Pre-Existing Antibodies: When do they matter? What to do with them?

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Outline

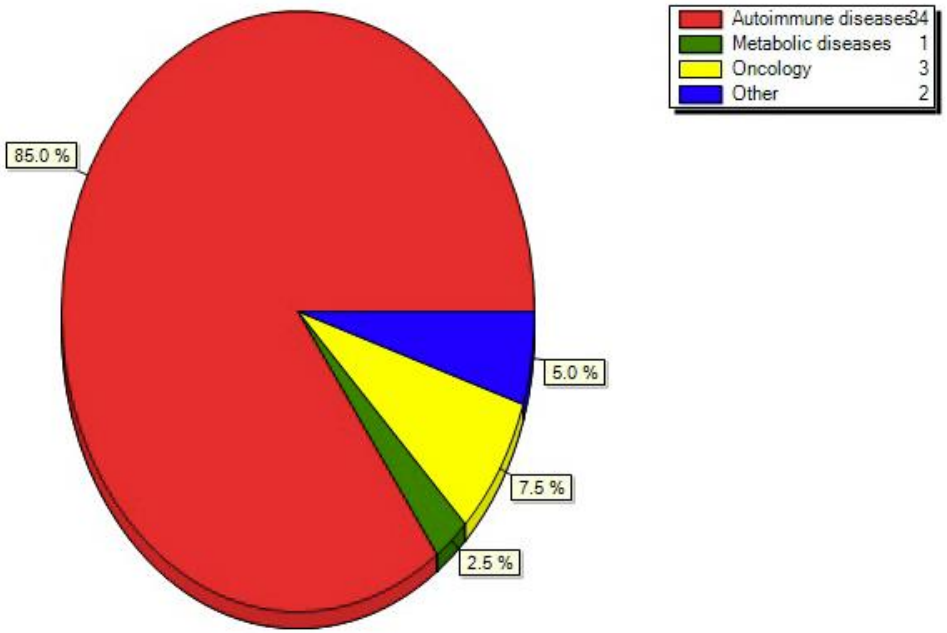
- Introduction
  - **Pre-existing antibodies?**
    - How are they defined?
    - Are they real? How big is the problem?
    - Current landscape in the industry
- Survey results from the AAPS Focus Groups
    - What is the prevalence?
    - Is there an impact?
    - What are we doing about them?
- What is the view from the industry and regulators?
  - **Are investigations *always* necessary?**
  - **Potential ways to deal with pre-existing antibodies**
    - Within the assay
    - Evaluation of impact
    - Reporting of Immunogenicity of a product: what to do with pre-existing antibodies?

Pre-existing Antibodies (Pre-Abs) What is the problem?

- **Definition of pre-existing antibodies:**
  - **Biotherapeutic-reactive antibodies present in samples from treatment-naïve subjects**
    - Confirmed anti-drug antibodies (ADA) in pre-dose subject samples
    - Antibody (immunoglobulin) mediated reactivity
- Impact:
  - **Cetuximab: Pre-existing IgE antibodies leading to serious hypersensitivity reactions**
  - **Panitumumab and many other humabs: no impact**
- How do we deal with them?
  - **Perform routine investigation/s of any positive baseline signal in the assay? How much characterization needs to be done?**
  - **Is there always an impact? Is there a trend? Does the biology of the drug matter?**

