FDA Regulatory Perspectives on Therapeutic Protein Immunogenicity- an Update

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Immunogenicity- clinical concerns raised by Anti-drug Antibodies (ADA)

Clinical Concern	Clinical Outcome
Safety	• Hypersensitivity reactions •Neutralize activity of endogenous counterpart with unique function causing deficiency syndrome
Efficacy	Enhancing or decreasing efficacy by: • changing half-life. • changing biodistribution.
Pharmacokinetics	• Changes to PK • Changes to PD
None	• Despite generation of antibodies, no discernable impact

FDA Immunogenicity Guidances

- Guidance (2014): Immunogenicity Assessment for Therapeutic Protein Product-
  - discusses product and patient risk factors that may contribute to immune response rates.

- **Draft Guidance (2016): Assay Development for Immunogenicity Testing of Therapeutic Proteins**
  - **Discusses how to set up immunogenicity assays**

- Guidance (2015): Scientific Considerations In Demonstrating Biosimilarity To A Reference Product
  - Discusses immunogenicity assays in context of 351K pathway

- *Guidance (2011) General Principles for the Development of Vaccines to Protect against global infectious diseases*
  - assessment of immune response to preventative and therapeutic vaccines for infectious disease indications

Therapeutic Protein Immunogenicity at the FDA

- Who reviews it?
  - CBER- allergenics, blood and blood components including clotting factors, cellular and gene therapies, vaccines
  - CDER - Hormones, cytokines, enzymes, monoclonal antibodies, fusion proteins, growth factors, thrombolytics, therapeutic toxins

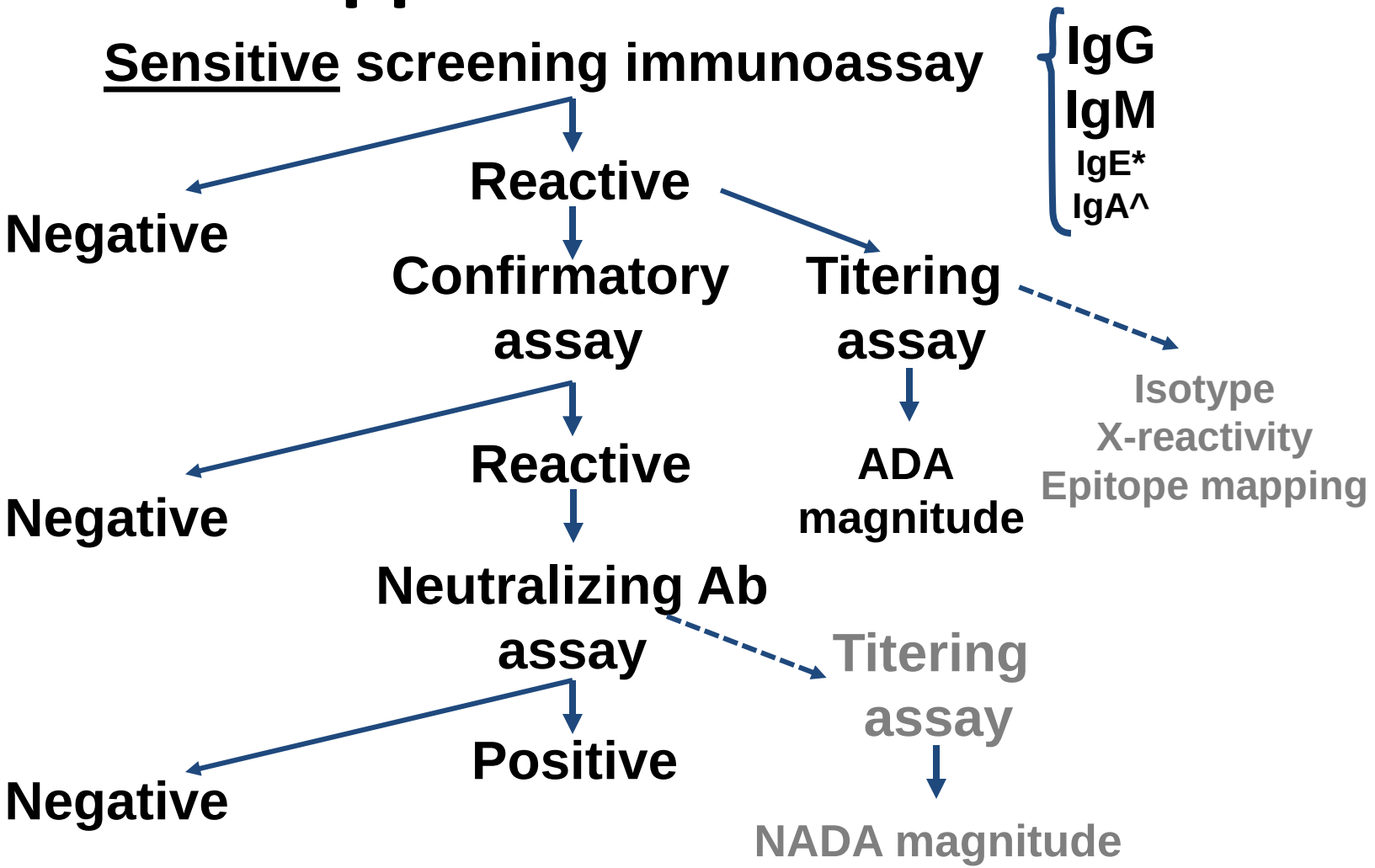
Office of Biotechnology Products (OBP)

- CMC for therapeutic proteins under CDER purview
  - Historically divided along product classes
  - Currently 4 product divisions with mixed portfolios
- Collaborate in immunogenicity risk assessments and review validation of clinical immunogenicity assays for biologics and drugs at CDER
  - Involved in writing FDA Immunogenicity guidances
  - Immunogenicity Working group

