Integrated Summaries of Immunogenicity: An FDA Reviewer's Wish List

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EIP Short Course Lisbon

Nov 13, 2017

Disclaimer

- Views expressed in this presentation are personal, and reflective of my experience as an immunogenicity reviewer for the Office of Biotechnology Products.
- My views are not necessarily reflective of views or current policies of the FDA.
- **The "Integrated Summary of Immunogenicity" is optional for BLAs**
  - **FDA may include an ISI recommendation in new version of 2016 guidance**

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

Office of Biotechnology Products (OBP)

- CMC for 351 (a) and 351 (k) biologics under CDER purview
  - Currently 4 product divisions with mixed portfolios

- Collaborate in immunogenicity risk assessments and review validation of clinical immunogenicity assays for 351 (a) and 351 (k) biologics at CDER
  - Involved in writing FDA Immunogenicity guidances
  - Immunogenicity Working Group

FDA Immunogenicity Guidances

- Guidance (2014): Immunogenicity Assessment for Therapeutic Protein Product
  - Discusses product and patient risk factors that may contribute to immune response rates.
- Draft Guidance (2016): Assay Development for Immunogenicity Testing of Therapeutic Proteins
  - Discusses the development and validation of immunogenicity assays
- Guidance (2016): Immunogenicity-Related Considerations for Low Molecular Weight Heparin
  - Provides recommendations on addressing impurities and their potential effect on immunogenicity for ANDAs
- Guidance (2015): Scientific Considerations In Demonstrating Biosimilarity To A Reference Product
  - Discusses immunogenicity assays in context of 351(k) pathway
- Guidance (2017): Considerations in Demonstrating Interchangeability to a Reference Product
  - Discusses immunogenicity studies required for interchangeability in context of 351(k) pathway
- Draft Guidance (2017): ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin
  - Discusses immunogenicity considerations for recombinant peptides under ANDA

CDER Immunogenicity Review Committee

- IRC is a new cross-center committee with members from:
  - Office of Pharmaceutical Quality's Office of Biotechnology Products (OBP)
  - Office of Translational Sciences' Office of Clinical Pharmacology (OCP), Office of Scientific Integrity and Surveillance (OSIS) and Office of Bioequivalence (OB)
  - Office of New Drugs' clinical review divisions (DPARP, OHOP, DGIEP, DMEP, DBRUP)
  - Office of Statistics and Epidemiology (OSE)
  - Office of Generic Drugs (OGD)
  - Office of Medical Policy (OMP), Office of Regulatory Policy (ORP), and Office of Chief Council (OCC)
  - Observers from CBER and CDRH

CDER Immunogenicity Review Committee

- The IRC provides a multi-disciplinary space to:
  - Develop and maintain risk-based frameworks for evaluating immunogenicity risk
  - Provide advice and expertise to review programs evaluating BLAs, NDAs, and ANDAs with product-specific immunogenicity concerns
  - Internally and externally communicate interdisciplinary product-specific immunogenicity evaluations, as well as broader immunogenicity-related issues and initiatives

