Immunogenicity Advanced Training

Interactions With Health Agencies: Real Life Examples

European Immunogenicity Platform Symposium

18 March 2026

Agenda

01	**Introduction**: FDA meeting types: regulatory context and strategic use *Lydia Michaut (Novartis)*
02	**«Real life» examples**
2.1	Example 1: Drug tolerance at clinical relevant levels: type C and D meetings with FDA *Lydia Michaut (Novartis)*
2.2	Example 2: IRA for biologic drug depleting autoantibodies: pre-IND type B meeting with FDA *Sebastian Spindeldreher (IBx)*
2.3	Rapid fire examples: Information requests at IND stage; Applicability of validation cut-points for ADA/nAb testing in study; Non-clinical immunogenicity testing for novel modalities *Daniel Kramer (Sanofi)*

FDA meeting types: regulatory context and strategic use

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Real Life Examples

EIP Open Symposium

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FDA formal meeting types - Overview

Meeting Type	Purpose	Use Cases for Immunogenicity-Related Questions	Timeline Intensity
Type A	Resolve stalled programs / urgent issues	Unexpected high-titer ADA, clinical hold, safety risk	Shortest timelines
Type B	Key development milestones (Pre-IND, EOP1/2, Pre-BLA)	Strategic immunogenicity alignment, labeling risk	Standard milestone timelines
Type C	Non-urgent scientific advice	Cut-point strategy, assay format, drug tolerance	Longer timelines than Type A
Type D	Focused, limited questions (≤ 2–3)	Statistical method, confirmatory approach clarification	Expedited, narrow scope
INTERACT	Early engagement for innovative modalities	Immune risk framework, translational strategy	Early-stage structured interaction

FDA formal meeting timelines

Source: PDUFA VII performance goals

Meeting Type	FDA Response to Meeting Request	Meeting Scheduled / WRO (written response only) Issued
Type A	Within **14 days**	Meeting held within **30 days** of request
Type B (Pre-IND, Pre-NDA/BLA)	Within **21 days**	Meeting held within **60 days** of request
Type B (EOP)	Within **14 days**	Meeting held within **70 days** of request
Type C	Within **21 days**	Meeting held within **75 days** of request
Type D	Within **14 days**	Written response within **50 days** of request
INTERACT	Within **21 days**	Meeting held within **90 days** of request

FDA formal meetings guidances

Define meeting types, procedures, formats, and timelines under PDUFA and BsUFA

Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products

- Guidance for Industry - Latest release 2023 (draft, but implemented; see backup)
- https://www.fda.gov/media/72253/download (2009: all drugs*)
- Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (2023)
- Covers CDER and CBER-regulated products
- Prescription Drug User Fee Act: U.S. law enacted in 1992 that authorizes the FDA to collect fees from pharmaceutical companies to fund the review of human drug and biologic applications.
- The program is periodically reauthorized by Congress (e.g., PDUFA VII covers FY2023–FY2027). Each reauthorization updates fee structure, review commitment, new initiatives (e.g., real-world evidence, digital tools, rare disease focus)

Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products

- Guidance for Industry – Published July 18, 2025
- Applies to biosimilar and interchangeable products (CDER & CBER)
- https://www.fda.gov/media/172311/download
- Biosimilar User Fee Act: U.S. law first enacted in 2012 that authorizes the FDA to collect fees from sponsors of biosimilar and interchangeable biological products to fund the review of 351(k) applications and associated development-phase regulatory activities.
- The program is periodically reauthorized by Congress (e.g., BsUFA III covers FY2023–FY2027). Each reauthorization updates the fee structure, performance goals for meetings and application review, and operational commitments aligned with evolving biosimilar development models.

