***Examples of biosimilars:***
  - ***Adalimumab***
  - ***Pegfilgrastim***
  - ***Infliximab***

# WHAT ARE BIOSIMILARS?

- **What is meant by "*no clinically meaningful differences*"?**
  - ***The biosimilar must have the same mechanism of action as the reference product***
  - ***Must have the same route of administration***
  - ***Must have the same dosage form***
  - ***Must have the same strength***
  - ***Elicit the same clinical efficacy***
  - ***No differences in safety***

***Biosimilars can be thought of as the generics of the large molecule world……however, there are some very significant and important differences to keep in mind with biosimilars, for example Immunogenicity, that will be the emphasis of this talk***

# WHAT REGULATORY PATHWAYS APPLY TO BIOSIMILARS?

- ***Biological products are regulated under Section 351 of the Public Health Service (PHS) Act***
- ***Specifically, biosimilars are regulated under Section 351(k) of the PHS Act, which defines the requirements for a proposed biosimilar application***
- ***Abbreviated licensure pathway for biologics***
- ***A biosimilar is evaluated against a reference product licensed under 351(a)***

***While biosimilars are licensed under the PHS Act, there are aspects of these drugs that still fall under the Food Drug and Cosmetic (FD&C) Act***

https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products

# WHAT REGULATORY PATHWAYS APPLY TO BIOSIMILARS?

- ***There are multiple guidance documents available for Biosimilars:***
  - ***Scientific Considerations in Demonstrating Biosimilarity to a Reference Product***
  - ***Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product Guidance for Industry***
  - ***Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product***
  - ***Questions and Answers on Biosimilar Development and the BPCI Act Guidance for Industry***
  - ***Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry***

https://www.fda.gov/regulatory-information/search-fda-guidance-documents

# WHAT REGULATORY PATHWAYS APPLY TO BIOSIMILARS?

- ***Under Section 351(k) of the PHS Act, the following data are required for a biosimilar application:***
  - ***Analytical data: demonstrate that the biosimilar is highly similar to the reference product; structural and functional characterization; stability; manufacturing processes; etc.***
  - ***Toxicity data from animal-based studies***
  - ***Clinical data: demonstrate efficacy and safety; comparative human pharmacokinetic (PK) and pharmacodynamic (PD; if needed) data; immunogenicity***

# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

## *PK Studies*

- *Clinical studies should be conducted to assess PK and PD (if needed) for a biosimilar application*

- *Conducted in a normal healthy human population; single dose; similar to a bioequivalence study for generic drugs*
- *Can also be conducted in the targeted patient population(s), often with multiple doses; e.g. rheumatoid arthritis patients for infliximab*

- *On the analytical side, large molecule PK studies analyzed using plate-base ligand-binding assays*
- *The PK assay should be able to accurately and precisely quantitate drug concentrations for the biosimilar and reference drug(s)*
- *Acceptance Range: 80% - 125% with a 90% confidence interval*
- *PK parameters; $C_{max}$, AUC*

- *PD studies – assess, for example, the absolute neutrophil count (ANC) for a filgrastim or pegfilgrastim biosimilar*

# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

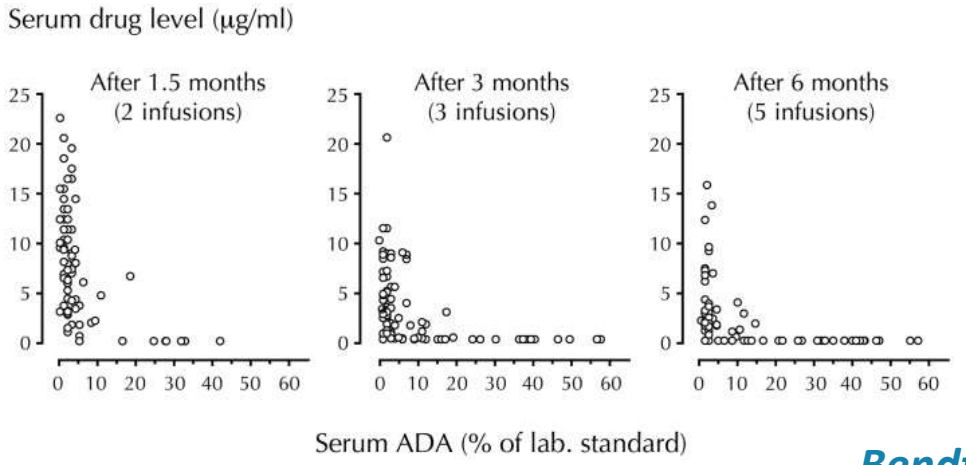
## *Immunogenicity*

- *How can immunogenicity affect efficacy/safety of a biosimilar?*
  - *Could affect the PK profiles of a drug*
    - *Block target binding*
    - *Increase clearance*
    - *Induce aggregation of the drug*
    - *Induce steric changes*
    - *Any of these could lead to loss of efficacy*
  - *Could increase the rate of adverse reactions; e.g., injection site reactions or anaphylaxis*
  - *If the drug mimics an endogenous protein (e.g., erythropoietin), ADAs could inhibit not only the drug but the endogenous protein as well*

# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

## *Immunogenicity*

- ***Development of ADAs against TNF antagonists is common; often within the first 6 months***
- ***Associated with diminished drug availability in circulation and reduced efficacy/response failure***
- ***A study of rheumatoid arthritis patients receiving infliximab revealed that 40% had infliximab ADAs; accompanied by reduction in serum drug levels***