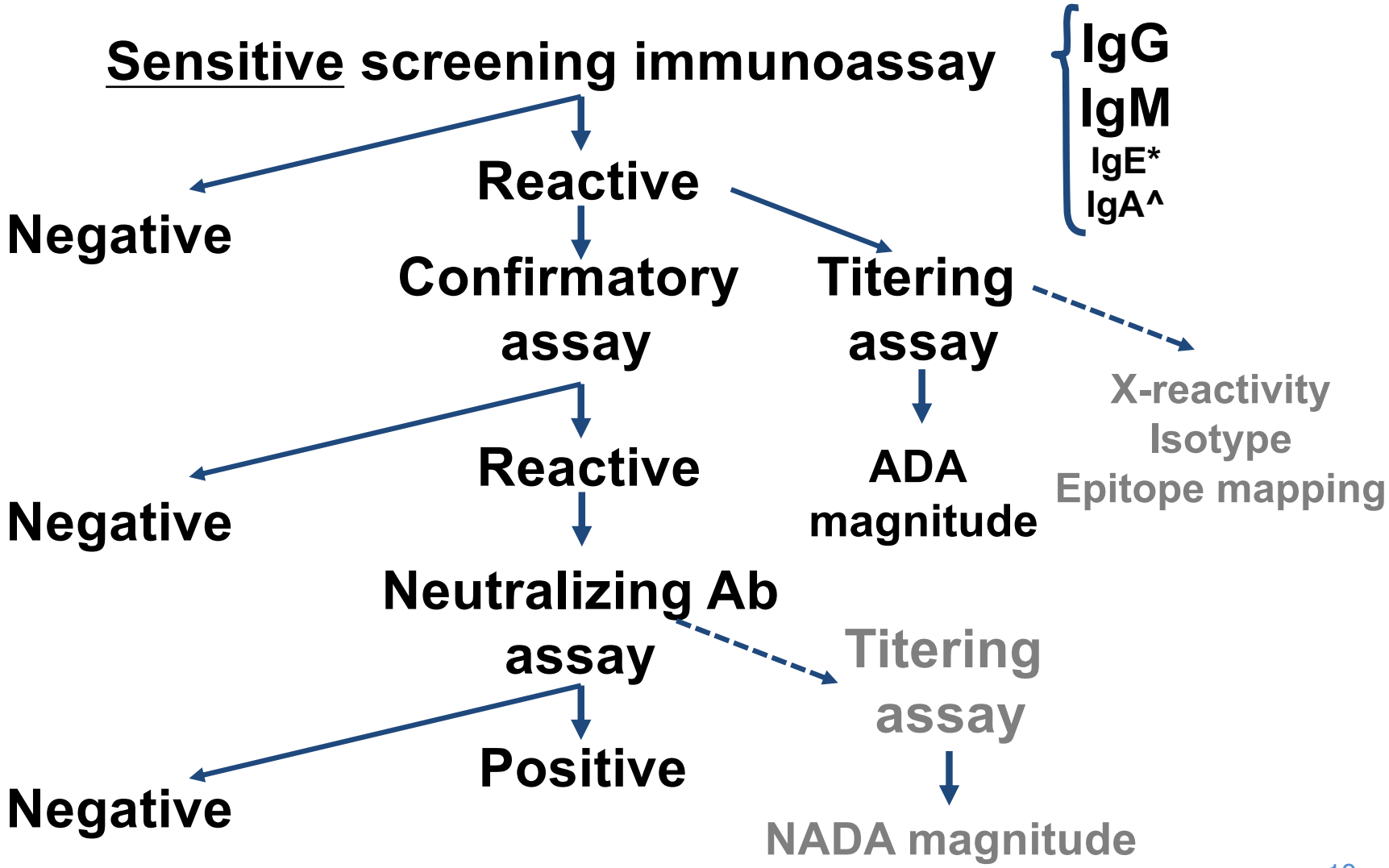
FDA regulatory perspectives

- Immunogenic responses to therapeutic proteins arise from complex multi-factorial interactions
  - Patient, drug product, and clinical trial specific factors impact each other
  - Perform a multi-disciplinary risk based analysis as early as possible in the product development cycle
  - Perform risk re-assessments as part of comparability during product & process development

FDA regulatory perspectives

- Immunogenicity is a safety concern, there is a need to assess/measure it.
  - ADA and NAbs may impact safety and/or efficacy
  - Correlate with clinical data (AE, PK and PD, efficacy) **if possible**
    - Linear or non-linear correlations with patient subset analysis

Multi-Tiered Immunogenicity Approach



Expectations for Immunogenicity Assessment

- Sponsors should develop validated immunogenicity assays
  - ADA assays
    - Binding
    - Confirmatory
    - Titering
  - NAb assay (s)
    - Format may depend on mechanism of action
    - Qualitative
    - Semi-quantitative/titering for some assay formats

