Overview of immunogenicity inspections

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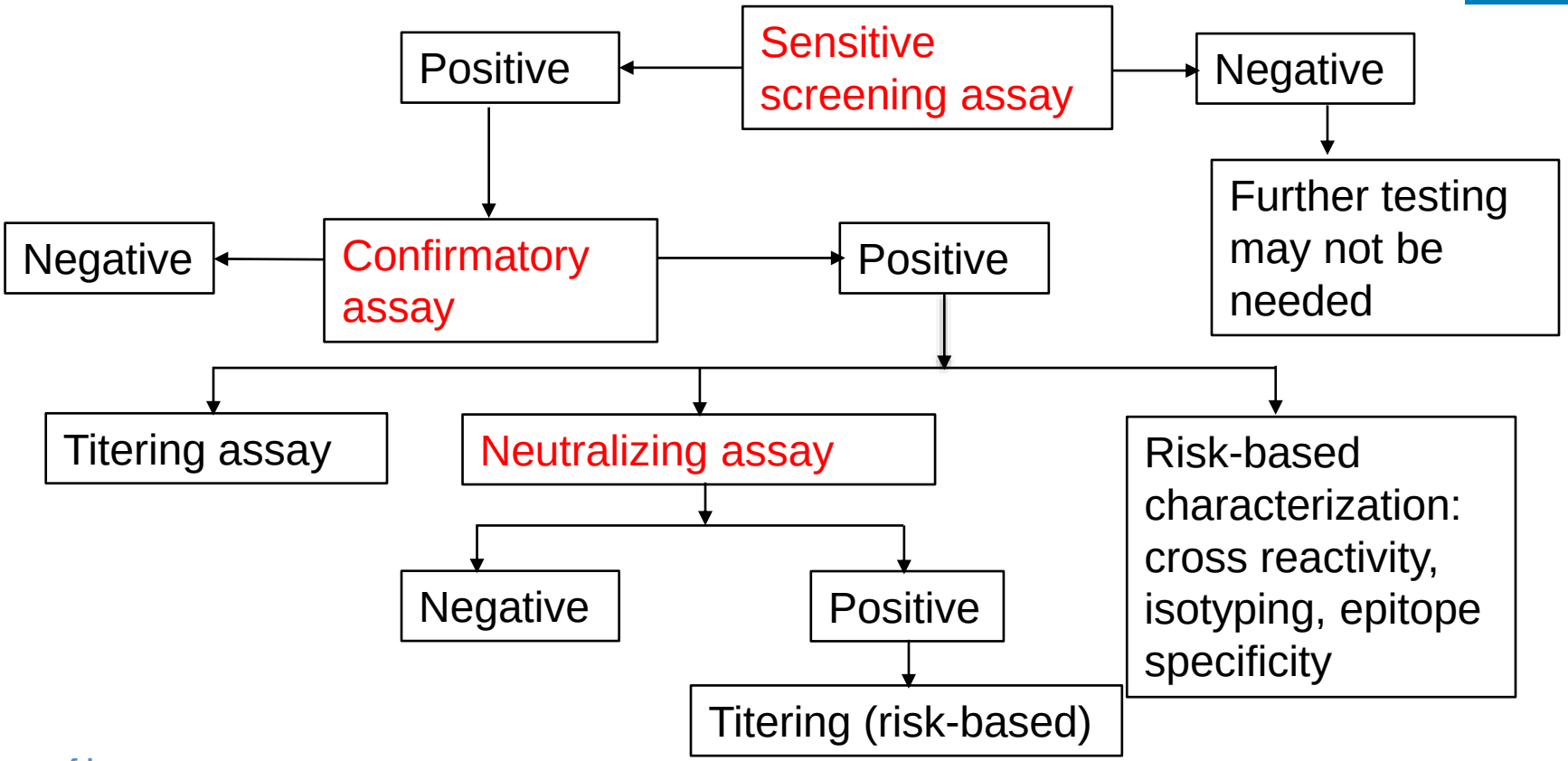
Outline

- Immunogenicity testing strategies
- Validation of immunogenicity assay critical parameters
- Common findings found during inspections
- Conclusions

Why immunogenicity testing?

- Immune responses to therapeutic protein products have the potential to affect product pharmacokinetics, pharmacodynamics, safety, and efficacy.
- Understanding anti-drug antibodies (ADA) responses is a key aspect of therapeutic protein product development.

