Don’t Challenge This

The OBP BUZZ on Signal-to-Noise (S/N) as an alternative to titer and PK/PD + titer as an alternative to NADA Assessment

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OPQ/CDER/FDA

EBF 2023 **Challenging the Current Paradigm for ADA Testing**

MC Immunerdy

Office of Pharmaceutical Quality

- A quality product of any kind consistently meets the expectations of the user.
- Patients expect safe and effective medicine with every dose they take.
- Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.
- It is what gives patients confidence in their *next* dose of medicine.

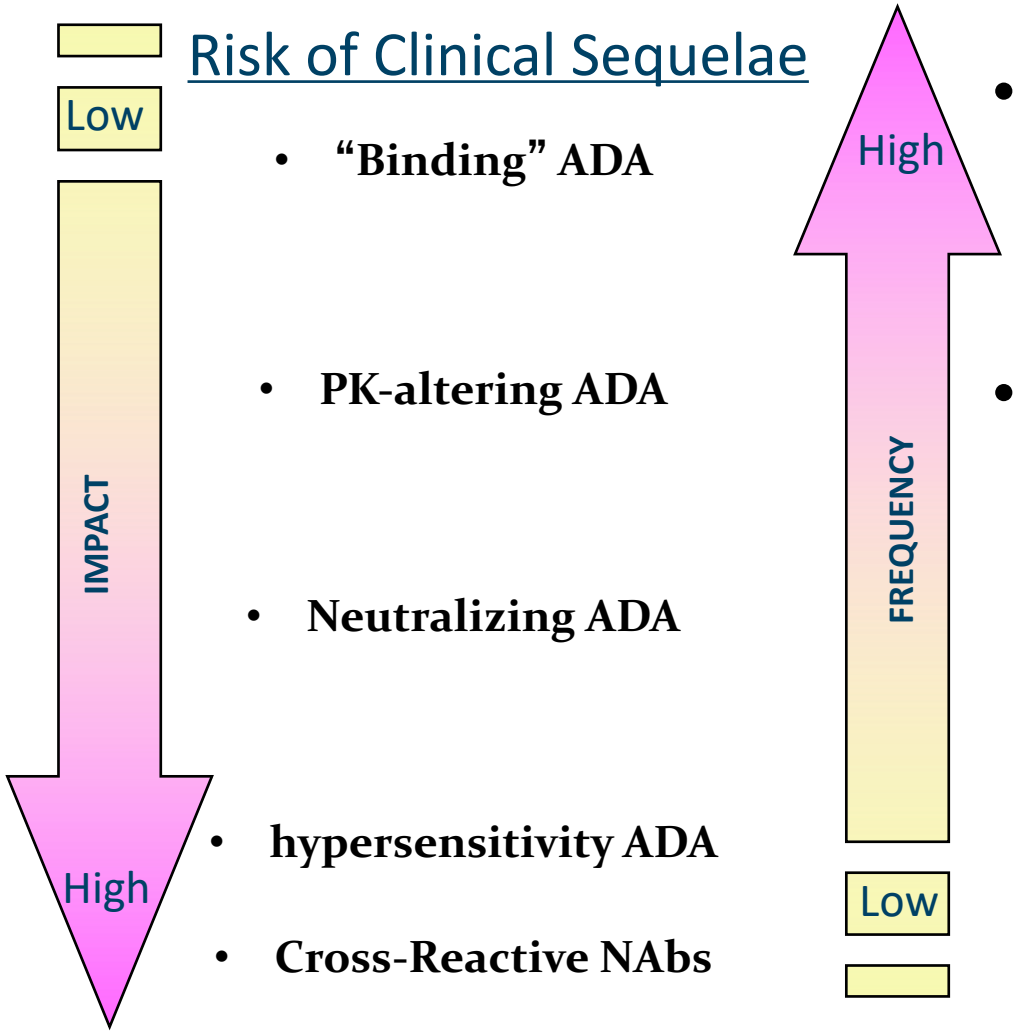
Disclaimer

- The views and opinions expressed herein should not be used in place of regulations, published FDA guidances, or discussions with the Agency in a program specific manner
- Presentation discusses primarily 351(a) biologics regulated by CDER under the US Public Health Service Act

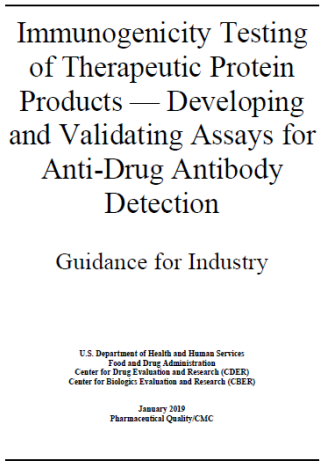
Immunogenicity at the FDA

- Who reviews it?
  - Depends on the class of product
    - CDER - monoclonal antibodies, growth factors, fusion proteins, cytokines, enzymes, therapeutic toxins
    - CBER- allergenics, blood and blood components including clotting factors, cellular and gene therapies, vaccines