**Biosimilar legal pathway did not exist yet in 2009: the BPCIA—the Biologics Price Competition and Innovation Act—was enacted in 2010, creating the 351(k) biosimilar pathway and setting the stage for a separate biosimilar development framework*

PDUFA vs BsUFA fees

Stage / Aspect	PDUFA (Originator NDA/BLA)	BsUFA (Biosimilar 351(k) BLA)*
Pre-IND	No fee	No fee (unless BPD entry triggered)
IND submission	No fee	Triggers Biological Product Development (BPD) fee
First formal meeting	No fee	Triggers BPD fee if not already paid
NDA/BLA submission	Application fee due at submission	Application fee due at submission
Post-approval	Annual program fee	Annual program fee
Practical meaning	Sponsor can engage FDA extensively during development without financial trigger; first payment only at commercial filing stage.	Sponsor commits financially early in development; regulatory interaction is tied to annual BPD participation.
Strategic consequences	Development discussions can be exploratory without financial pressure. Decision to file BLA is the first major financial inflection point.	Entering BPD signals serious biosimilar intent. Financial commitment encourages structured development, disciplined regulatory engagement, and clear similarity strategy early.

**The U.S. FDA biologics license application (BLA) for a biosimilar product, submitted under section 351(k) of the Public Health Service Act.*

Meeting types for biosimilars

Follow BPD (Biological Product Development) program categorization
Conceptually similar with PDUFA meetings

BPD Meeting Type	Purpose	Analogy to PDUFA terminology
Biosimilar Initial Advisory (BIA) Meeting	Early feasibility discussion on whether licensure as a biosimilar is plausible Scope: High-level scientific and regulatory discussion (no full data review) Typical timing: Very early — often before IND-enabling studies Not required, but commonly used strategically	Closest functional equivalent to a Pre-IND meeting
BPD Type 1	Urgent issues (e.g., stalled development, critical safety concern)	Type A
BPD Type 2	Targeted scientific questions at key points in development (not tied to formal milestones)	Type B
BPD Type 3	In-depth data review and scientific advice	Type C
BPD Type 4	Pre-submission (351(k) BLA) meeting	Pre-submission

Strategic Positioning

Avoid

- Purely technical assay focus without clinical linkage
- Overloaded briefing book without clear regulatory question
- Implicit assumptions instead of explicit positioning

Emphasize

ADA Clinical consequences

- Exposure-response integration
- Risk mitigation strategy
- Consistency with regulatory and industry precedents

Anticipate key agency concerns

Framework

- Define the decision needed
- Be explicit about risk assessment and articulate all available data
- Propose a path forward and justify it

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Example 1: Regulatory interaction history and strategy *via* type B and Type D meetings

Monitoring Anti-Drug Antibodies During Clinical Development: When Biological Factors and High Dose Clinical Regimens Create an Analytical Challenge

Thank you

And to all the co-authors and collaborators:

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Case study

mAb anti-TGF beta

- High dose and high frequency dosing
- Very high on-treatment drug concentrations (hundreds of micrograms per mL)
- Drug interference and target interference risks
- Classical acid dissociation not implementable due to target biology

Initial strategies tested: bridging ECLIA without acid dissociation

- Assay with apparent low drug tolerance but no target interference
- **Testing four alternative sample pretreatments**

Antibody competition	⊘ *Mass action law*
ACE: Affinity Capture Elution	⊘
PANDA: Precipitation and Acid dissociation	⊘
SPEAD: Solid-Phase Extraction with Acid Dissociation	⊘ *Improved drug tolerance, but unacceptable target interference and noise*

First interaction with the FDA

- **Meeting:** Type B
- **Stage:** pre-IND (Investigational new drug application)
- **Agency feedback:**
  - Current bridging format would not be capable of being sufficiently sensitive to provide meaningful results at high drug concentrations in serum other than washout phase
  - “Sufficient patient samples should be banked for analysis by this and other assays that may be developed”
  - Additional development of ADA assay is advised to provide more meaningful results related to the development of ADA against the drug.