Expectations for Immunogenicity Assessment

- Phase dependent assay development
  - Have assays validated prior to testing clinical phase 3 study samples
  - For 351 (k) start discussions early concerning study design
  - Crucial to have appropriately stored study samples

Risk-based Approach to Immunogenicity Assay Development

- Provide a rationale for immunogenicity testing strategy at IND stage, preferably during phase 1

- Assays are critical when neutralizing immunogenicity poses a high-risk therefore real time data concerning patient responses are needed
  - Part of risk mitigation
  - Preliminary validated assays should be implemented early (preclinical and phase I)

For Other Products

- Sponsor may store patient samples to be tested when suitable assays are available
- Phase 1 and phase 2 study samples may be tested using “fit-for-purpose” assays
- Pivotal study/phase 3 samples need to be tested using fully validated assays
- Provide data supporting full validation of the assays at license

Current Challenges for FDA reviewers

- IND Stage
  - Lack of clearly delineated immunogenicity risk assessment section with summary sampling plans for clinical studies with an immunogenicity component during IND stage.

Current Challenges for FDA Reviewers

- BLA Stage
  - Immunogenicity information is scattered throughout the eCTD in the BLA file.
    - 2.7.4 Summary of Clinical Safety
      - Summary of immunogenicity results
    - 5.3.1.4 Reports on Biopharmaceutical Studies
      - The rationale and information about the chosen immunogenicity testing strategy
      - Assay Validation Reports
    - 5.3.5 Reports of Efficacy and Safety Studies
      - Immunogenicity data set

OBP Reviewer's Perspective

- Review CMC for therapeutic proteins under CDER purview-
  - Linear progression through eCTD
- Collaborate in immunogenicity risk assessments with clin/pharm and clinical reviewers and review validation of clinical immunogenicity assays for biologics and drugs at CDER
  - challenging to review immunogenicity because of the scattered nature of the information

Regarding Immunogenicity

Desired information for review:

- An immunogenicity risk assessment specific to their product,
- Details on the tiered immunogenicity strategy being followed
- Immunogenicity sampling plan(s) for proposed clinical studies with suitable justification
- Method development and validation reports for all the immunogenicity assays used
  - Particularly those used to test immunogenicity samples from pivotal clinical study(ies)

Regarding immunogenicity

Desired Information for review:

- Tabular summary identifying which immunogenicity assays were used to test samples from individual clinical studies
- Results of immunogenicity analysis for clinical studies having immunogenicity component
  - Correlation of ADA with PK/PD/efficacy/safety (adverse-events)
  - Traceability of drug product lots used in clinical study

Possible Model

- EMA 2015 draft guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins
  - A recommendation for an "Integrated Summary of Immunogenicity" to submit in licensing dossier
  - Included in eCTD 2.7.2.4 *Special Studies* or in Section 5.3.5.3 *Reports of Analysis of Data from More than One St*udy
    - Introduction/Risk analysis
    - Methodology for Risk evaluation
    - Results
    - Conclusions

Possible Model

- Envision a "living" integrated summary document that sponsors would begin populating early in product development , and would update as clinical program progresses through IND stages into BLA
  1. Immunogenicity risk assessment
  2. Tiered strategy and bioanalytical assays with stage-appropriate information
  3. Clinical study design and sampling strategy
  4. Clinical immunogenicity data analysis
  5. Conclusions and Risk Mitigation

Immunogenicity Risk Assessment

- Analysis of program and product risk factors as per FDA Guidance (2014*) Immunogenicity Assessment for Therapeutic Protein Product*:
  - Product/CMC related factors
    - What is the immunogenic potential of the product?
  - Patient related factors
    - How likely is the patient population and clinical indication to produce an immune response to the product?
  - Trial design-related factors
    - How likely are the study conditions to facilitate an immunogenic response?