FDA Regulatory Expectations

- There are regulatory expectations from the FDA
  - Sponsors need to provide immunogenicity risk assessment and suitable sampling plan for clinical studies
    - Multi-disciplinary risk based analysis early in product development
    - Follow a multi-tiered approach to analyze immunogenicity
  - Sponsors need to develop validated immunogenicity assays
    - Binding antibody assay
    - Confirmatory assay
    - Titering Assay
    - Neutralizing antibody assay(s)

Multi-tiered immunogenicity approach



Preclinical Immunogenicity

- How much preclinical immunogenicity data is needed?
  - Immunogenicity in animal models is typically not predictive of immunogenicity in humans
  - Assessment of immunogenicity in animals is primarily useful to interpret nonclinical toxicology and pharmacology data.
  - Immunogenicity in animal models may reveal potential antibody related toxicities that could be monitored in clinical trials.
  - May reveal immunogenicity differences between biosimilar and reference product.

- What level of immunogenicity assay validation and is needed for preclinical studies?
  - Assay Validation reports required for the BLA

What level of immunogenicity testing is needed in each phase of a clinical program?

- Phase-dependent assay development
  - For initial phase I studies, ADA can be measured with a suitable assay fit for intended purpose,
  - Have all assays validated prior to testing clinical phase 3 study samples for 351 A (Innovator) product
  - For 351 K (Biosimilar) start discussions early
  - Crucial to have appropriately stored study samples.

- Assays are critical when neutralizing immunogenicity poses a high-risk
  - real time data concerning patient responses may be needed as part of risk assessment and mitigation
  - Preliminary validated assays should be implemented early (preclinical and phase I)

ADA Assay Design

- ADA assays are qualitative or quasi-quantitative (e.g. titer format)
  - Assays are generally threshold assays
  - Assay results reported as positive or negative or some form of titer
  - Assay results are not reported in absolute values such as mass
- Matrix effects are evaluated during assay development
  - Matrix dilution
  - Assay format
  - Assay platform

NAb (me well) Assay Design

- Types of assays generally used: cell-based biologic assays and non cell-based competitive ligand-binding assays.
- **FDA recommends use of cell-based bioassays as they tend to be more reflective of the in vivo situation**
- The bioassay should be related to product MOA to be informative as to the effect of NAb on clinical results
- Competitive ligand-binding assays may be the only alternative in some situations
- Assays may use direct (inhibition of stimulation) or indirect (inhibition of inhibition) assessment

Immunogenicity Assay Development for Biosimilars

- Allow for single assay based on the biosimilar product used to test serum samples from both biosimilar and reference product treated subjects.
  - For NAb assay, if bioassay is used, should show cellular responsiveness to both biosimilar and reference product.
    - Even if reference product had no NAb assay, you should develop one to test ADA+ samples

Immunogenicity Validation Parameters

- Assay cut points- 95% SA and 99% CA , TA, and NAbA
- Sensitivity- recommended 100 ng/ml* for SA and CA
- Drug tolerance
- Specificity
- Selectivity/ Matrix interference
- Minimum Required Dilution
- Precision and reproducibility
- Robustness and sample stability
- System suitability controls (LPC, *MPC*, HPC, NC)

Post-Assay Validation:

- Life-cycle management of immunogenicity assays
  - Novel clinical indications may require assay requalification
  - Phase IV/post marketing surveillance could provide continued immunogenicity monitoring
  - NAb Assays may be improved/modified with increased understanding in the product mechanism of action

Recommendations for conducting worldwide immunogenicity clinical trials

- Same standards of Good Clinical Practice as for clinical trials conducted under IND in the United States
- For biosimilars, **comparative parallel trial design** (i.e., a head-to-head study) in treatment-naïve patients as the most sensitive design for a premarketing study
  - Sponsors should justify the study population used to compare immunogenicity
  - Sponsors should obtain agreement from FDA on these criteria before initiating the study

Recommended clinical sampling strategy

- Pre-exposure samples should be obtained from all patients.
- Samples to determine serum concentrations of therapeutic protein product should be obtained at the same time as immunogenicity samples.
- Subsequent samples should be obtained with timing depending on the frequency of dosing.
- Samples should be obtained when there will be minimal interference from product present in the serum.
- If drug-free samples cannot be obtained during the treatment phase of the trial, then additional samples should be obtained after an appropriate washout period (e.g., five drug half-lives).
- If the drug is itself an immune suppressant, obtain samples from patients who have undergone a washout period.
- Under circumstances when testing for IgE is needed, the timing of sample collection should be discussed with FDA.

Recommended terminology and classification of responses:

–Qualitative Status
- •screen positive at baseline and/or during trial
- •confirmed positive at baseline and/or during trial
- •NAb positive at baseline and/or during trial

– Specificity
  - Confirmation with cold competition

– Titer

– Isotype

– Time course of development,

– Persistence/disappearance,

– Association with clinical sequelae
  - Safety/Adverse Events
  - Efficacy
  - Impact on PK/PD

FDA regulatory perspectives

- Immunogenicity *will* likely happen for most therapeutic proteins
  - Multi-disciplinary risk based analysis early in product development.
    - The higher the risk category for the product, the faster the pace of assay development should take place.

FDA regulatory perspectives

- There are many product related factors which influence immunogenic responses to therapeutic proteins
  - It is a safety concern, there is a need to assess/measure it.
    - ADA may impact safety and/or efficacy
    - NAb assessment is expected
    - Correlate with clinical data (AE, pK and pD) **if possible**
    - A combination of ADA & PK/PD does not (yet) serve as alternative to dedicated NAb assays
    - Life-cycle management of immunogenicity assays

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