Approaches for addressing FDA feedback

1. Additional assay development using beads-based approach to improve drug tolerance without compromising on target interference

2. Initiation of additional tool production for positive control

Strategy 1: ADA bead-based method

- Improved drug tolerance and sensitivity
- Complexity of bead-pretreatment step incurred high variability
- Lacked performance in terms of robustness or precision

Drug interference		
Anti-ID mAb Positive Control (PC)	**100 ng/mL**	**5000 ng/mL**
Tolerated drug level (µg/mL)	1000	1000

Validation Parameter	ADA Assay (in healthy matrix)
Minimal required dilution (MRD)	1:25
Sensitivity	15.0 ng/mL of PC in 100% serum
Precision (%CV)	0.6 and 141% (average: 10.0 - 127%)
Assay passing rate	47 runs out of 62 (75%)

Details of assay format and performance in Saxena et al., (2026, submitted)

Strategy 2: back to ECLIA assay

Additional positive controls were introduced and characterized for drug tolerance and target interference

Drug Tolerance				
ADA Positive Control (ng/mL)	**100**	**500**	**2000**	**10,000**
	Drug tolerance (µg/mL)			
mAb clone (origin: mouse hybridoma)	<10	<10	59.9	162
mAb anti-ID (origin: mouse hybridoma)	120	435	764	>1500
pAb (origin: rabbit)	<10	80.5	358	1283

Target interferenceRLU (PC= mAb anti-ID)				
(SCP=71)	**Drug Nov-ABC**			
	0	**100**	**500**	**1000**
Target (ng/mL)	Response (ECL)			
0	66	61	62	58
2	196	69	64	64
5	423	71	59	57
20	1497	97	62	62

Clinical relevance of drug tolerance (DT) assessments

- Recommended ADA assay sensitivity by FDA guidance (2019): 100 ng/mL
  Might not always be clinically relevant, e.g. 100 ng/mL of ADA* in presence of 800 µg/mL drug mAb → effective concentration of drug = 799.9 µg/mL

- Sensitivity and DT nominal values depend on choice of positive control antibody (binding affinity, epitope specificity, etc.)

- According to FDA guidance (2019):
  *"The sponsor may examine drug tolerance by deliberately adding **different known amounts of positive control** antibody into ADA-negative control samples in the absence or presence of different quantities of the therapeutic protein product to determine whether the therapeutic protein product interferes with ADA detection."*

  ➢**Characterization of DT at different levels of PC is clinically relevant**
  ➢**Cannot define one single DT value to qualify inconclusive negative results**

- Therefore:
  ➢The ECLIA ADA assay described represented a good compromise between drug tolerance (DT), target interference (TI), shows low background & adequate sensitivity
  ➢**Interaction with FDA re-initiated to present the revised assay characteristics**

**assuming ADA is mostly IgG*

Second Interaction with FDA

Meeting: Type D

- New meeting type authorized in 2022 under PDUFA VII, providing the opportunity to address a narrow set of issues on a shorter timeline than other meeting types
- Limited to no more than 2 focused topics
- Meeting package (briefing book) must be submitted at the same time as meeting request
- FDA response expected within 50 days of receipt of request (vs. 75 days for Type C meetings)
- Written response only (WRO) requested in this case

**assuming ADA is mostly IgG*

Metrics and Outcome of the Type D meeting

Metrics

- Time elapsed between our decision to contact FDA and Briefing book (BB) completion → 30 working days (WD)
- Briefing book → 12 pages (1 question + background information)
- Time elapsed between reception of BB by FDA and their response = 34 WD

Outcome

- Agency acknowledged that the additional DT study data provided for positive control (PC) antibodies show enhanced drug tolerance compared to original PC used during method validation study and supports the continued development of the ECLIA method.
- Agency request prior to resuming sample analysis in patients:
  - Cut-point and use of normalization factor should be assessed and submitted for review
  - Target interference in presence of multiple positive controls should be assessed

Conclusion

- Invest in the production of multiple tools
- Extensively characterize the assay at different concentration levels of PC

Nurture cross-functional collaboration with Clinical Pharmacology, Regulatory Affairs and Medical team

Engage in Type D meetings to align with HA on clear path forward for clinical development

Bring BA question to health authority in context with clinical development, safety & dose regimen

Key takeaways

For agency engagement

- Anchor validation and interpretation in clinical exposure

- Use multiple PCs spanning affinities and epitopes;

- Test multiple levels of PC

- Present DT as a range, not a single number

Engage early and often; align on interpretation rules

Close partnership with regulatory Affairs department is a key enabler

For Industry practice

- Build on cross industry recommendations
- Validate clinically relevant DT using multiple PC levels
- Extend into patient centered practice: within study validation, conduct, reporting
- Avoid “inconclusive” driven by non meaningful validation configuration