Clinical significance of ADAs



- Binding ADA Assay
  - Screening
  - Confirmatory
  - **Titering or alternatives**
- Neutralizing ADA (NAb) Assay
  - Single tier
  - Multi-Tier (S, C/T)
  - **Integration of titer and PK/PD (rare alternative)**


Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection

Guidance for Industry

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)

January 2019
Pharmaceutical Quality/CMC

My BUZZ on the use of Signal/Noise

Acceptability of S/N for ADA Quantitation

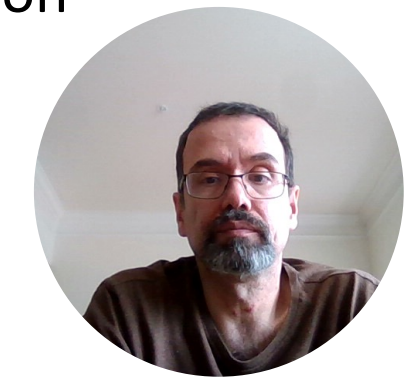
- Alternative methods of ADA quantitation besides titer may be used:
  - 2019 Immunogenicity Guidance:
    - "Several approaches may be used to report positive antibody responses, and the appropriateness of the approach used should be evaluated **on a case-by-case basis.**"
    - S/N is a novel approach with limited experience in the therapeutic protein setting
    - CDER is gathering experience to establish scientific merits and build confidence in the approach

- Dependent on assay validation characteristics
  - Good sensitivity, precision, linearity (including hook effect) **drug tolerance** and **broad dynamic range**
  - **Continue to develop your titer assay at this stage**

Acceptability of S/N for ADA Quantitation

- Sponsors should provide a justification for choice of S/N for ADA quantitation in eCTD 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies, 2.7.1 Summary of Bioanalytical Methods and 5.3.5.3 Integrated Summary of Immunogenicity

- Discuss the choice of approach with Agency during program development
    - Agency reserves the right to request additional titer characterization
        - Store samples appropriately