***Graphs show increasing rate of ADAs over time with concurrent decreases in drug concentrations***

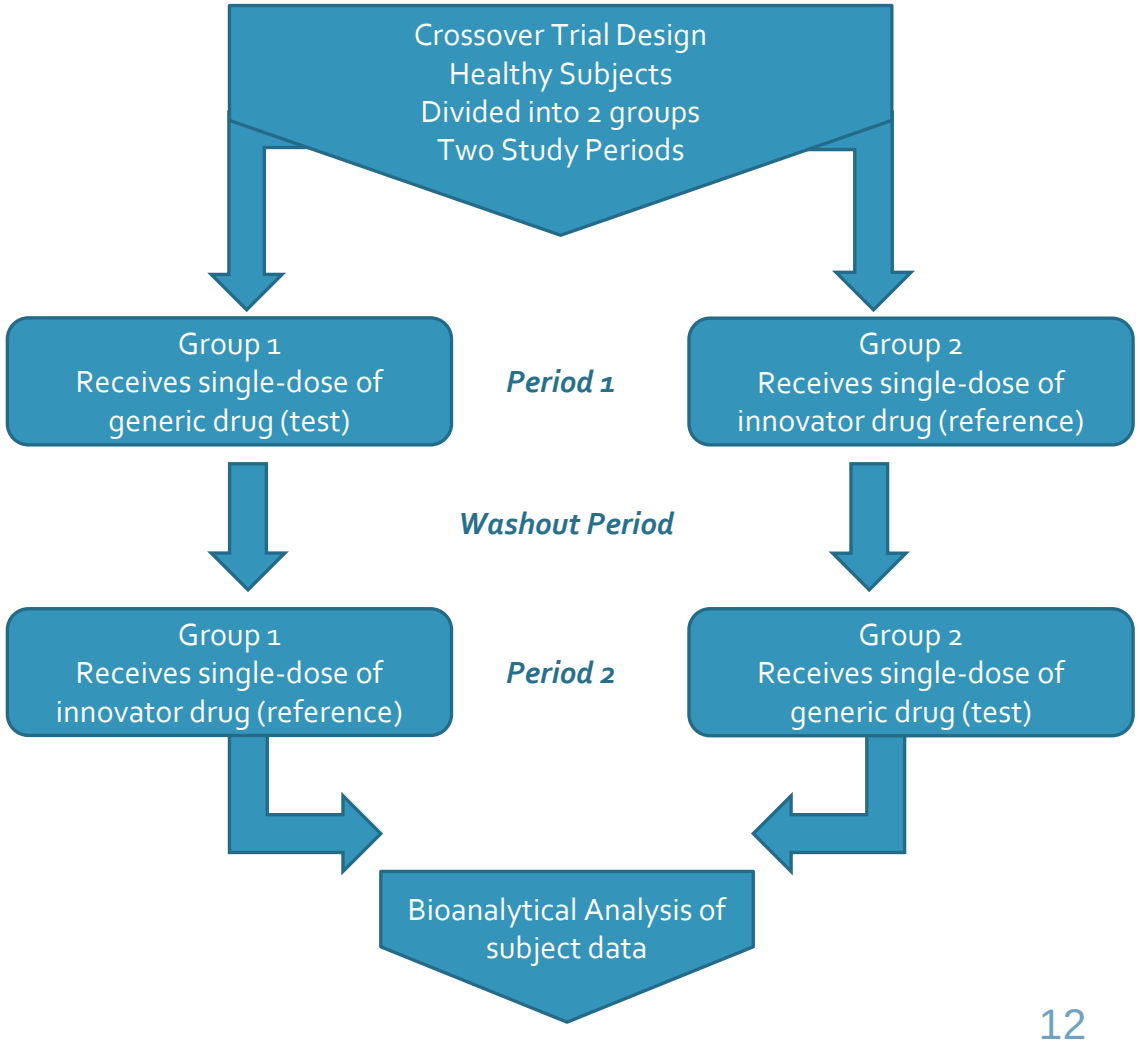
***Bendtzen, 2015***

# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

## *Immunogenicity*

- ***How is Immunogenicity assessed?***
  - ***Assessed as part of the clinical study data in addition to PK/PD***
  - ***Compare the rate of ADAs between the biosimilar and the reference drug***

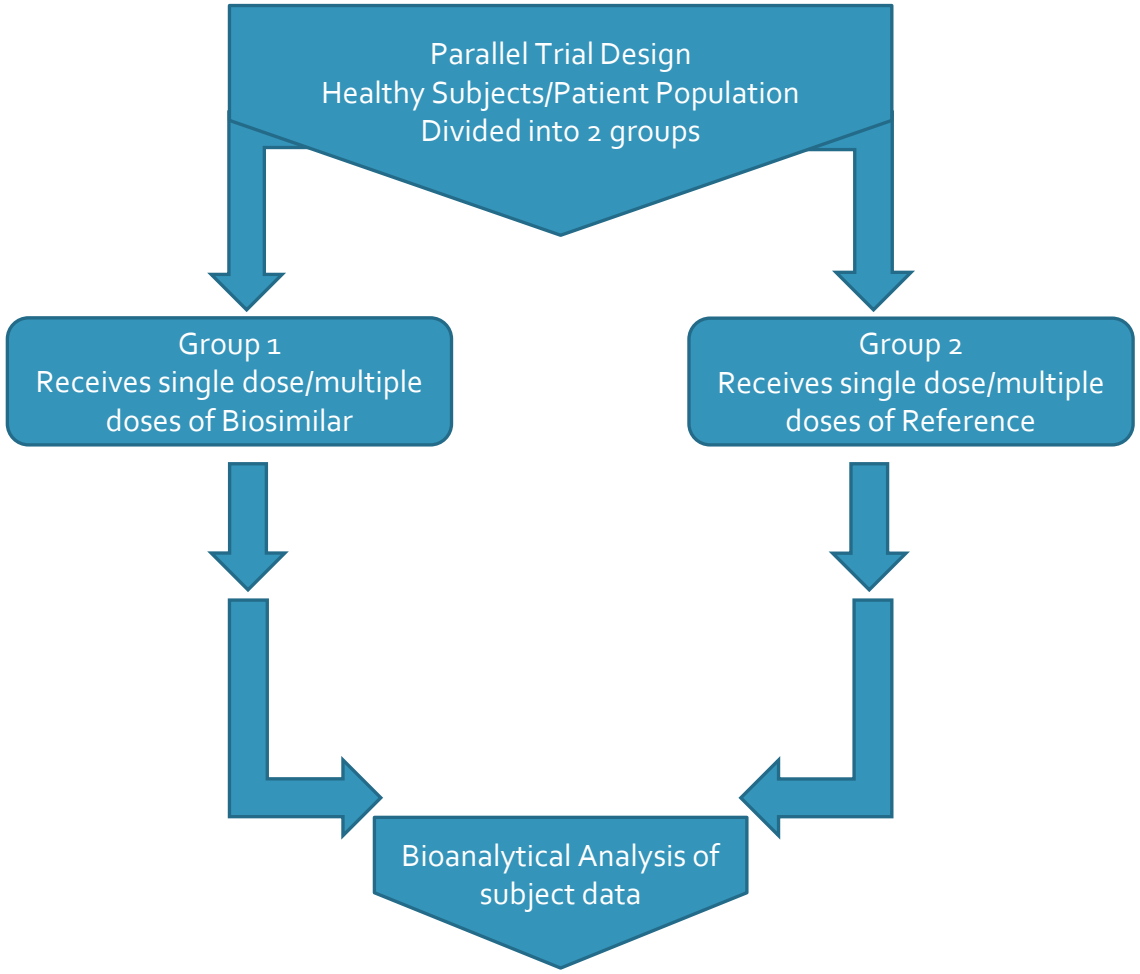
- ***Parallel vs. Crossover Study Design:***
  - ***Most BE studies are conducted using a <u>Crossover Design</u>***
  - ***Every subject in the trial receives one dose of test and one dose of reference***
  - ***Washout period in between***
  - ***Can be used for biosimilar PK assessments***



# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

## *Immunogenicity*

- ***Biosimilar studies, especially for immunogenicity, are conducted using a <u>Parallel Design</u>***
  - ***Why?***
  - ***An immune response/development of ADAs takes time***
  - ***Long half life of ADAs***
  - ***Typical washout period insufficient***
  - ***Cannot distinguish ADAs generated in response to the biosimilar compared to those generated from the reference drug***
  - ***Also, more conducive for multi-dose studies***

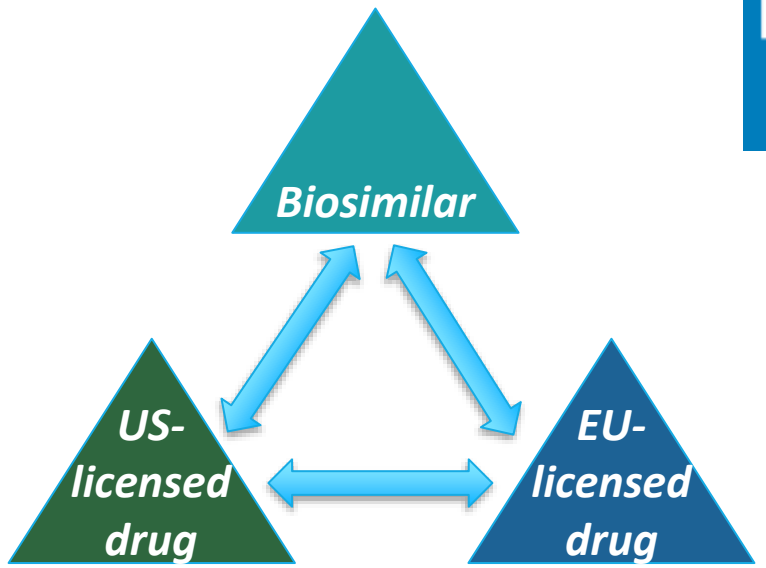


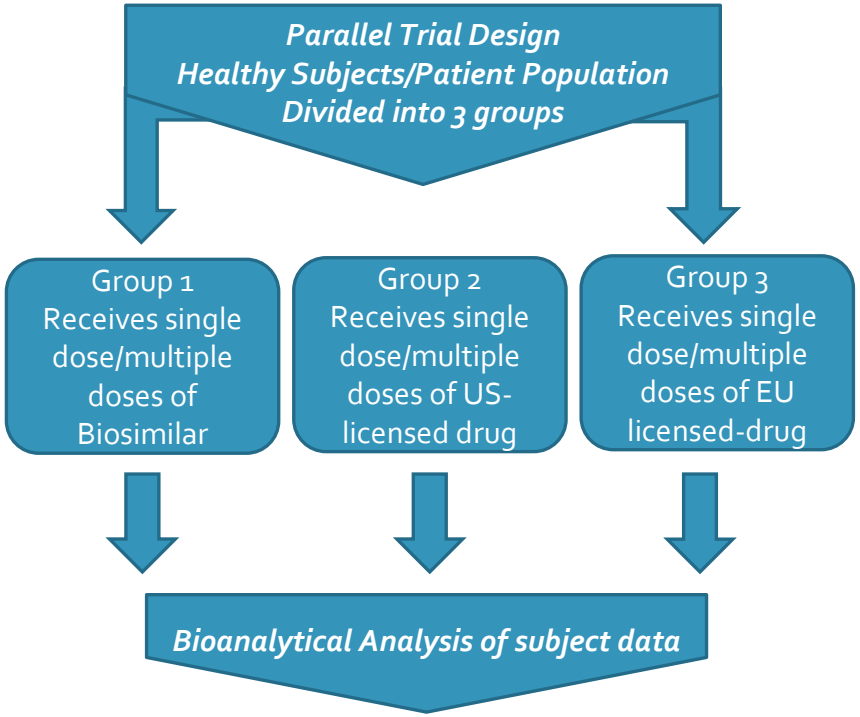
# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

## *Immunogenicity*

- *A biosimilar must be compared to a US-licensed reference product; cannot be, for example, an EU-licensed product*
- *Frequently, companies have extensive data for the non-US-licensed reference drug*

- *Bridging Study:*
  - *Compare biosimilar to US-licensed reference drug*
  - *Compare biosimilar to EU-licensed reference drug*
  - *Compare the US-licensed reference drug to the EU-licensed reference drug*



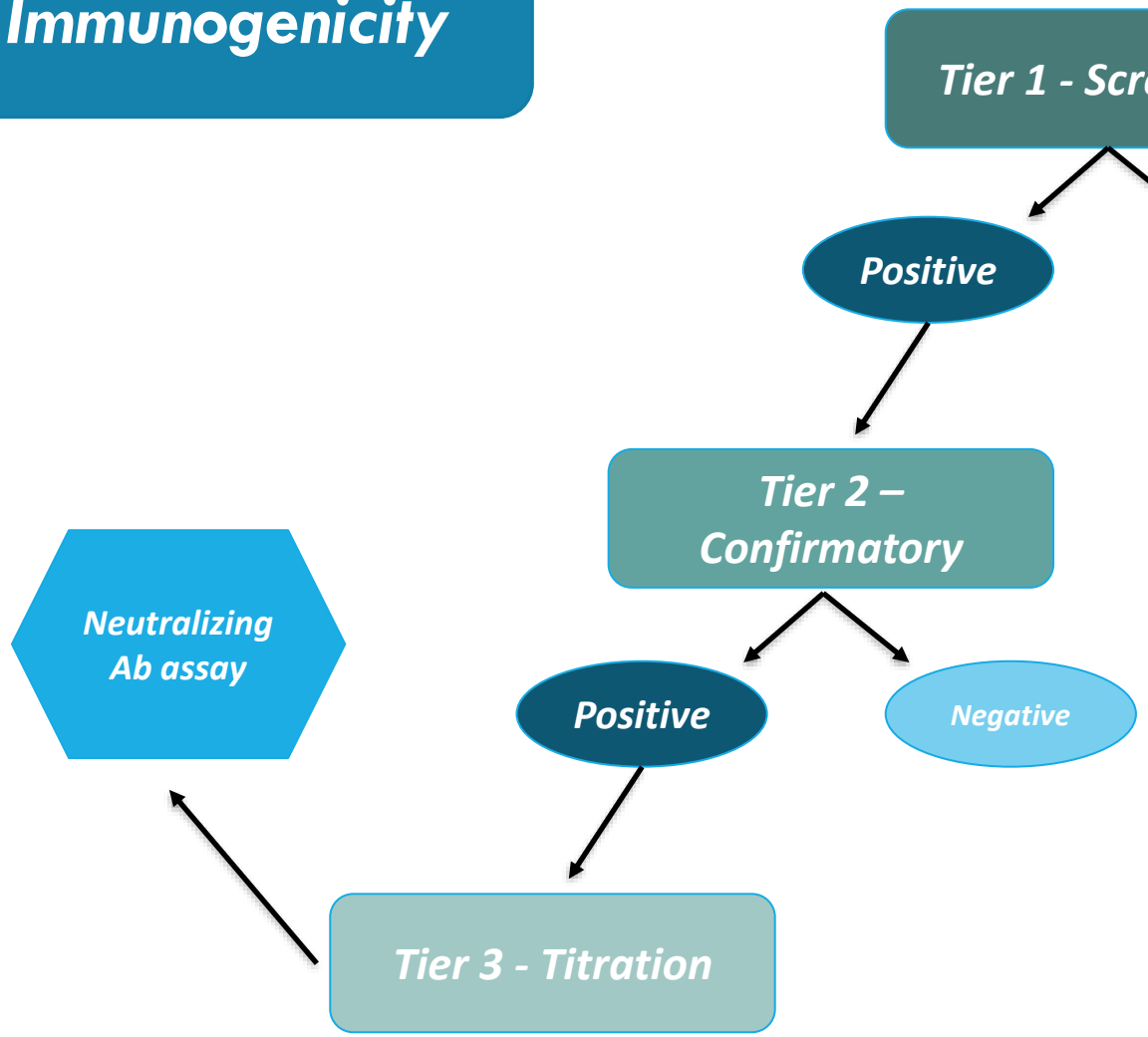
# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