Example 2: IRA for Biologic drug depleting autoantibodies: PIND meeting with FDA

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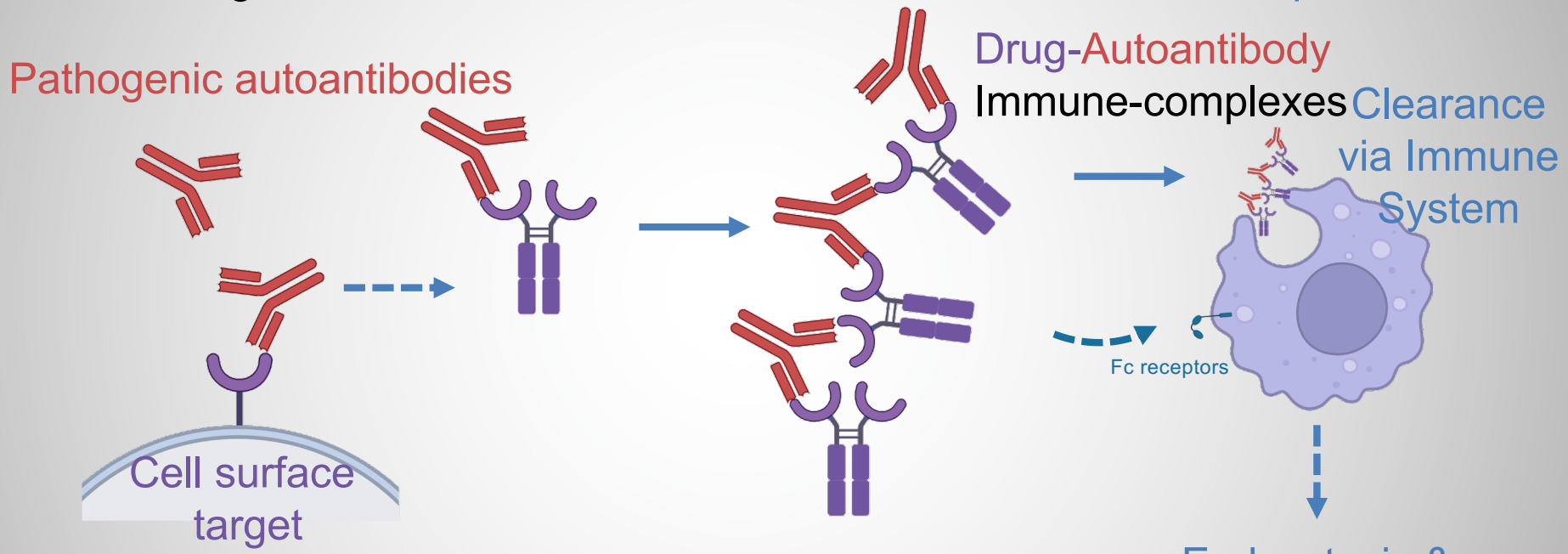
Mechanism of action

Drug binds and Neutralizes Autoantibodies → Immune Complex Clearance



- Patients present with high baseline antibody levels
- Antibody levels correlate with disease severity

Therapeutic Biologic

- ✓ Binds pathogenic antibodies
- ✓ Blocks receptor interaction
- ✓ Activates inhibitory FcγRs

Key Immunogenicity Challenge

- Patients already have high antibody levels at baseline
- Disease antibodies may be detected in ADA assays
- Therapy forms immune complexes with pre-existing antibodies
- **Potential concern:** immune complex effects or cytokine release

NCIRA Strategy

- Combination of in-silico, in-vitro, and in-vivo approaches
- Evaluation of intrinsic immunogenicity, immune complex risk, cytokine release
- Binding studies and mechanistic characterization performed
- Animal studies conducted to evaluate pharmacology and safety

In-Silico Immunogenicity Evaluation

- T-cell epitope prediction using computational algorithms
- MHC class II binding potential assessed
- Sequence comparison to human proteins
- Immunogenicity score benchmarked vs known biologics
- Elevated immunogenicity potential identified

