The BUZZ on Signal-to-Noise (S/N) as an alternative to titer- perspectives from CDER's Office of Biotechnology Products

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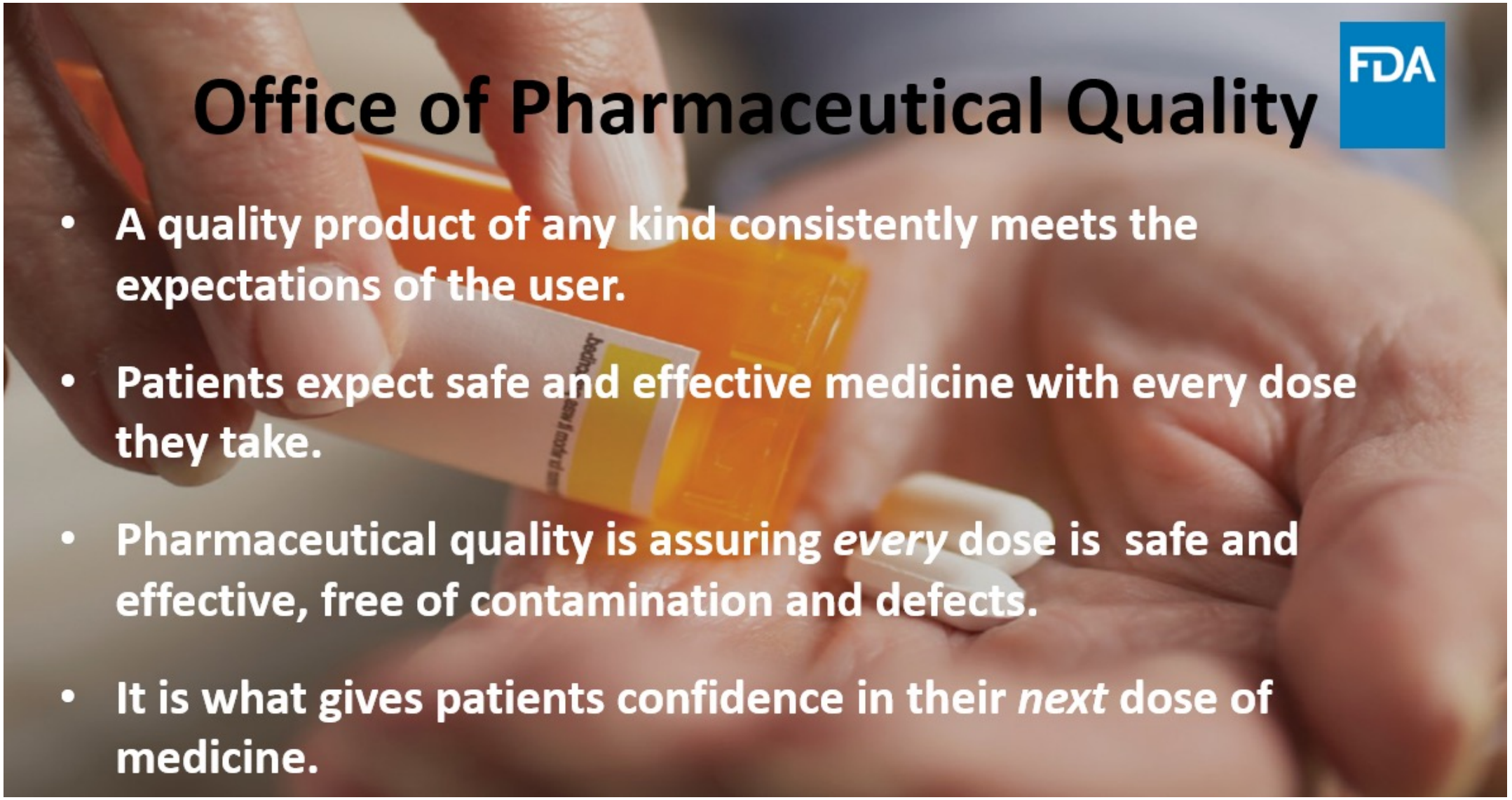

Office of Pharmaceutical Quality
FDA
• A quality product of any kind consistently meets the expectations of the user.
• Patients expect safe and effective medicine with every dose they take.
• Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.
•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