Immunogenicity testing strategy



Types of immunogenicity assays

ADA assays

- Radioimmunoassay (RIA)
- Enzyme Linked Immunosorbent Assay (ELISA)
- Electrochemiluminescence (ECL)
- Surface plasmon resonance (SPR)

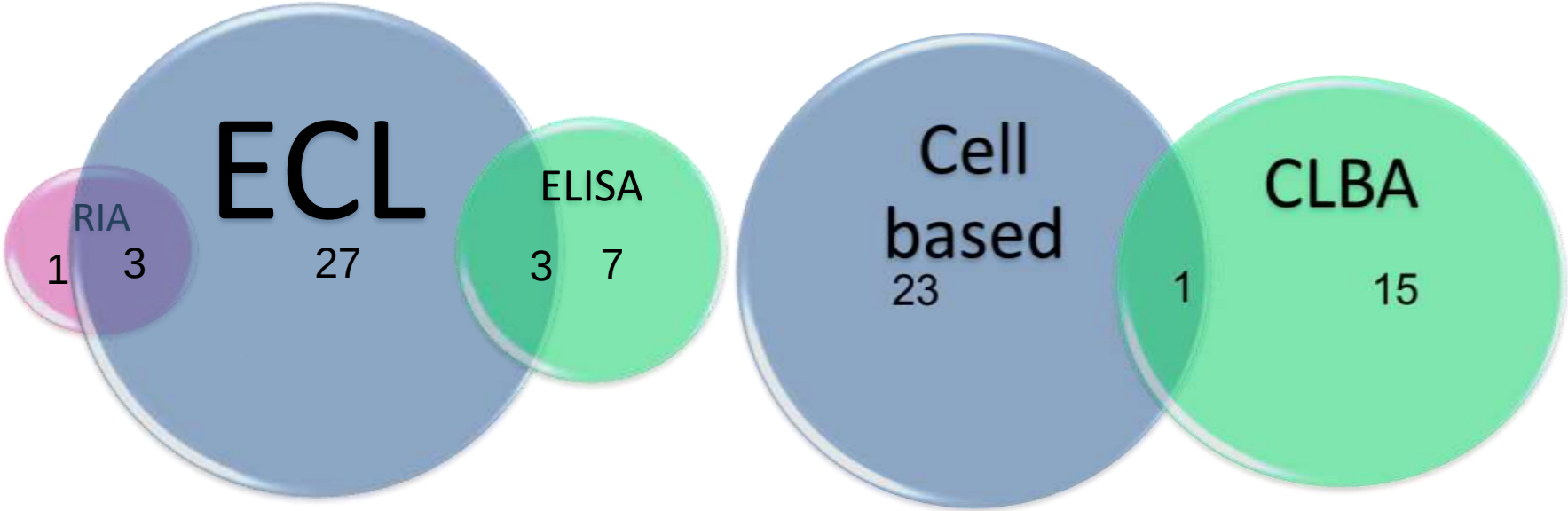
NAB assays

- Cell-based
- Competitive ligand binding assays (CLBA)

Assays used in OSIS inspected BLAs – last 5 years

ADA assays

NAB assays



- In four BLAs, SPR was used for isotyping

Immunogenicity inspection components*

- Method validation
- Study sample analysis
- Documentation of study conduct
- Facility and operations
- Equipment maintenance and calibrations
- Employee training records
- Data security

*For more details - “Bioanalytical Inspections: Overview and Case Studies” by Dr. Seongeun (Julia) Cho, SBIA Webinar on Regulatory Education for Industry (REdI): How should I measure this? An FDA perspective on the Bioanalytical Method Validation (BMV) – June 17, 2019.