Cytokine Release Risk Assessment

- PBMC-based cytokine release assays performed
- Multiple donors evaluated to capture variability
- Cytokines measured included IL-6, TNFα, IL-1β, IFNγ and others
- Positive controls confirmed assay sensitivity
- No concerning cytokine release signals observed

Non-Clinical Animal Studies

- Pharmacology and toxicology studies performed
- Assessment of PK, PD, and safety
- Monitoring for immune responses
- No unexpected immune-mediated toxicity observed

Overall Non-Clinical Conclusions

- No concerning cytokine release signals observed
- Animal studies supported acceptable safety profile
- Mechanistic studies confirmed biological activity
- Overall immunogenicity risk considered manageable

Clinical Development Strategy

- Single ascending dose FIH study
- Sampling for 12 weeks
- Assessment of safety, PK and PD biomarkers
- Integrated immunogenicity monitoring plan implemented

Clinical Immunogenicity Testing Strategy

- Multi-tier ADA testing: Screening, confirmatory, titer
- CPs determined in healthy subjects
- Drug tolerance evaluated during assay validation
- No standalone nAb assay developed
- Samples collected at baseline and multiple post-dose timepoints (last 12 weeks after dose)

Interpreting ADA with Baseline Positives

- Baseline reactivity expected due to disease antibodies
- Baseline signals may reflect disease biology
- Treatment-emergent ADA defined relative to subject baseline
- Interpretation relies on intra-individual changes
- PK and PD biomarkers help interpret ADA

ADA Patterns with Baseline Positives

1. **Stable baseline signal**
   Likely disease antibody background
2. **Declining signal after dosing**
   Pharmacologic removal of disease antibodies
3. **Transient increase**
   Possible immune stimulation but limited persistence
4. **Sustained increase**
   Potential treatment-emergent ADA requiring further evaluation

Sponsor Preparation for FDA Interaction

- Developed detailed immunogenicity risk assessment
- Integrated assay strategy (ADA, PK, pharmacodynamics)
- Evaluated cytokine release using PBMC and whole blood assays
- Prepared contingency plans for nAb assessment
- Prepared responses to potential FDA questions

Discussion

If You were FDA Reviewers…

- What immunogenicity concerns might you raise?
- What additional studies might you request?
- Is the proposed strategy sufficient?

Questions the Sponsor Anticipated

- In-silico identified elevated risk: Did you consider additional methods to assess antigenicity?
- How will disease antibodies be distinguished from ADA?
- Why do you establish ADA cut points using healthy donors and are these relevant?
- Which drug concentration do you expect at ADA sampling timepoints and how do you ensure appropriate drug tolerance?
- Please justify why a dedicated nAb assay is not planned ?
- How will epitope spreading be monitored?
- How will immune complex related risks be assessed?

Outcome of FDA Interaction

- FDA reviewed the proposed program
- No major immunogenicity concerns were raised
- No additional studies were requested
- Regulators considered overall immunogenicity risk manageable
- Sponsor preparation proved more conservative than necessary

Framework Regulators use to Evaluate Immunogenicity Risk

- Is the product intrinsically immunogenic?
- Could the mechanism amplify immune responses?
- What would be the clinical consequence of ADA?
- Is the monitoring strategy adequate?

Why Sponsors tend to overestimate Immunogenicity Risk?

- Sponsors evaluate theoretical mechanisms extensively
- Regulators focus on clinical consequences
- Single-dose studies with robust monitoring often considered low risk
- Strong scientific rationale reduces perceived concern

Key Lessons from the Case Study

- Thorough preparation is valuable for regulatory interactions
- Anticipate regulatory questions early and prepare clear scientific rationale
- Integrated interpretation of ADA, PK and PD data is critical
- Regulators may view risk differently than sponsors anticipate