Key Points from the AAPS- FG lead Survey of Biopharma Scientists

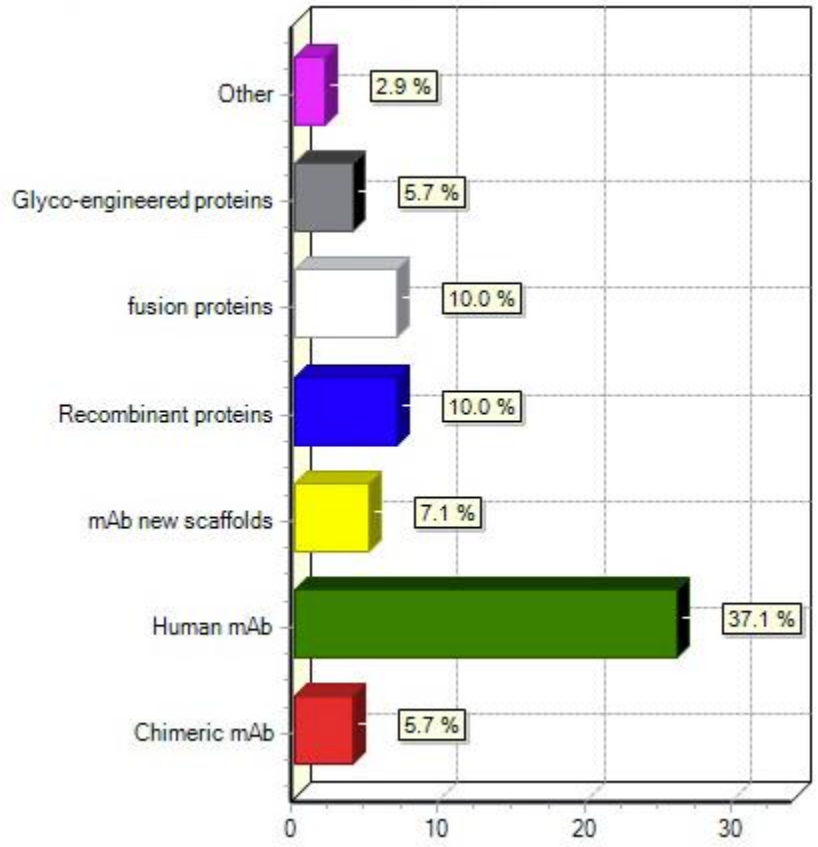
- 70 Scientists participated from the Biopharma Industry
  - **Presence of pre-Abs observed in both pre-clinical and clinical studies**
  - **Prevalence varied based on the disease population, and product modality**



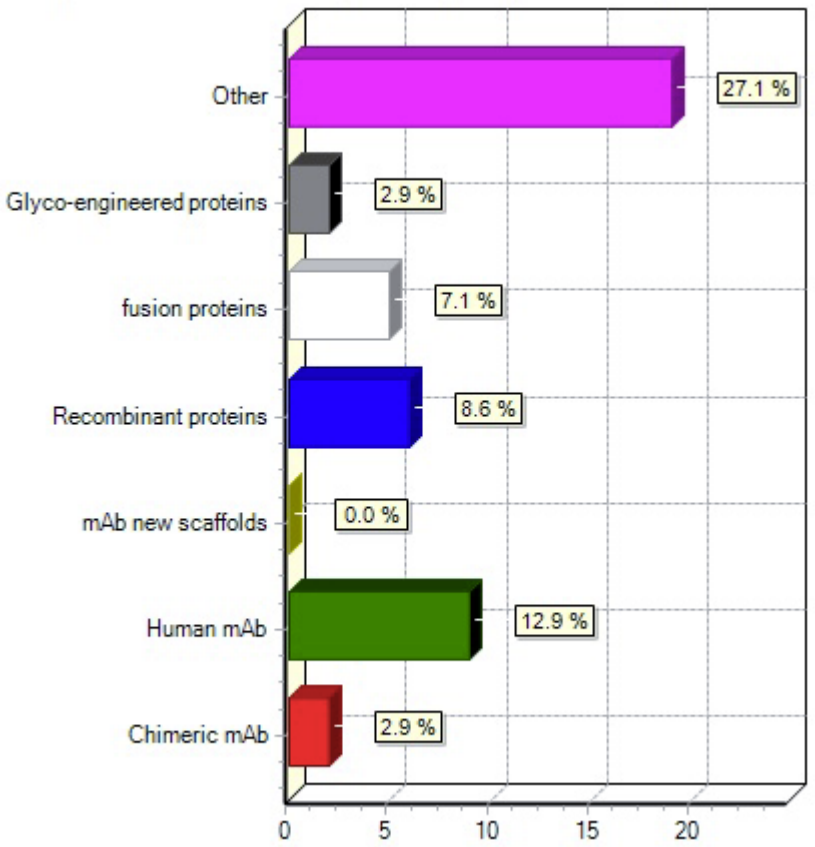
Xue et al., AAPS J. 2013,15(3):852-855.

