FDA Draft Guidance on Immunogenicity Testing

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General Overview: ADA Testing

- Sponsors should assess ADA for therapeutic proteins using a tiered approach with multiple, sensitive assays
  - Screening Assay with a 5% false positive rate
  - Confirmatory with a 1% false positive rate
  - Titering Assay
  - Neutralizing Assay with a 1% false positive rate
  - In some situations, sponsors combine the screening and confirmatory, or screening and titering assay, into a single assay.

Assay Validation

- Validation of ADA assays assures the employed assays are suitable for their intended use
- The level of validation depends on the stage of development
- Fully validated assays should be in place prior to testing pivotal studies
- FDA recommends assay validation reports be submitted to the Agency prior to testing clinical samples from pivotal studies

Guidance for Industry

Development and Validation of Assays for Detection of Anti-Drug Antibody (ADA) for Immunogenicity Testing of Therapeutic Protein Products

2016

Draft Guidance

U.S. Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

Center for Devices and Radiological Health (CDRH)

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Assay Design Elements: Immunoglobulin Isotypes

- Screening assays should be able to detect all relevant immunoglobulin isotypes
  - For non-mucosal routes of administration, relevant isotypes are IgM and IgG
  - For mucosal routes of administration, IgA isotypes are expected in addition to IgM and IgG

Assay Design

- Screening assays do not necessarily need to identify isotypes, but need to be capable of binding multiple.
  - For example, the use of Protein A as a detection reagent is not optimal as it fails to detect all immunoglobulin isotypes
  - Conversely, a bridging assay format, with plate bound antigen and label-antigen as a detector, works equally well for all isotypes.
    - Bridging assays detect all isotypes but present their own concerns
      - Multivalent binding of ADA to the antigen on the plate can prevent binding of the detecting reagent
      - Are highly dependent on the product coating density and would be unable to detect lower affinity interactions
      - The labeling of the detection reagent may obscure critical antigenic determinants

- Summary: A single example about how “one size does not fit all”, and you should consider the product in your design of the ADA assay should

Assay Design Elements: Immunoglobulin Isotypes

- IgE-specific assays may be informative for products with a history or high risk of anaphylaxis
- IgG4-specific assays may be informative for products that are chronically administered, or on erythropoietin-treated patients with pure-red cell aplasia.
- IgE and IgG4-specific assays may be requested on a case-by-case basis.

Assay Sensitivity

- ADA assays need to be sufficiently sensitive to detect low levels of ADA before the amount of ADA impact the PK, PD, safety, or efficacy.

- ADA sensitivity generally determined using serial dilutions of positive control antibody into pooled samples from treatment-naïve subjects.

Assay Sensitivity: Positive Control Antibodies

- The assessed sensitivity is highly dependent on the antibody preparation used
  - Polyclonal
  - Affinity purified polyclonal
  - mAb

- The Agency takes the positive control into consideration when reviewing assay sensitivity and modifies its assessments accordingly
- The evaluation of assay sensitivity is useful for gaining understanding overall assay performance and the development of appropriate positive and negative controls

Assay Sensitivity: Positive Control Antibodies

- FDA recognizes that many positive control antibodies are typically xenogeneic to the product and have greater affinity than clinical ADA
  - The affinity purification process may result is loss of low avidity antibodies
  - Sponsor should consider characterizing positive control antibodies prior to and after purification to determine the loss of avidity
  - Selection of positive controls that are more representative of clinical ADA will provide for improved applicability of the ADA assays