Example 3: Information Requests at IND Stage

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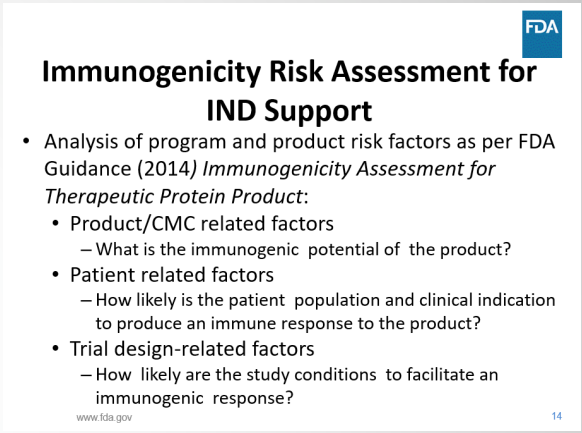
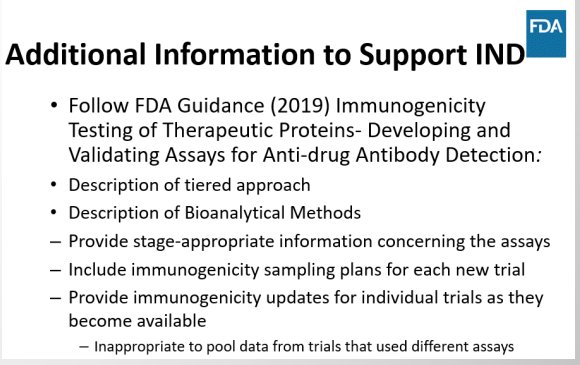
Information Requests from FDA at IND Stage

- In the past we did receive several information requests from FDA regarding immunogenicity at IND stage
  - Questions were mainly regarding our NAb testing strategy, sampling plan,…
    - "*Provide your plan for assessing neutralizing activity against SARXXXXXX. Refer to the FDA guidance for industry Immunogenicity Assessment for Therapeutic Protein Products and Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection. In addition, provide an immunogenicity risk assessment for your product*"
    - "*Include a plan to conduct assessment of neutralizing antibodies among patients who are positive for anti-drug antibodies*"
    - "*In your abbreviated protocol, you state that you will be collecting samples to assess immunogenicity of SARXXXXXX, however your schedule of activities does not include any information of when these samples will be collected*"

“Immunogenicity Summary“ in IND

- Since a few years we are providing an „Immunogenicity Summary“ in chapter 5.3.5.3 of any IND
  - It contains:
    - The “Immunogenicity Risk Assessment (IRA)“
    - The bioanalytical testing strategy (tailored based on the IRA)
    - The immunogenicity sampling plan
    - Available immunogenicity results from previous clinical trials
- Since this time we did not receive information requests for immunogenicity at IND stage!





Example 4: Applicability of Validation Cut-Points

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Applicability of Validation Cut-Points

- We received several request to prove that the cut-points determined during validation is adequate for clinical trial
  - *"You used commercial serum samples to determine the screening cut-point. Please provide evidence that this cut-point is adequate to test samples from the phase 3 in XXX"*
  - *"Commercially available plasma samples were used for the pre-study assay validation exercises. FDA guidance recommends that cut points (CP) determined during pre-study validation with commercial samples be evaluated with treatment-naïve samples from the study population. We recommend that you confirm all NAb assay CP using treatment-naïve, in-study pre-dose samples from your clinical trials, as available*"
    - We pushed back that usually NAbs are only assessed in confirmed positive samples (not negative pre-dose samples) but FDA insisted

Example 5: Non-Clinical Immunogenicity Testing for Novel Modalities

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Non-clinical Immunogenicity Testing

- For classical biotherapeutics, we did not yet receive any question for non-clinical immunogenicity testing or assessment
  - Immunogenicity in animals is not deemed predictive for humans (ICHS6R1)
  - ADA testing is only done to help interpreting the tox studies
  - ADA assay validation and sample testing efforts are significantly reduced compared to the assessment of clinical immunogenicity
- For a LNP gene therapy we recently received the following request:
  - "*We note that in your non-human primate studies you observed development of ADAs . It is unclear if the ADAs are directed against the targeting moiety on the LNP, PEGylated liquid, or both. Please provide any data that further characterizes the underlying immunogenic response*"
- Are there are different regulatory expectation for immunogenicity assessment in animals for these new modalities compared to classical biotherapeutics???