Association of Pre-Abs with Product Modality

Clinical



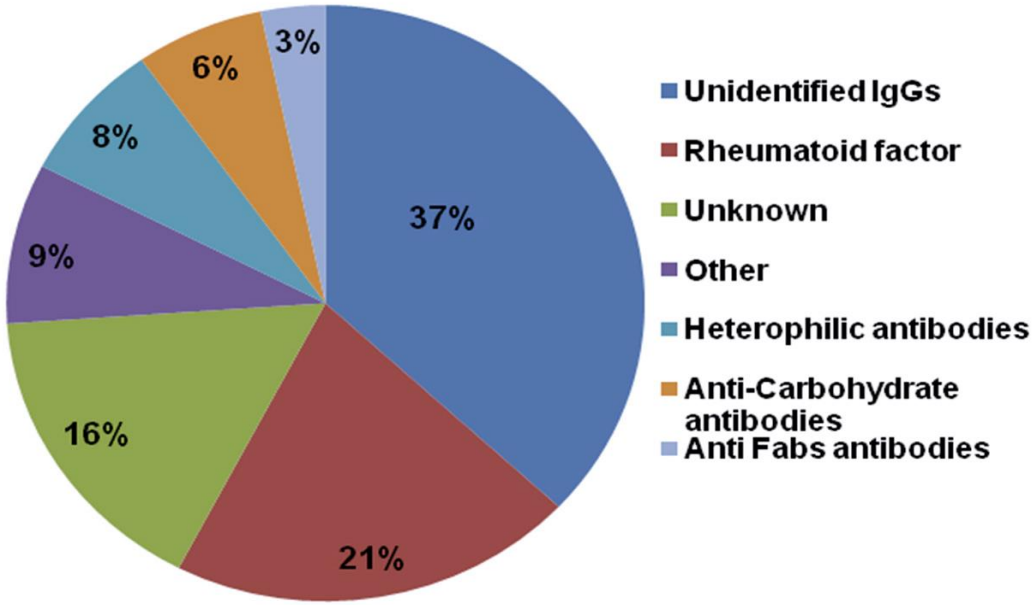
Pre-clinical



AAPS Pre-Ab industry survey results (2013)

Nature of Pre-existing Antibodies (from the initial survey)

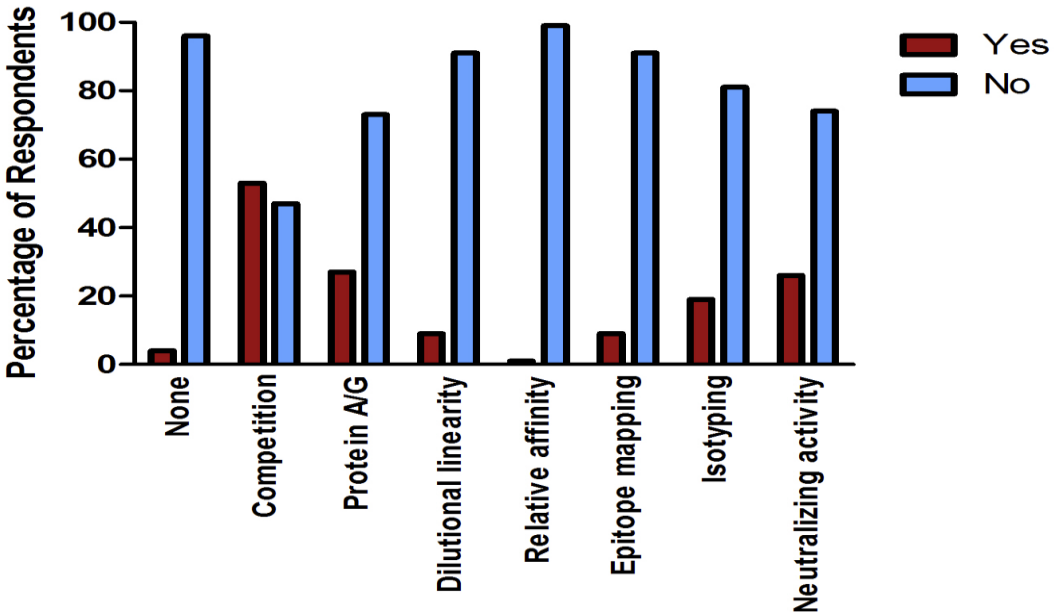
- Most commonly reported sources of pre-existing antibodies were non-specific immunoglobulins and Rheumatoid factor (Rf)