## *Immunogenicity*

- *How is immunogenicity analyzed?*
  - *Detection of ADAs generated in response to treatment*
  - *Can use multiple assay types to assess ADAs*
    - *Plate-based ligand-binding assays (e.g., ELISA, electrochemiluminescence [ECL])*
    - *Cell-based assays*
    - *Radioimmunoassays*
  - *ADA assays are typically semi-quantitative*
  - *Assessed using a tiered assay system*

# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

**Immunogenicity**




*Highly sensitive; rapid; err on the side of false positives; negative samples not assessed again*

*Less sensitive, but highly specific; weed out false positives;*

*Obtain a relative level of ADAs in a sample which has been confirmed positive; back to high sensitivity*

# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

## *Immunogenicity*

- *Neutralizing Antibodies: A subset of ADAs that bind to the drug and inhibit its pharmacological functions*
  - *NAbs are the ADAs that contribute to treatment failure, and other efficacy and safety issues*
  - *Most clinically relevant ADAs; important to know if NAbs are present; considered in assessment of biosimilarity*

- *Samples that confirm positive in Tier 2 of an ADA assay should be assessed for the presence of NAbs*

- *Types of NAb assays:*
  - *Plate-based, ligand-binding assays (similar to ADA assays)*
  - *Cell-based assays – directly assess the effect of an NAb on the biological response of a drug (e.g., cell growth, apoptosis, cytokine release, phosphorylation, etc.)*

  - *Pros and cons to each type*

# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

## *Immunogenicity*

- *Challenges in assessing immunogenicity (many of these also apply to PK assays too!)*
  - *Drug tolerance – interference in the assay from the drug itself*
  - *Target interference – the drug target (e.g., cytokine) may bind to assay components and interfere with the assay*
  - *Matrix effects/interferences – rheumatoid factors, soluble receptors, non-specific binding proteins, etc.*
  - *Pre-existing antibodies*

  - *Balancing sensitivity and specificity while trying to account for all potential interferences is highly challenging*

# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

**Challenge Question #1**

- *Is the following statement True or False?*
- *Under 351(k) of the PHS Act, biosimilars must be demonstrated to be highly similar to and have no clinically meaningful differences from an existing reference product licensed in the US or elsewhere*

# WHAT TYPES OF CLINICAL STUDIES ARE REQUIRED FOR A BIOSIMILAR APPLICATION?

**Challenge Question #2**

- *Which of the following study designs can be used in a biosimilar application?*
  - *a) Crossover Design*
  - *b) Parallel Design*
  - *c) Bridging Design*
  - *d) All of the above*