FDA Regulatory Perspectives on Therapeutic Protein Immunogenicity—an Update

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

<table>
<thead>
<tr>
<th>Clinical Concern</th>
<th>Clinical Outcome</th>
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<tbody>
<tr>
<td>Safety</td>
<td>• Hypersensitivity reactions&lt;br&gt;• Neutralize activity of endogenous counterpart with unique function causing deficiency syndrome</td>
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<tr>
<td>Efficacy</td>
<td>Enhancing or decreasing efficacy by:&lt;br&gt;• changing half-life.&lt;br&gt;• changing biodistribution.</td>
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<tr>
<td>Pharmacokinetics</td>
<td>• Changes to PK&lt;br&gt;• Changes to PD</td>
</tr>
<tr>
<td>None</td>
<td>• Despite generation of antibodies, no discernable impact</td>
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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• Draft Guidance (2016): Assay Development for Immunogenicity Testing of Therapeutic Proteins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

www.fda.gov
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

www.fda.gov
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

Sensitive screening immunoassay

Reactive

Confirmatory assay

Reactive

Neutralizing Ab assay

Positive

Negative

Negative

Negative

Titering assay

ADA magnitude

Isotype X-reactivity Epitope mapping

IgG

IgM

IgE*

IgA^
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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