AAPS Pre-Ab industry survey results, 2013

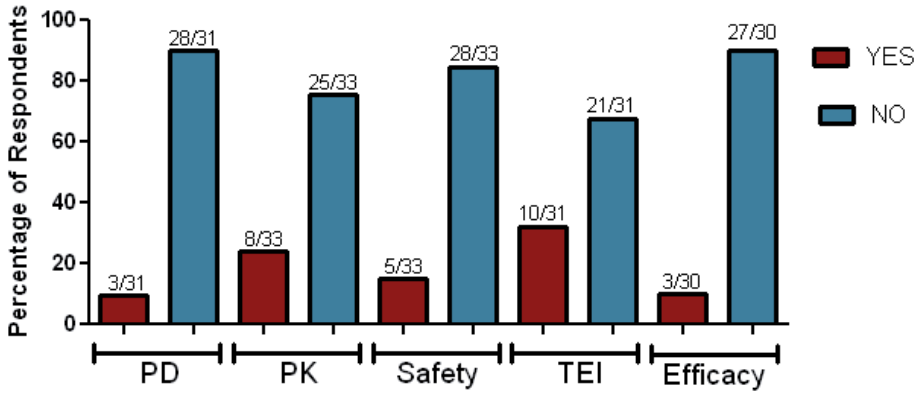
Characterization of Pre-existing Antibodies

- Most commonly used approach: Competitive inhibition assay



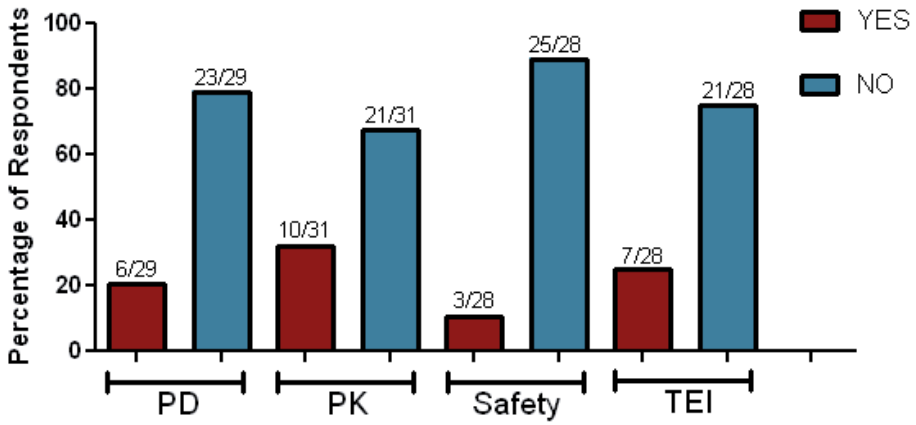
Is there a clinical impact due to pre-existing antibodies?

Clinical:



- Impact of pre-Abs on PK/PD, safety, efficacy and TEI observed in a few cases

Non-clinical:



- Further Evaluation of specific Drug programs and disease populations **now ongoing…**

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Reporting of Data: Survey Results

- Similar non-clinical and clinical pre-Abs reporting approaches
  - **Report prevalence of pre-Abs along with treatment induced ADA incidence**
  - **Include identified impact of pre-Abs on PK, PD, safety, efficacy and immunogenicity in study reports**

