FDA Recommendations on Integrated Summaries of Immunogenicity from Phase 1 IND to BLA and Beyond

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EIP 2019 Short course

Disclaimer

- My views are not necessarily reflective of views or current policies of the FDA.
- **The "Integrated Summary of Immunogenicity" is recommended for BLAs and suggested for INDs as per 2019 FDA Guidance Immunogenicity Testing of Therapeutic Protein Products- Developing and Validating Assays for anti-Drug Antibody Detection (Jan, 2019)**

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)

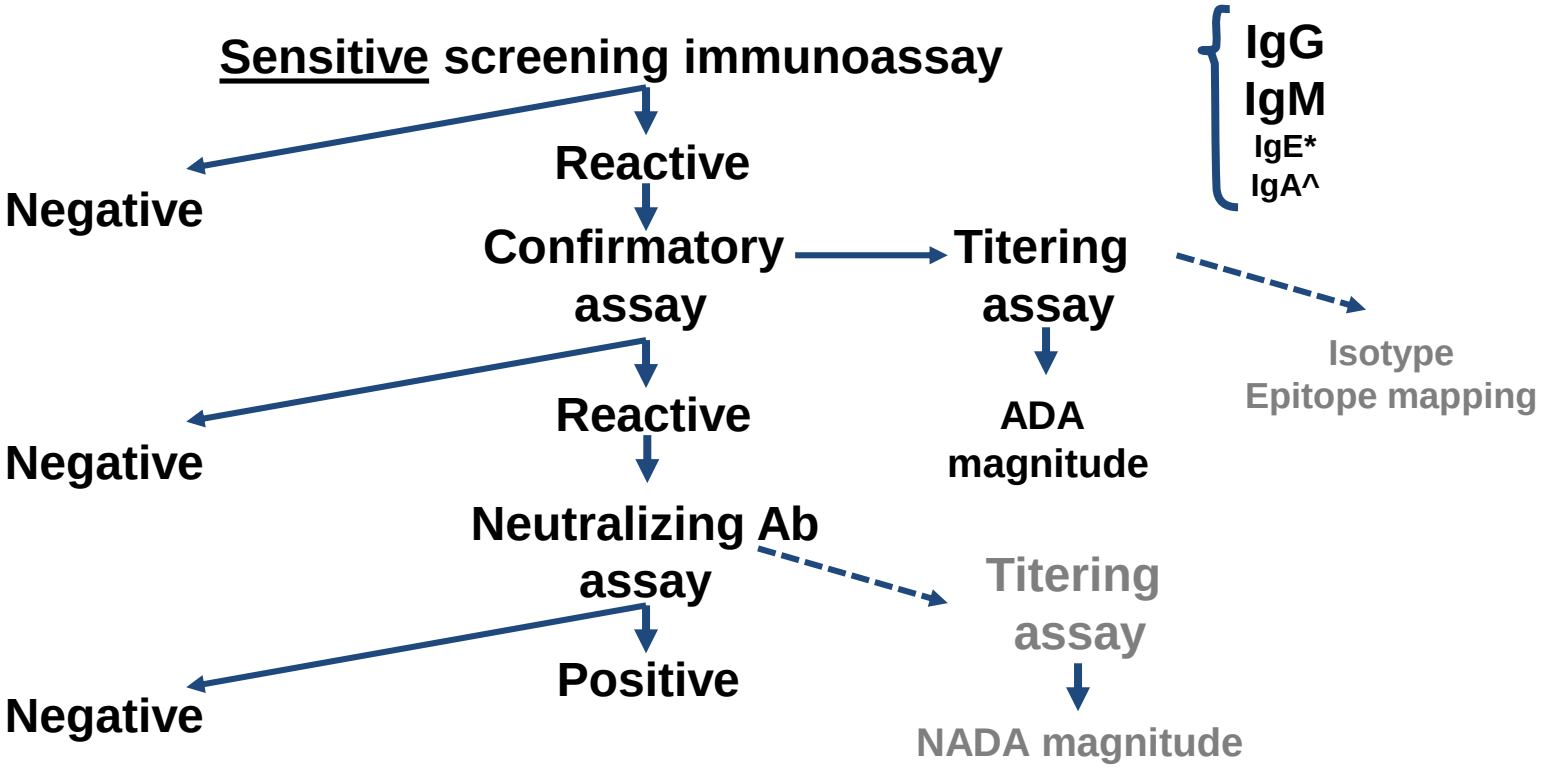
- CMC for 351 (a) and 351 (k) biologics (Public Health Service Act) under CDER purview
  - OBP product quality reviewers spread across 4 divisions