Assay Sensitivity

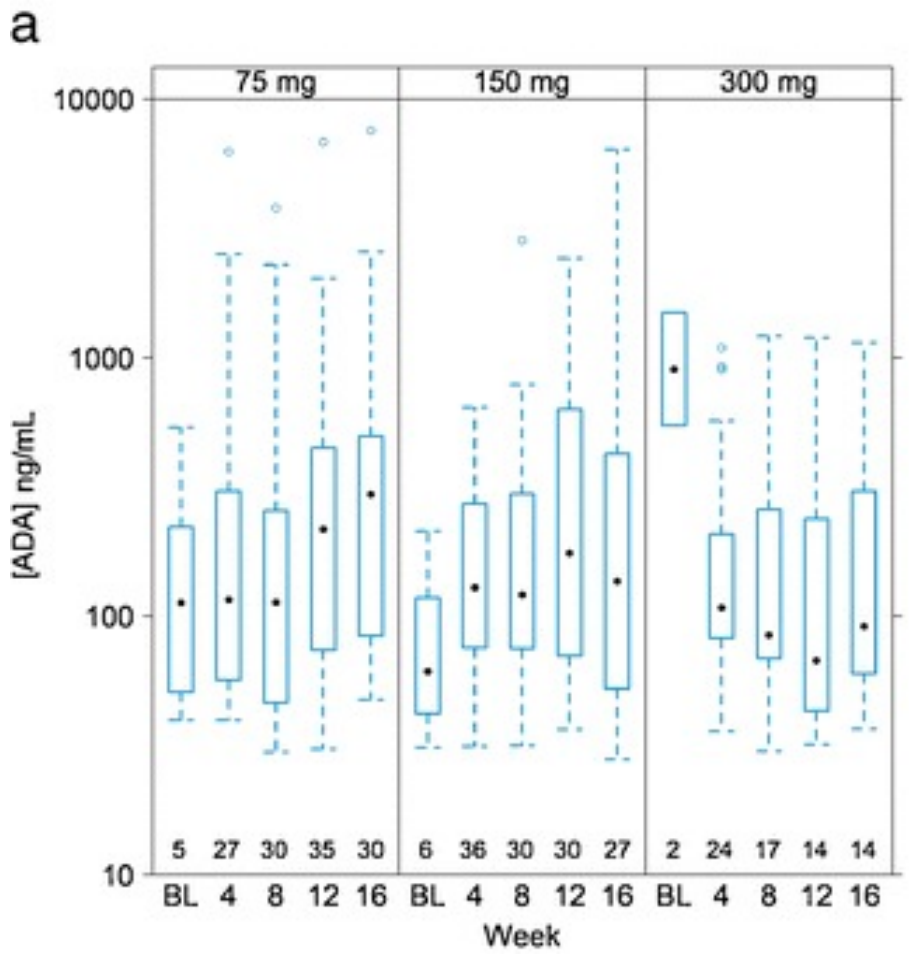
- FDA recommends that screening and confirmatory IgG and IgM assays achieve a sensitivity of 100-500 ng/mL
  - This represents an increased sensitivity from the 2009 draft guidance recommendation of 250-500 ng/mL.
  - Sensitivity recommendations are not requirements, but represent FDA's current expectations based on technology available and our current understanding of ADA's impact on PK, PD, safety, and efficacy.