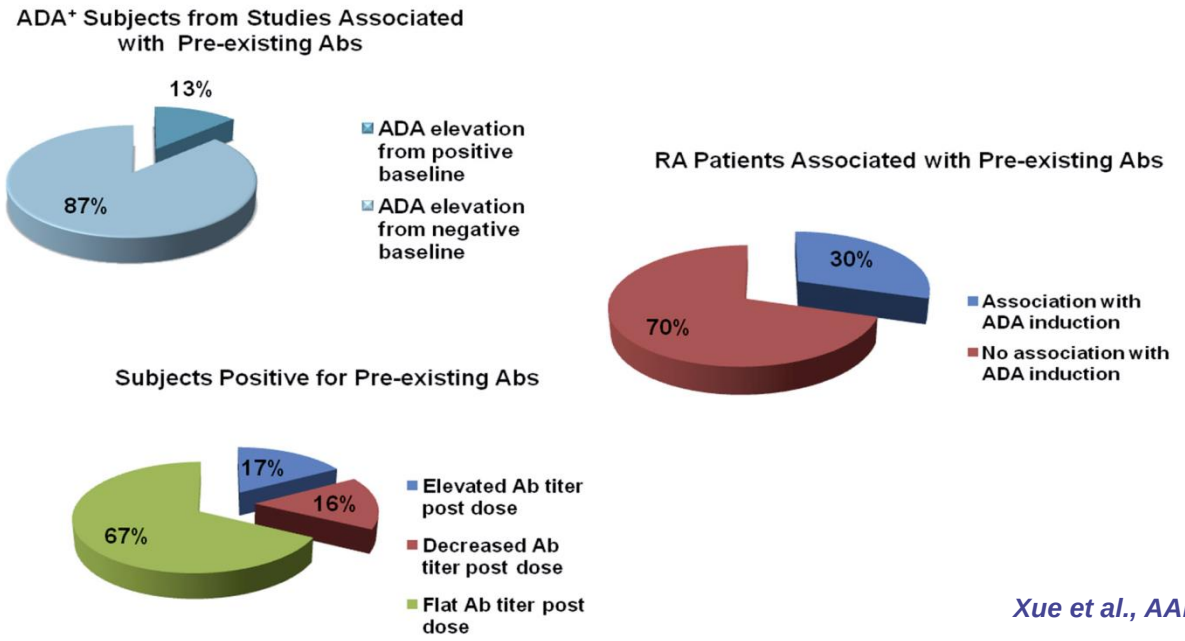
- Discrepancy in how to report ADA incidence for subjects with pre-Abs
  - **Half respondents (52% clinical, 58% non-clinical) indicated including the pre-dose positive subjects (that did not have post-treatment ADA titer increase) in the final reported immunogenicity incidence**

- Issues with this approach!!
  - **Ability to appropriately evaluate the immunogenicity impact**

Emerging Data and Trends

- Accumulating experience in dealing with pre-existing reactivity in the industry; trends suggest
- Incidence of pre-existing antibodies tends to be higher in auto-immune population
- With new modalities of treatment: The risk and the data need to be evaluated carefully
  - **Eg: Pegylated proteins, Certain antibodies to neoepitopes**
- Clinical Impact Assessment needs to drive next steps

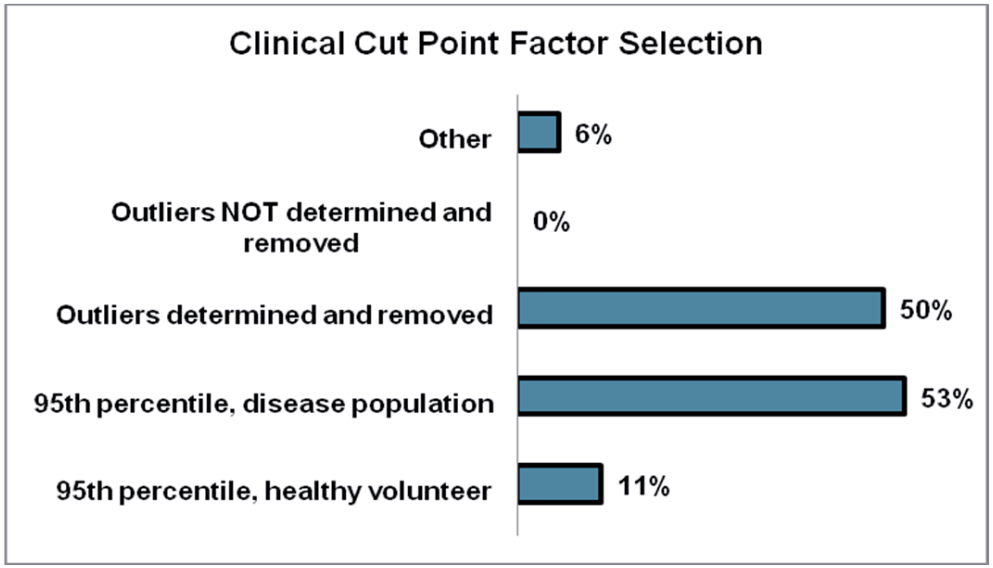
Example: Higher association of ADA incidence after treatment in RA population