- Collaborate in immunogenicity risk assessments and review validation of clinical immunogenicity assays for biologics and drugs under CDER purview
  - OBP immunogenicity reviewers spread across 4 divisions
  - **Immunogenicity Working Group SMEs**

Typical OBP Immunogenicity Reviewer Tasks

- Review proposed immunogenicity testing strategies
- Review clinical immunogenicity assay validation reports
  - innovator biologics and biosimilars under OBP CMC purview
    - Includes transition products initially regulated as NDAs
  - Therapeutic peptides and drugs submitted as immunogenicity consults to OBP

Multi-Tiered Immunogenicity Testing Strategies



Typical OBP Immunogenicity Reviewer Tasks

- Review clinical sampling plans for proposed clinical trials
  - Innovator biologics phase 1, 2 and 3 trials
  - Biosimilar comparative parallel group trials and interchangeability switching group trials
    - Sometimes collaborate in clinical trial design
  - Therapeutic peptides and drug clinical trials submitted as immunogenicity consults to OBP

More Specialized OBP Immunogenicity Reviewer Activities

- Multidisciplinary Review of clinical immunogenicity data in collaboration with Clinical, Clin-Pharm, Clin Stats reviewers
- Produce an immunogenicity review summarizing risk assessment, immunogenicity assay validation and clinical immunogenicity data evaluation
  - Review immunogenicity section of labelling/PI
- Strategies for ANDA immunogenicity assessment