Validation of immunogenicity assay critical parameters*

- Assay cut point
- Assay sensitivity
- Drug tolerance
- Specificity
- Selectivity/Matrix interference

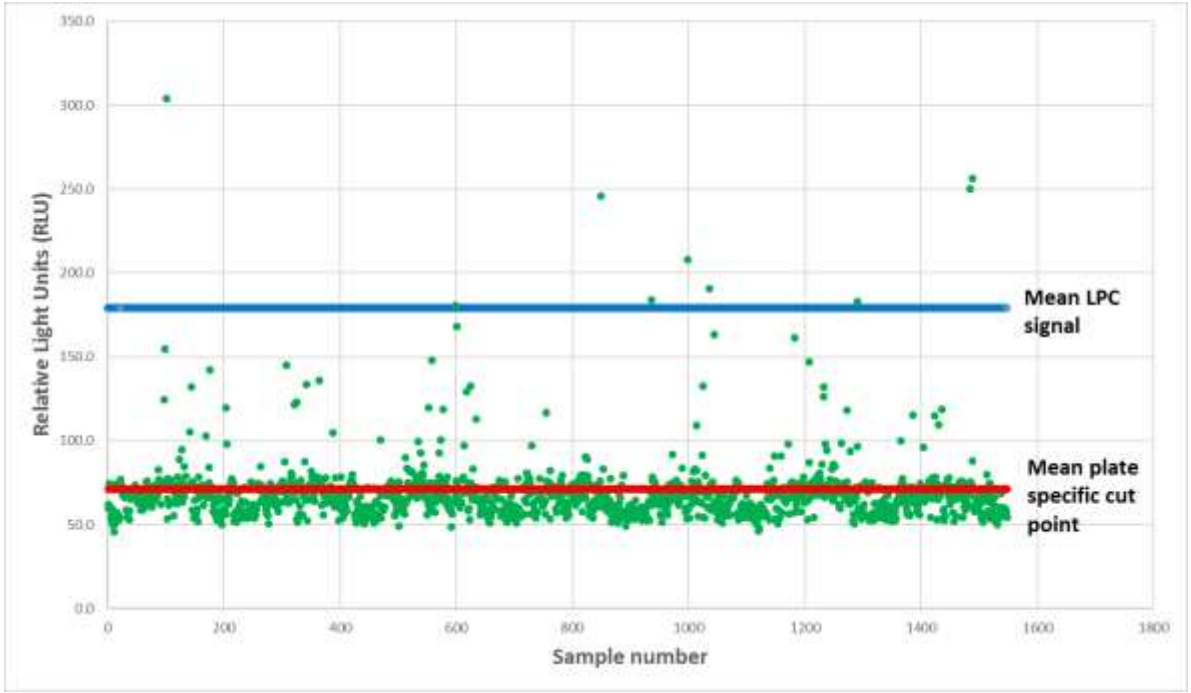
* FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products, Jan 2019

Immunogenicity assay critical parameters (continued)

- Minimum required dilution
- Precision
- Reproducibility
- Robustness
- Stability of critical reagents

Common findings during inspection

- LPC concentration not relevant



- Mean LPC signal ~ 2.5 x Mean PSCP
- 92% of potential positive samples had signals below the mean LPC signal

- "For the low-positive QC sample, we recommend that a concentration be selected that, upon statistical analysis, would lead to the rejection of an assay run 1% of the time." 2019 FDA Guidance Document on Immunogenicity Testing

Common findings (continued)

- Not all validation parameters were assessed
  - Precision, specificity, selectivity of confirmatory assay
  - Drug tolerance, selectivity in hemolyzed plasma
- F/T and benchtop stability assessments of PCs not done or inadequate
  - Number of sample F/T cycles exceeded established F/T cycles
  - No fresh comparator used
  - Assessed at HPC only

Common findings (continued)

- Cut point determination inadequate
  - Arbitrary cut point
  - Outlier removal by visual inspection
  - Not confirming cut point in target population

Common findings (continued)

- Lack of contemporaneous documentation
  - Sample movement, sample processing procedures, rationale for repeating assays, experimental errors
- Data exclusion without justification
  - Duplicate values
  - Precision data during method validation
- Use of expired reagents

Conclusions

- Immunogenicity assessment should be designed to detect ADA that could mediate unwanted clinical consequences.
- OSIS conducts inspections to ensure immunogenicity data submitted to FDA are accurate and reliable

Challenge question 1

When conducting immunogenicity testing, FDA's expectation does NOT include.

A. Use of multi-tiered testing approach

B. The screening ADA assay should be fully validated

C. Validation of assay cut point suffices for the confirmatory ADA assay

D. None of the above

Challenge question 2

Immunogenicity assay is a quantitative approach that determines the concentration of ADA in plasma samples.

True or False?

False

Thank you!