Xue et al., AAPS J. 2013,15(3): 893-896

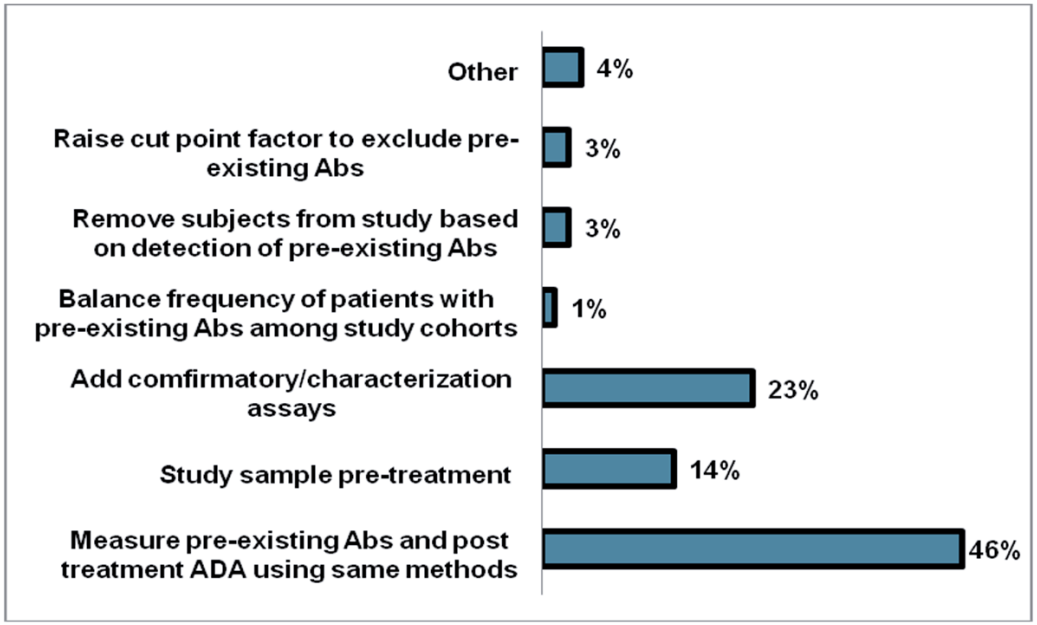
- Caveat: Autoimmune population (RA, Lupus) tend to exhibit higher immunogenicity incidence in general. Data needs to be evaluated further

Assays and Analytics: Cut Point Factor Selection



- Most commonly used cut point criteria:
  - ❖ The 95th percentile and removal of outliers in statistical calculations
- Use disease specific populations to establish screen cut point

Cut Point Issues: Approaches utilized



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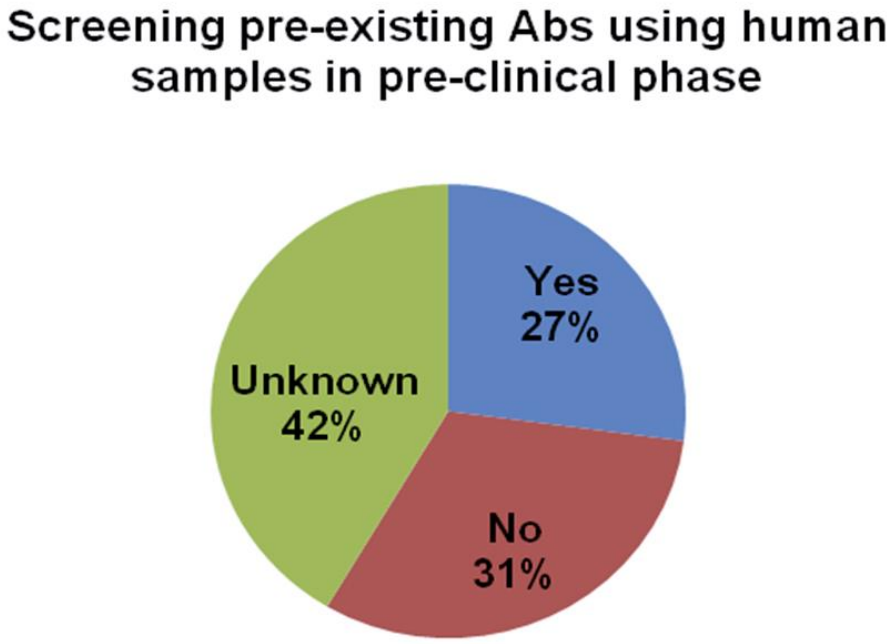
Risk Management: When there is a true impact