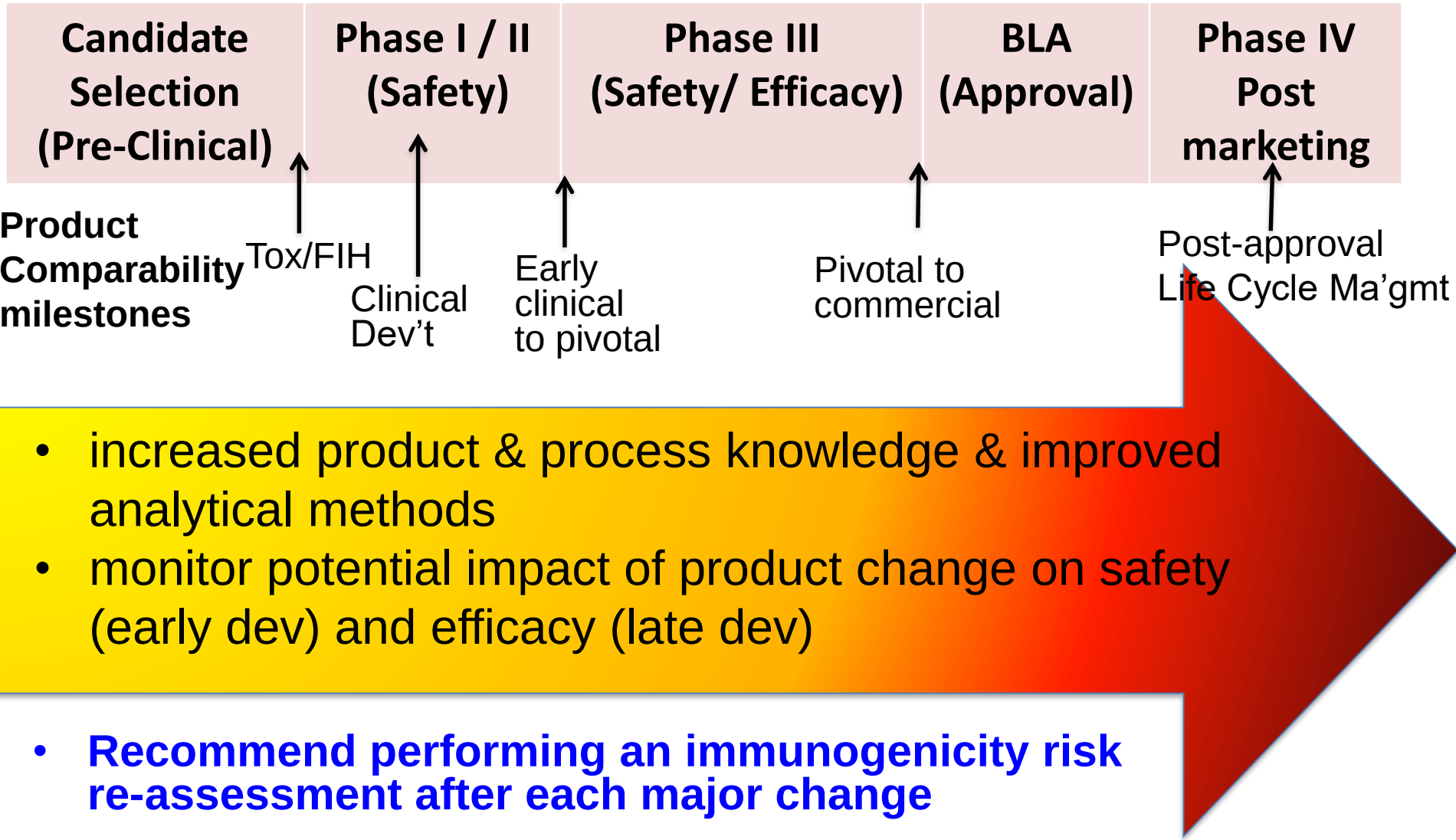
OBP Immunogenicity Working Group

- Immunogenicity SMEs from each of the 4 divisions
- Develop frameworks for immunogenicity risk assessments by OBP Reviewers
- Provide advice and expertise to OBP Reviewers evaluating BLAs, NDAs, and ANDAs with product-specific immunogenicity concerns
- Internally and externally communicate product-specific immunogenicity evaluations, as well as broader immunogenicity-related issues and initiatives
  - Involved in writing and communicating FDA Immunogenicity guidances to industry stakeholders

FDA Immunogenicity Guidances

- Guidance (2014): Immunogenicity Assessment for Therapeutic Protein Product
  - Discusses product and patient risk factors that may contribute to immune response rates, as well as risk mitigation strategies.
- Guidance (2015): Scientific Considerations In Demonstrating Biosimilarity To A Reference Product
  - Discusses immunogenicity assays in context of 351(k) pathway
- Guidance (2016): Immunogenicity-Related Considerations for Low Molecular Weight Heparin
  - Provides recommendations on addressing impurities and their potential effect on immunogenicity for ANDAs
- 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
- **Guidance (2019): Immunogenicity Testing of Therapeutic Proteins-Developing and Validating Assays for Anti-drug Antibody Detection"**
  - **Discusses the development and validation of immunogenicity assays**

Typical Biotech Product Development



Stages of Immunogenicity Assessment

- *biotherapeutic candidate selection (not FDA)*
- PreIND
- IND support
  - Initial IND/Phase 1 (FIH)
  - Mid-development (Phase 2 and Pivotal)
- BLA submission
- Post-Aproval/life-cycle management

Reviewed by OBP

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

Immunogenicity Risk Assessment for IND Support

- 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?

Product/CMC-Related Factors

- Essential to understand the critical quality attributes (CQA) of the biotherapeutic:
  - Degree of “foreignness”/immune tolerance and molecular size
  - Chemical composition and molecular complexity
  - Stability/degradability/impurities
    - Purity on release, storage and handling
    - Upon contact with biological matrices

Recommendations

A RISK-BASED approach is required to balance the potential harm with potential good of a new biotherapeutic throughout clinical development

- Likelihood of developing an immune response
- Risk of immune response to patient
- Are there therapeutic alternatives
- Reversibility of response

Additional Information to Support IND

- Follow FDA Guidance (2019) Immunogenicity Testing of Therapeutic Proteins- Developing and Validating Assays for Anti-drug Antibody Detection*:*
- Description of tiered approach
- Description of Bioanalytical Methods
  - Provide stage-appropriate information concerning the assays
  - Include immunogenicity sampling plans for each new trial
  - Provide immunogenicity updates for individual trials as they become available
    - Inappropriate to pool data from trials that used different assays

Current Challenges for OBP Immunogenicity 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.

Suggestion: eCTD 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

To Support A BLA:

Applicants should provide:

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

To Support a BLA

Applicants should also provide:

- Tabular summary identifying which immunogenicity assays were used to test samples from individual clinical studies
  - Include list of testing site(s)
- 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 the clinical studies
    - » Study and individual patient level

Post-Aproval/life-cycle management

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

Current Challenges for OBP Immunogenicity 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

EMA 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

Recommendations

- Recommend the use of a “living” integrated immunogenicity summary document that sponsors would begin populating early in product development , and would update as clinical program progresses through IND stages into BLA and post-approval
  1. Immunogenicity risk assessment
  2. Tiered bioanalytical strategy and assay validation summaries (with stage- appropriate information)
  3. Clinical study design and detailed immunogenicity sampling plans
  4. Clinical immunogenicity data analysis
  5. Conclusions and Risk Evaluation and Mitigation Strategies (REMS)
     a) Include post-marketing/Life-Cycle management plans