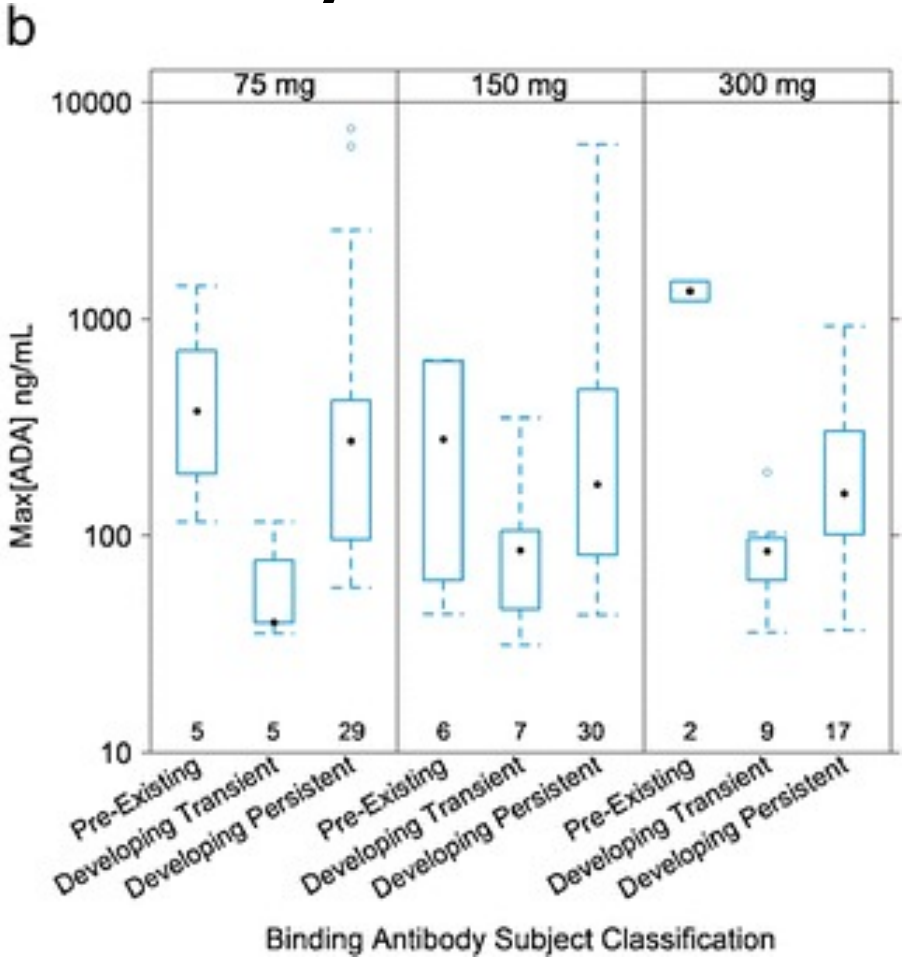
Assay Sensitivity

- The increased sensitivity recommend is based on the current state of the science observed in our filings as well as publicly available studies.

- Zhou et al, AAPS, 2012
- Phase 2 study with AMG 317, a fully human monoclonal antibody with weekly administration on 75 mg, 150 mg, or 300 mg
- Antibody assessment performed at baseline at weeks 4, 8 and 12
- Antibodies classified at Pre-Existing, Developing Transient or Developing Persistent.

Assay Sensitivity





- Patients with developing, persistent ADA responses had ADA levels lower than 100 ng/mL.

Assay Design: Drug Tolerance

- The drug tolerance of the assay is the sensitivity of the assay in the presence of expected levels of interfering therapeutic protein
- Drug tolerance can be determined by adding known amounts positive control antibodies into ADA-negative control samples in the presence or absence of different quantities of therapeutic protein
- Drug tolerance may be improved by disrupting ADA-drug complexes via acid dissociation
- FDA recommends sampling times be chosen when interference from therapeutic proteins is decreased to levels below the drug tolerance level of the assay

General Considerations for Assay Validation

- Assay Validation should include:
  - Cut Point
  - Sensitivity
  - Specificity and Selectivity
  - Precision
  - Reproducibility
  - Robustness

Assay Validation: Cut Point

- Cut points for ADA assays should be set using treatment-naïve patients from an appropriate patient population.
- If appropriate patient samples are not available for pre-study validation, alternative, commercial samples may be used.
  - If alternative samples are used for validation, the cut point should be re-assessed when treatment native patients are available, typically from baseline samples from the clinical study

General Considerations for Assay Validation

- FDA recommends inter-assay precision be assessed on at least 3 different days with two analysts each preparing a minimum of 6 independent preparations of the sample using the same instrument platform and model.
- Intra-Assay Precision: six independent preparations on a single plate.
- FDA recommends a coefficient of variance (%CV) to be under 20%
  - Sponsor's should consider refining assay parameters with higher %CV or provide further justification

Changes to the Validated Process

- Over the course of development, changes to the assay may occur
  - New Testing Labs
  - New Positive Controls
  - New Patient Population
- Sponsors need to determine how much additional validation is needed
- Occasionally, samples may need to be re-tested with an optimized assay
  - Consider preserving sufficient sample volume under appropriate conditions to allow retesting

Summary

- The 2016 update to the Immunogenicity ADA Assay Draft Guidance represents FDA's current thinking

- Some of the most concerned feedback I have received pertain to the increased in the recommended sensitivity of the assay to (100-500 ng/mL), and recommendation to limit %CV to 20%.
  - Based on the reviews I see, many sponsor's are well within our new expectations, and sensitivities < 10 ng/mL, and %CV < 10-15%, are becoming common.

- FDA guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required
  - Guidance for Industry: Enforcement Policy Concerning Certain Prior Notice Requirements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