Disclaimer

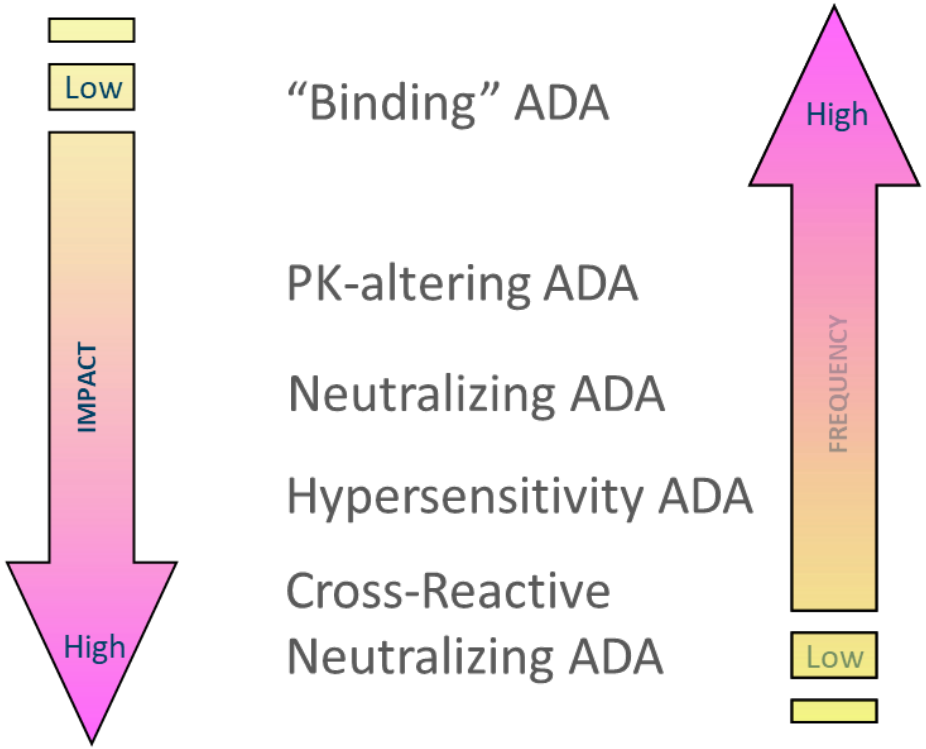
- The views and opinions expressed herein should not be used in place of regulations, published FDA guidances, or discussions with the Agency

- Presentation discusses primarily to 351 (a) and 351(k) biologics 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 Anti-drug Antibodies



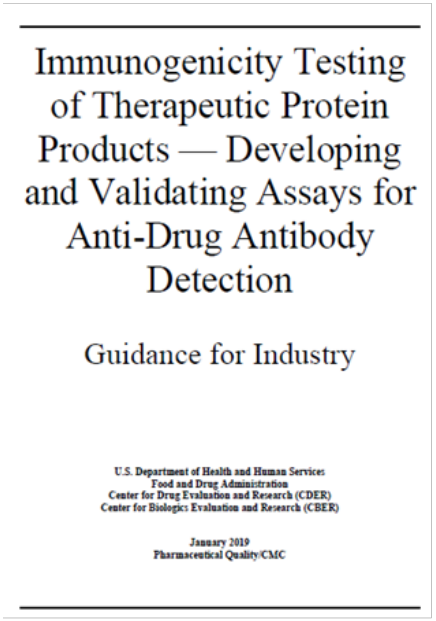
An ADA positive sample can have a mixture of any of these ADAs

