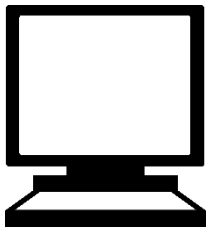
Immunogenicity Assessments for Biologics– Current Perspectives from FDA's Office of Biotechnology Products

João Pedras-Vasconcelos, PhD
Product Quality and Immunogenicity Senior Staff Fellow
OBP, OPQ, CDER, FDA
EBF virtual 2020, Nov 18, 2020

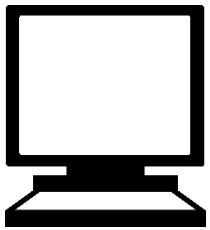
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.




Drugs are no different.


FDA
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 considerations for 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

Current FDA thinking on Predicting Immunogenicity Risk :

- Challenges for Immunogenicity risk assessment:
  - Is the biologic likely to induce immunogenicity?
  - what subset of patients will be impacted?
  - how will IR impact the clinical outcome?
- At this time immunogenicity cannot be accurately predicted from product structure and formulation
  - Clinical studies with suitable immunogenicity component are needed to answer above questions
    - Sampling and testing strategy to monitor clinical development of ADA
    - In near future, bioanalytical assays to monitor innate Immune responses and T cell responses ?

Office of Biotechnology Products (OBP)

- CMC for 351 (a) and 351 (k) biologics under CDER purview
  - OBP product quality assessors spread across 4 divisions

- Collaborate in immunogenicity risk assessments and assess validation of clinical immunogenicity assays for biologics and drugs (oligos, peptides etc.) under CDER purview
  - OBP immunogenicity assessors (Immunerdies) spread across 4 divisions

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-Approval/life-cycle management

Reviewed by OBP

Typical OBP Immunerdy Tasks

- Assess clinical ADA sampling plans and ADA testing strategy for proposed clinical trials- IND Stage
  - Innovator biologics phase 1, 2 and 3 trials
  - Biosimilar comparative parallel group trials and interchangeability switching group trials
- Assess clinical immunogenicity assay validation reports (Screening, Confirmatory, Titering, and Neutralizing assays)
    - innovator biologics and biosimilars under OBP CMC purview
    - Therapeutic peptides and drugs submitted as immunogenicity consults to OBP
  - Typically assessed at BLA, but for higher risk products could take place at mid to late IND stage

More Specialized OBP Immunerdy Activities

- Immunogenicity Risk Assessment based on product, patient and trial design factors- IND stage
- Multidisciplinary assessment of clinical immunogenicity data in collaboration with Clinical, Clin-Pharm, Clin Stats reviewers – BLA stage
  - Assay status, ADA incidence and titers generally handled by OBP
- Produce a BLA immunogenicity memo summarizing risk assessment, immunogenicity assay validation and in study assay performance
  - Review immunogenicity section of labelling/PI

Additional Immunerdy stakeholders

- The PK assays are reviewed by the Office of Clinical Pharmacology
  - Impact of ADA on PK/PD generally handled by OCP
- Impacts on safety, including hypersensitivity, and anaphylaxis are led by the clinical reviewers
- All review disciplines participate in discussions, and experts from all disciplines provide guidance and recommendations regarding regulatory decisions.

Additional Immunerdy stakeholders

- Office of Study Integrity and Surveillance (OSIS) is consulted to evaluate needs for inspection of clinical or bioanalytical sites, for PK, PD, and immunogenicity testings
  - OSIS responsibilities include audit of bioavailability/bioequivalence and nonclinical Good Laboratory Practice (GLP) studies
  - On inspection, OSIS may make FDA Form 483 observations and classify inspections and make recommendations for primary reviews of applications. OSIS works with the Office of Scientific Investigations (OSI) to resolve OAI cases
  - OSIS consults OBP before/during/after inspections and participates in the OBP immunogenicity working group discussions

ADA Assays & Product Life Cycle - IND

- During the IND phase, validation of ADA assays is typically not expected
  - Under rare circumstances where there is an increased safety risk FDA may ask the ADA assay be validated for early studies
  - Fit-for-purpose assays for phase I and II
- FDA's review emphasis is primarily on immunogenicity risk assessment and ADA/PK sample timing
  - Generally a recommendation to bank samples of early phase studies until ADA assays are fully validated
  - Phase III/Pivotal study samples should be tested using fully validated assays

BLA stage- Mature Immunogenicity Program

- Recommend submission of Integrated Summaries of Immmunogenicity (ISI):
  1. Immunogenicity risk assessment
  2. Tiered strategy and bioanalytical assays
     - Fully validated ADA and NAb Assays
  3. Clinical study design and sampling strategy
  4. Clinical immunogenicity data analysis
  5. Conclusions and Risk Mitigation
  6. Post-marketing/Life-Cycle management plans

Antibody-specific immunogenicity assessments

- Incidence of ADA/NABs
- Titer
  - treatment emergent vs treatment boosted
- Persistence, disappearance
- Cross-reactivity to endogenous protein
- Relevant isotype distribution (case by case)
  - Future technologies may allow for this more easily

- Comparison across testing platforms and/or assays is challenging:
  - recommend side-by-side testing using the same assay platform whenever possible
    - Provide scientific justification for comparisons

Additional immunogenicity assessments?

- T cell responses-
  - In silico
    - Binding to different MHC
    - T cell facing amino acids
    - Homology with endogenous proteins (tolerance considerations)
  - In vitro
    - Reactive naive T cells (DC-T cell assays)
    - Ag. processing and expression (MHC-associated Peptide Proteomics, or MAPPs)
  - Typically part of pre-clinical immunogenicity risk assessment

Additional immunogenicity assessments?

- Innate immune responses
  - In vitro assays
    - PBMC/whole blood
  - Cell lines:
    - Expressing different innate immune receptors
      - » TLR, CLR, NLR, SR, NAR
  - Typically part of pre-clinical immunogenicity risk assessment

Multi-Domain Biologics

- Complexity of the biologic will dictate bioanalytical strategy and pace of assay development
  - Importance of product knowledge and MOA to immunogenicity risk assessment and choice of tiered assays
    - Characterize ADA to whole molecule and to functional domains
      - Typically part of confirmatory assay
      - May choose single ADA assay or orthogonal domain characterization assays
      - Additional characterizations such as cross-reactivity to endogenous proteins on case by case
    - Characterize NADA to functional domains
      - May chose single NADA assay or domain-specific NADA Assays
        - » Format determined by MOA
      - Provide suitable justification for choice
    - Consult regulators during product development
      - Novel constructs

OBP Perspectives

- ADA assays are complicated because they measure a variable analyte in a varied population at various time points
- Suitable ADA assays are needed to help determine whether ADA cause adverse events and/or loss of efficacy in patients
- Well crafted ADA assessments in IND and BLA submissions provide needed understanding to FDA assessors

Acknowledgments

- Susan Kirshner, Review Chief
- Daniela Verthelyi, Lab Chief,
- Amy Rosenberg, Division Director
- Office of Biotechnology Immunogenicity Working Group
  - Haoheng Yan, Co-chair/IFF of IWG


FDA
U.S. FOOD & DRUG
ADMINISTRATION