Backup slides

Overview of FDA Formal Meeting Types (ADA Context)

Meeting Type	Purpose	Typical ADA Use	Timeline Intensity
Type A	Resolve stalled programs / urgent issues	Unexpected high-titer ADA, clinical hold, safety risk	Shortest timelines
Type B (Milestone)	Key development milestones (Pre-IND, EOP1/2, Pre-BLA)	Strategic immunogenicity alignment, labeling risk	Standard milestone timelines
Type C	Non-urgent scientific advice	Cut-point strategy, assay format, drug tolerance	Longer timelines
Type D	Focused, limited questions (≤ 2–3)	Statistical method, confirmatory approach clarification	Expedited, narrow scope
INTERACT	Early engagement for innovative modalities	Immune risk framework, translational strategy	Early-stage structured interaction

Backup information: Comparison of FDA Formal Meeting Guidances (2009 vs 2023 Draft)

Topic	2009 Guidance (all biologics*)	2023 Draft Guidance (PDUFA)
Status	Final guidance (Procedural, Revision 1, May 2009)	Draft guidance for comment (Procedural, Revision 1, September 2023)
Scope	Formal meetings between FDA and sponsors/applicants for drugs and biologics; excludes ANDAs	Formal meetings for **PDUFA products**; explicitly excludes ANDAs, biosimilars, and medical devices
Terminology	"Sponsors or applicants"	Introduces **"requester(s)"** terminology throughout
Meeting Types – Overall	Three meeting types: **Type A, Type B, Type C**	Six meeting types: **Type A, Type B, Type B (EOP), Type C, Type D, INTERACT**
Type A Meetings	Focus on stalled programs, dispute resolution, clinical holds, SPA follow-up; scheduled within 30 days	Expanded to include post-action meetings, refuse-to-file related meetings; still for stalled programs or urgent safety issues
Type B Meetings	Pre-IND, end-of-phase, pre-NDA/BLA; generally limited to one per milestone	More granular definition; **Type B (EOP)** separated out with distinct timelines; includes breakthrough/RMAT program discussions
Type C Meetings	Catch-all for meetings not Type A or B	Still catch-all, but more narrowly framed; guidance on when Type C vs Type D is appropriate
New: Type D Meetings	Not defined	**New meeting type** for narrowly focused issues (≤2 topics, limited disciplines) with shorter timelines
New: INTERACT Meetings	Not defined	**New early-development meeting type** for novel products before IND or pre-IND, focused on IND-enabling issues
Meeting Formats	Face-to-face, teleconference, videoconference	Explicitly defines **four formats**: in-person, virtual face-to-face, teleconference, and **Written Response Only (WRO)**
Written Response Only (WRO)	Not a formal meeting format	Fully integrated option across meeting types, with defined timelines equivalent to meetings
Meeting Request Content	12 required elements; emphasis on agenda and questions	More structured and expanded requirements (regulatory pathway, pediatric plans, human factors, question limits)
Limits on Questions	No explicit numerical limit	Explicit expectation of **≤10 total questions**, no sub-questions
Submission Method	Controlled document system; fax/email discussed for non-application meetings	**Electronic submission required** (gateway / CDER NextGen Portal) with limited exceptions
Meeting Package Timing	Fixed lead times (e.g., Type B/C: ≥4 weeks before meeting)	**Meeting-type-specific timelines**, some packages due **with the meeting request** (Type A, D, INTERACT)
Preliminary Responses	May be provided; could serve as final responses if meeting canceled	Strongly operationalized: defined timelines, requester must confirm whether meeting is still needed
Scheduling & Response Timelines	Narrative description of timelines by meeting	**Multiple explicit tables** (response, scheduling, WRO timelines, package deadlines)
Meeting Minutes	FDA issues official minutes within 30 days; dispute resolution process described	Retains 30-day timeline; adds detail on format, templates, WRO as minutes, and clarification requests
Overall Emphasis	General good meeting management practices	**Highly operational, time-bound, and differentiated**, reflecting PDUFA VII performance goals

**Biosimilar legal pathway did not exist yet in 2009: BPCIA (Biologics Price Competition and Innovation Act) was enacted in 2010*