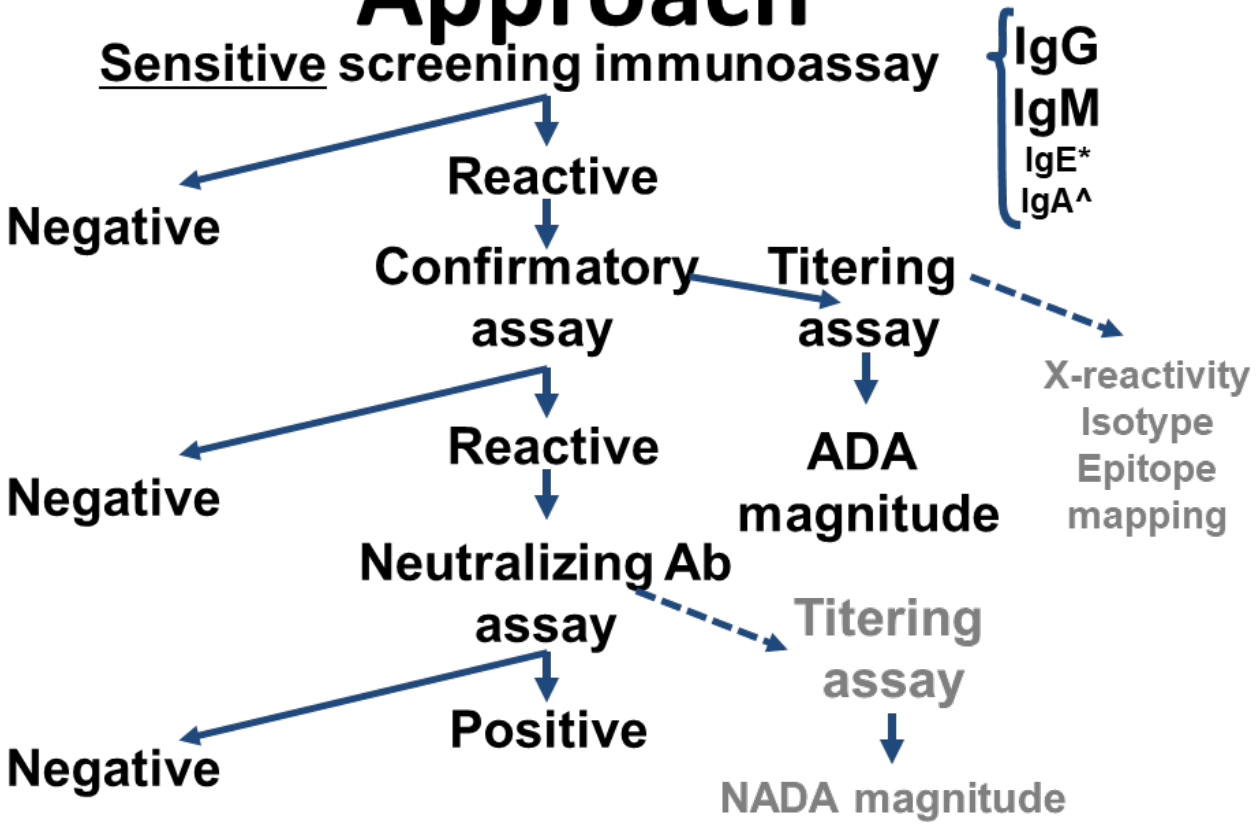
- ADA binding assay
  - Screening
  - Confirmatory
  - **Titer or alternatives**
  - Cross Reactivity
  - Epitope Specificity
- Neutralizing ADA (NAb) assay

ADA Assays & Product Life Cycle

- Low Risk Molecule:
  - Bank Samples
  - Testing early phase samples by qualified or validated assays (company's choice)
  - Phase III/Pivotal study samples should be tested using validated assays-
    - Fully mature program for BLA submission*
- High Risk Molecule:
  - FDA may ask the ADA assay be validated for early studies

Multi-Tiered Immunogenicity Approach





Quantitation of ADA responses

2019 guidance: Assays for ADA Detection

- "Titration assays characterize the magnitude of the ADA response. It is important to **characterize this magnitude with titration assays** because the impact of ADA on pharmacokinetics, pharmacodynamics, safety, and efficacy may correlate **with ADA titer** and persistence rather than incidence **".**

Quantitation of ADA responses

2019 Immunogenicity Guidance: Reporting Results for Qualitative and Quasi-Quantitative Assays

- "For subjects who are confirmed to be ADA positive, determining antibody levels can be informative because it allows for stratified assessment of ADAs and their impact on safety and efficacy. **Positive antibody levels may be evaluated using a titer. Reporting levels of antibodies in terms of titers is appropriate and generally understood by the medical community**. "

Quantitation of ADA responses

2019 Immunogenicity Guidance: Reporting Results for Qualitative and Quasi-Quantitative Assays

- "Most frequently **titer** is determined from the reciprocal of the highest dilution that gives a value at or just above the cut-point of the assay. Alternatively, titer may be determined by extrapolating the dilution to the assay cut-point using the linear portion of the dose response curve. All sample dilutions, such as the MRD and acid dissociations, should be factored into **the calculations of titers** and provided when **reporting titers.** "