- Screening out patients with pre-existing antibodies:
- **Do NOT recommend this practice routinely**
- **Recommended only when there is a true clinical impact of pre-abs**

Emerging Trends and Observation: pre-existing antibodies

- Growing number of biotherapeutics in development
  - **Auto-antibodies vs cross-reactive antibodies**
    - Next-generation therapies, biosimilars
- More experience gained across multiple clinical studies and programs (evaluation of pre-abs from Ph1 thru Ph3)
- Low level incidence of pre-existing antibodies are more common (especially in large studies)
- Accumulating experience with evaluation of incidence and impact
  - **warrants a deeper discussion**

Analytics Reconsidered

- Cut points: Ensure that the cut point set in validation is appropriate for the study population
  - **Consider resetting the cut point if not suitable for the study population (in-study cut point)**
- Ensure that cut point methodology is appropriate and fit for the immunogenicity assessment goal
- High sensitivity assay platforms now available and routinely used

Assay Analytics: what is the issue?

- High Sensitivity Assay Platforms routinely employed in the analytical laboratories:
  - **Robust, precise and high sensitivity immunogenicity assays are now possible**
  - **Very low cut points that are close to the noise threshold in the assay**
  - **Result: several borderline positives are commonly found**

- Investigations:
  - **Expect to compete these positives in the confirmation assay**
  - **Low sample volumes, inconclusive results**
  - **Can spend enormous amount of time investigating the nature of antibodies, isotype, etc.**

- Perfectly fine assay: why is it detecting positives with no clinical meaning?
  - **Consider: both analytical and biological noise (borderline positives)**

What is important to ask before performing extensive analytical investigations?

- Is there a clinical impact??
  - **Impact on safety, efficacy**
- Is there a higher incidence/likelihood of immunogenicity in those subjects with pre-abs?
- What is the strength of immune reactivity in the pre-dose samples? (high titers)?
- What is the Immunogenicity Risk associated with the therapeutic
  - **Gene therapy, enzyme replacement therapies and other**

What is important to report?

- Observed immunogenicity of a therapeutic and impact
  - **Differentiate pre-existing vs post-treatment result**
  - **Example: set a threshold level above pre-existing signal if necessary to define treatment emergent response**
  - **Other approaches may be warranted depending on the situation**
- Impact can be evaluated for both categories (pre-Abs vs treatment-induced)
  - **Label vs CSR**
  - **Scientific and clinical judgment should prevail**
  - **CSR: Both pre-existing and post-treatment data are reported separately**
  - **Label: Therapeutic induced immunogenicity incidence along with impact reported**
    - pre-Ab prevalence relevant when associated with clinical impact

Summary

- Detection of pre-Abs is an increasingly common phenomenon during clinical and non-clinical immunogenicity assessment
- Various pre-Ab characterization, reporting and management approaches necessitate industry harmonization together with regulatory input
- Immunogenicity incidence # can not stand alone: interpret incidence together with clinical impact
- Same holds true for pre-existing immunogenicity: Apply totality of evidence approach in pursuing investigations, reporting data for the drug label etc.
- A new team under AAPS-TPIFG:
  - **Analyzing data from specific drug programs**
  - **Goal: to propose recommended approaches to investigate, analyze and report pre-ab data**

Acknowledgements

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Thank you