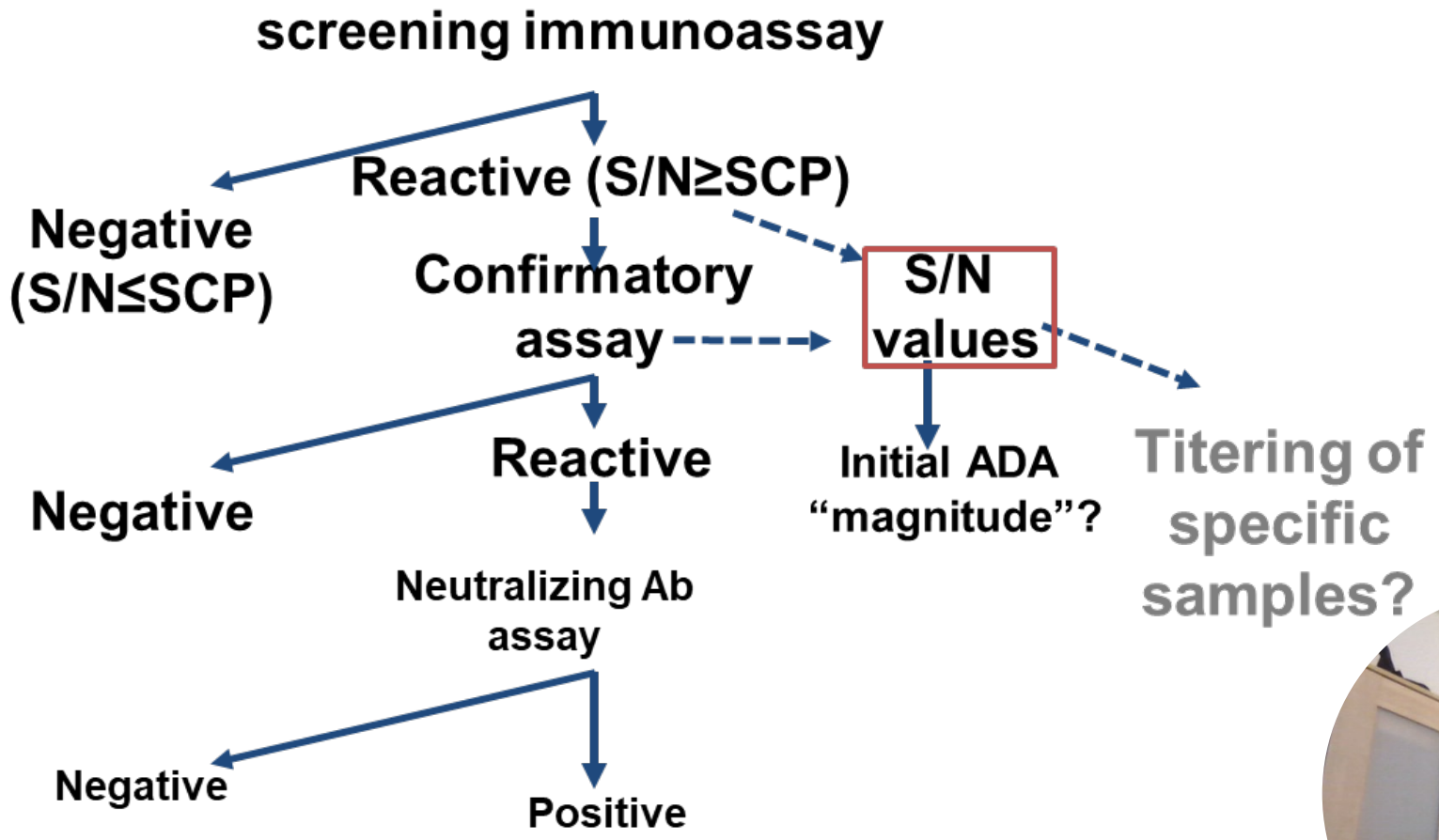
Type of supportive data requested

- Continue to develop your titer assay at this stage
- S/N and titer development/validation data, including a correlation between S/N and titer-based measurements using an appropriate anti-drug product antibody control
- Early clinical study data correlating the effect of ADA on PK using both S/N approach and titer-based approach
  - Data can be generated using clinical samples from a PK study to demonstrate suitability of S/N approach as an alternative to titer-based approach.
  - Using clinical samples, consider performing a parallelism study for S/N and titer, using samples with different ADA levels, and on on-board drug levels
  - Include an evaluation of effect of ADA on PK/PD using both titer and S/N data
  - Establish S/N criteria for assigning study samples as treatment-boosted ADA positive prior to the study

Utility of S/N approach vs Titer

- Useful for sample semi-quantitation in early-stage development, prior to development of titer assays?
  - “fit for purpose” assay(s)
- Useful to select samples for potential additional titer characterization, if needed?
  - Alternate early tier approach for low immunogenicity risk products
- With time and experience, S/N approach as an alternative to titer will gain greater acceptance from regulatory Agencies for BADA assays
  - NADA assays?

Alternative Initial tier for low-risk biologics?



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Outstanding issues

- How do you report S/N values on product label as per recommendations in 2022 immunogenicity draft labelling guidance?
  - (Draft) Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling. February 2022.

- Historical use of titers to communicate ADA magnitude to stakeholders
  - Conceptual understanding and acceptance by Health Care Practitioners

My BUZZ on the use of PK/PD+Titer as a NAb assay alternative

Clinical Significance of NAbs

- In a patient both BAbs and NAbs can lead to loss of efficacy and/or negatively impact safety, therefore both may be clinically important
- NAbs may be more effective in directly impacting efficacy
  - E.g. IFN-b and IL-2
- Multi-disciplinary risk-based analysis early in product development.
  - The higher the risk category for the product, the faster the pa of assay development should take place.

Risk Assessment

- NAb Assays are critical when neutralizing immunogenicity poses a high-risk to patient safety
  - High Risk: preliminary validated assays should be implemented early (preclinical and phase I)
  - Medium to lower risk: have assay validated prior to testing clinical phase 3 study samples
    - 2019 Immunogenicity guidance allows for a flexible approach in limited cases

The alternative approach- Neutralizing/inhibitor activity

- 2019 FDA immunogenicity guidance

  "In **selected** cases, where there is a **highly sensitive (*and stable*)** PD marker or an **appropriately designed** PK assay **or both** that generate data that inform clinical activity, it **may be** possible to use these in lieu of a NAb assay."

  - For medium or lower risk products

Survey of Approved 351(a) BLAs (Jan 2019-Dec 2022, n=92)- NAb assays

NAb Assay Type	Number of BLAs	Type of products
CBA only	**26/92= 28.2%**	MAbs, ADC, GF
CLBA only	**29/92= 31.5%**	MAbs
CBA+CLBA	4/92= 4.3%	MAbs (solo or combos)
CBA+ IEA	5/92= 5.4%	ERTs, combo products
IEA	2/92= 2.2%	Other enzymes
Alternative (Titer + PK/PD)	**5/92= 5.4%**	**MAbs**
None (ADA only or not reported)	20/92= 21.7%	MAbs (solo or combos), Insulins, labelling kits
Other (animal protection assay)	1/92= 1.1%	Therapeutic Toxin

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