Integrated Summaries of Immunogenicity

- As per Jan, 2019 FDA Guidance "Immunogenicity Testing of Therapeutic Protein Products- Developing and Validating Assays for anti-Drug Antibody Detection" (section VIII. Documentation)
  - ISIs are requested for all new 351(a) and 351(k) BLA submissions.
    - Provide brief summaries of the immunogenicity results in relevant places in eCTD section 2.7. Clinical Summary and the full report in section 5.3.5.3 Reports of Analysis of Data from More than One Study
      - Will receive IR if absent at filling.
    - Harmonizes with EMA guidelines

Integrated Summaries of Immunogenicity

- New sBLA efficacy supplements should include ISIs
  - Minimally an immunogenicity risk assessment if clinical ADA rates were not determined
- New NDAs (oligos, peptides, carbohydrates) are recommend to include ISIs as well
- New and ongoing INDs are suggested to include ISI with stage appropriate information.
  - Regular updates as clinical program progresses
- **"Never too early or too late to Integrate!"**
  - **Personal opinion**

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- Office of Biotechnology Immunogenicity Working Group

Section VIII documentation

FDA Guidance (Jan, 2019): Immunogenicity Testing of Therapeutic Proteins- Developing and Validating Assays for Anti-drug Antibody Detection”

Currently the data relevant to the assessment of immunogenicity are dispersed throughout different locations of the eCTD. To facilitate the clinical development of therapeutic biologics, we recommend a life-cycle management approach to immunogenicity through the creation of an integrated immunogenicity summary report that sponsors begin populating early in therapeutic protein product development and update at regular intervals as the individual product clinical program progresses through IND stages into the BLA and even postapproval stages. We recommend that the document be arranged into distinct sections to be populated with stage-appropriate information as it becomes available, including (1) Immunogenicity Risk Assessment, (2) Tiered Bioanalytical Strategy and Assay Validation Summaries, (3) Clinical Study Design and Detailed Immunogenicity Sampling Plans, (4) Clinical Immunogenicity Data Analysis, and (5) Conclusions and Risk Evaluation and Mitigation Strategies (REMS).

For the BLA file, we recommend that the applicant provide brief summaries of the immunogenicity results in relevant places in eCTD section 2.7. Clinical Summary and the full report in section 5.3.5.3 Reports of Analysis of Data from More than One Study.[39] This Integrated Summary of Immunogenicity should provide the following:

a. Immunogenicity Risk Assessment: This section should provide a concise immunogenicity risk assessment specific to the therapeutic protein product.[40] This section should include discussions on therapeutic protein product quality-related factors

and how these may impact the immunogenic potential of the therapeutic protein product; subject-related factors, including a discussion on how likely is the subject population and clinical indication to result in immunogenic responses to the therapeutic protein product; and a section on trial design-related factors, as well as a discussion of any strategies or clinical study conditions implemented to manage the immunogenic response to the therapeutic protein product.

b. Tiered Strategy and Stage-Appropriate Bioanalytical Assays: This section should provide a summary of the immunogenicity assessment strategies used during each phase of the clinical program and a characterization for the various methods that were developed throughout the program. In addition, this section should provide links to the method development and validation reports for the pivotal clinical studies supporting the application.

c. Clinical Study Design and Sampling Strategy: This section should include the immunogenicity sampling plan(s) for all clinical studies that had an immunogenicity assessment performed. This section should also include sampling time points for immunogenicity and pharmacokinetics of the therapeutic protein product, where applicable.

d. Clinical Immunogenicity Data Analysis: This section should provide summary results of immunogenicity analyses for all clinical studies having an immunogenicity component, including the results of linear or non-linear correlation analyses between ADA status and titers with PK, PD, efficacy, and safety (adverse event) data. This section should include drug levels measured in the samples tested for ADA and should trace drug product lots used in the individual clinical studies. Discussion should examine the impact of any pre-existing antibodies or treatment-boosted or treatment-induced antibodies on pharmacokinetics, pharmacodynamics, efficacy, and safety of the therapeutic protein product.

e. Conclusions and REMS, if applicable: This section should discuss how therapeutic protein product immunogenicity affects the safety and efficacy of the therapeutic protein product for the subject population. In addition, consideration should be given to how therapeutic protein product immunogenicity will be monitored in the postmarketing stage and how this will be incorporated into any planned risk evaluation and mitigation strategies. Lastly, a discussion should be provided regarding life-cycle management of approved immunogenicity assays, including an assay requalification schedule and assay transfer to contract testing laboratories for postmarketing surveillance.