Proposed Immunogenicity Tiered Strategy and Methodology

- Section aligned with FDA Draft Guidance (2016): *Assay Development for Immunogenicity Testing of Therapeutic Proteins:*
- Description of tiered approach
- Description of Bioanalytical Methods
  - Populate this section as development progresses
  - For clinical phase 1 and 2 fit-for-purpose immunogenicity assays
  - For phase 3 fully validated immunogenicity assays
  - Generally inappropriate to pool data from trials that used different assays

Clinical Study Design and Sampling Strategy

- Sampling for immunogenicity testing
  - Justification for the length of the follow up
    - on-treatment
    - off-treatment, post-exposure
  - Sampling for Pharmacokinetics

Clinical Study Design and Sampling Strategy (cont)

- Pharmacodynamics, efficacy and safety trials
  - how the program aims to reveal the incidence, persistence, and clinical significance of ADAs
  - antigen tolerance of the ADA assay and the drug concentrations at sampling times

Clinical Immunogenicity Data Analysis

- Immunogenicity in clinical trials (relative immunogenicity in case of manufacturing changes and biosimilars)
  - Incidence of ADAs, including NAbs
  - Titres and persistence over time
  - Further characterization if appropriate,
    - cross-reactivity with related therapeutic or endogenous proteins,
    - isotyping,
    - epitope mapping

Clinical Immunogenicity Data Analysis (cont)

- Immunogenicity in clinical trials (relative immunogenicity in case of manufacturing changes and biosimilars)
  - Impact of ADAs on pharmacokinetics
  - Impact of ADAs on pharmacodynamics, efficacy and safety
  - Impact of pre-existing antibodies on pharmacokinetics, safety and efficacy

Conclusions and Risk Mitigation

- Discuss impact of immunogenicity on the benefit/risk of drug to the patient
- How will immunogenicity be monitored post-marketing, if warranted?
  - Tied to life-cycle management of immunogenicity assays

Post-Aproval/life-cycle management

- How will immunogenicity be monitored post-marketing?
  - REMS and adverse event reporting
  - Efficacy supplements
  - Post-Approval Manufacturing Supplements
  - Support cross-referencing IND(s) / clinical Investigator IND(s)?

Closing remarks

- OBP is currently encouraging the submission of Integrated Summaries of Immunogenicity prepared as per EMA guidelines for BLAs
  - Has made immunogenicity reviews less time-consuming
  - Revised FDA Draft Guidance (2016): "Assay Development for Immunogenicity Testing of Therapeutic Proteins" may include a section discussing recommendations for Integrated Summaries of immunogenicity

Example of Pre-BLA comment

- Currently the data relevant to the assessment of immunogenicity are dispersed throughout different locations of the eCTD including 2.7.4 Summary of Clinical Safety, 5.3.1.4 Reports on Biopharmaceutical Studies and 5.3.5 Reports of Efficacy and Safety Studies.
- For your BLA we encourage you to provide an Integrated Summary of Immunogenicity that includes:
  - An immunogenicity risk assessment specific to your product,
  - Details on the tiered immunogenicity strategy that you followed in your clinical program, and validation summaries for the various immunogenicity assay methods you developed in your program
  - Links to method development and validation reports for all the immunogenicity assays used in your clinical studies, particularly those used to test immunogenicity samples from your pivotal clinical study(ies)
  - Immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed
  - Summary results of immunogenicity analysis for all clinical studies having immunogenicity component, including the results of your correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data
  - Traceability of drug product lots used in all your clinical studies
- The Integrated summary may be submitted in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study.

Acknowledgements

- Susan Kirshner, Review Chief
- Daniela Verthelyi, Lab Chief,
- Amy Rosenberg, Division Director
- Emanuela Lacana, OBP policy director
- Office of Biotechnology Immunogenicity Working Group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