Quantitation of ADA responses

2019 guidance: Pre-Existing Antibodies

- "An alternative to the qualitative screening assay approach may be needed to assess the **quantity and quality of ADA** when pre-existing antibodies are present. For example, **testing samples for an increase in ADA using a semi-quantitative assay such as a titration assay… ".**
- "When there are pre-existing antibodies **and the titer of antibodies increases after exposure** to the therapeutic protein product, they can be reported as *treatment-boosted* to differentiate them from *treatment-induced* antibody titers. For example, a boosted ADA response **may be defined as a titer that is two dilution steps greater than the pre-treatment titer, when twofold dilutions are used to determine the titer.**

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
- Sponsors should provide a justification for choice of S/N for ADA quantitation in eCTD 5.3.14 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
    - Include development data of S/N vs titer , if available
    - Agency reserves the right to request additional titer characterization
      - Store samples appropriately

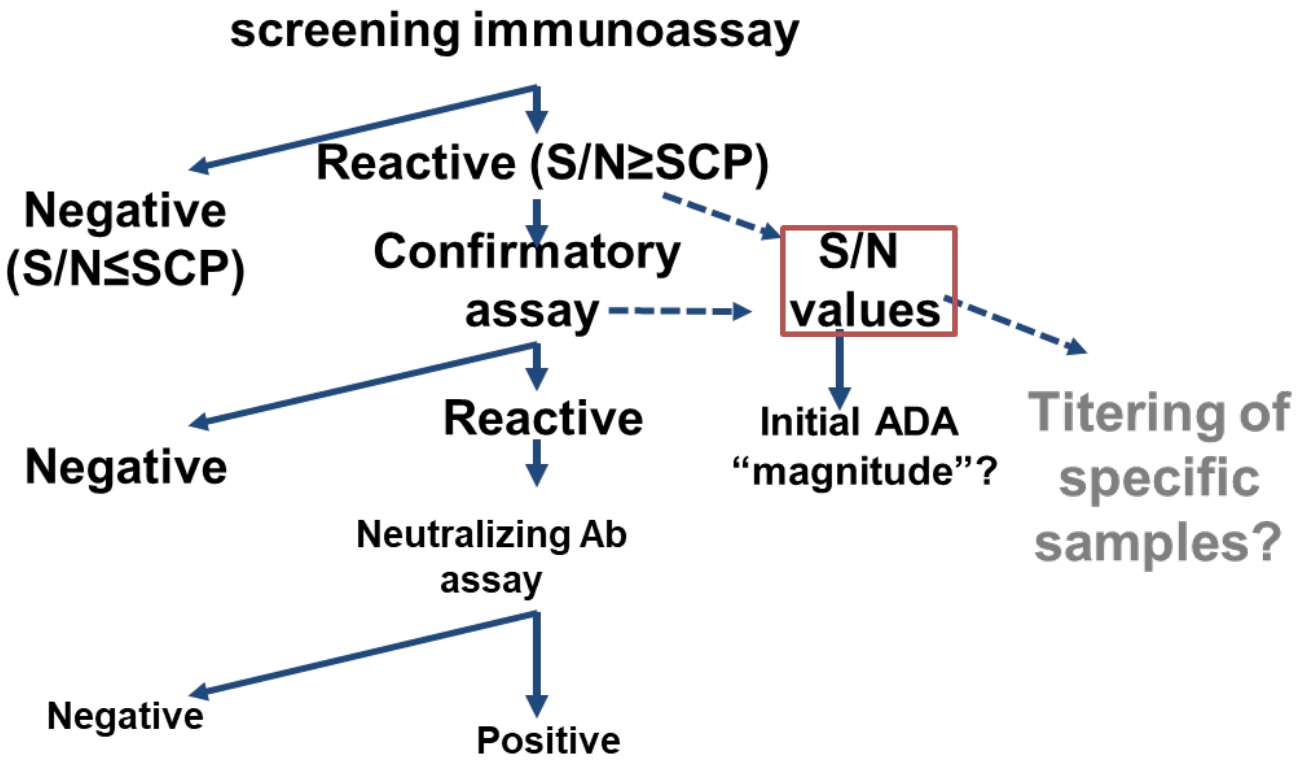
Type of supportive data requested

- S/N and titer development 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.
- Establish S/N criteria for assigning study samples as treatment-boosted ADA positive

Utility of S/N approach vs Titer

- Dependent on assay validation characteristics
  - Good sensitivity, precision, **drug tolerance** and **broad dynamic range**
- 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

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

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