FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Suffering the Slings and Arrows of Outrageous Product Quality Fortune: Current Immunogenicity Risk Perspectives from CDER's Office of Pharmaceutical Quality

João A. Pedras-Vasconcelos, PhD
Senior Pharmaceutical Scientist (Product Quality and Immunogenicity)
Office of Product Quality Assessment III, OPQ, CDER, FDA
EIP 17th Open Symposium
March 17, 2026

Disclaimer

- Views provided herein represent those of the presenter. The presentation today should not be considered, in whole or in part as being statements of policy or recommendation by the United States Food and Drug Administration.
- Focus on biologics regulated under PHS act 351(a) Innovator products.

Overview

- Immunogenicity Stakeholders at the FDA
- The Importance of Immunogenicity Risk Assessment (IRA) from a CDER/OPQ perspective.
- Product Quality-related risk factors as a key, and often controllable, drivers of immunogenicity.
- Connecting Product Critical Quality Attributes (PCQAs) to clinical immunogenicity outcomes.
- Regulatory expectations for assessing and controlling these risks throughout the product lifecycle.
  - Possibility of more tailored, risk-based strategies.

Human Immunogenicity at the FDA

- Who reviews it?
  - ➢ Depends on the class of product
    - CDER
      - therapeutic peptides (including hormones <40 amino acids (aa)) and therapeutic oligonucleotides
      - therapeutic proteins (>40 aa): monoclonal antibodies, growth factors, fusion proteins, cytokines, enzymes, hormones, therapeutic toxins
    - CBER
      - therapeutic products: allergenics, blood and blood components including clotting factors
      - cellular and gene therapies
      - vaccines

The Clinical Stakes: Why We Care About Immunogenicity

A brief review of the potential clinical consequences that drive our collective efforts.

- **Safety:**
  - Neutralization of an endogenous counterpart.
  - Hypersensitivity and infusion-related reactions.
- **Efficacy:**
  - Neutralization of the therapeutic, leading to loss of effect.
  - Altered pharmacokinetics (PK), impacting exposure.

The Challenge:

- While these are the stakes, we acknowledge that predicting these clinical outcomes from preclinical and quality data is uncertain.
- A direct translation of risk factors into clinical outcomes is not always possible.

Stages of Immunogenicity Assessment

- *PreIND*/ biotherapeutic candidate selection*
- IND support
  - Initial IND/Phase 1 (FIH)
  - Mid-development (Phase 2 and Pivotal)
- BLA/NDA submission
- Post-Approval/life-cycle management

Reviewed by CDER

*when meeting is requested

Risk factors influencing product immunogenicity

Product Immunogenicity results from complex interactions

Product Attributes

Drug Substance

- Amino acid sequence
- Post translational modifications
  - Glycosylation
  - Backbone modifications
- Misfolding / disulfides

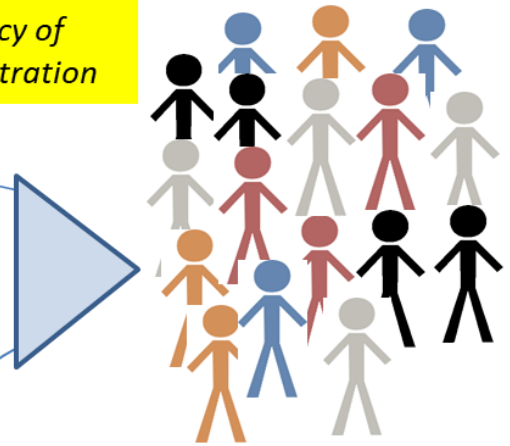
Drug Product

- Higher order structure
- Aggregation
- Impurities (Host Cell proteins / DNA)
- Formulation components
- Extractables / leachables

+

Host Attributes

Trial design: Route, dose and frequency of administration



Heterogeneity of human population

- *Genetic differences*
- *Pre-existing clinical conditions / co-meds*
- *Age, Gender*
- *Environment*
- *Stress*
- *Microbiome*

Immunologic Consequences

- **Anaphylaxis (IgE)**
- **Cytokine storm (TCRs)**
- **Infusion site reactions - histamine release**
- **Altered PK (IgG) – increase or decrease**
- **Altered PK and efficacy (IgG) – Neutralizing Ab**
- **Activation of immune system (IgG)**
  - **– Immune complexes (FcγRs)**
- **Delayed hypersensitivity (IgG w/ epitope spreading)**
- **Endogenous protein cross-reactivity (deficiency syndromes)**
- **Other Clinical sequelae**

CDER Immunogenicity perspectives

- Does the drug or biologic induce an immune response in study subjects?
- Is there a relationship between anti-drug immune responses and safety and/or efficacy of the product?
- Assessment of the immunogenicity information submitted to a regulatory dossier requires an integrative multi-disciplinary review process:
    - Office of Pharmaceutical Quality (OPQ)
    - Office of Clinical Pharmacology (OCP)
    - Office of New Drugs (OND)
    - Office of Scientific Integrity and Surveillance (OSIS)

CDER Immunogenicity Stakeholders

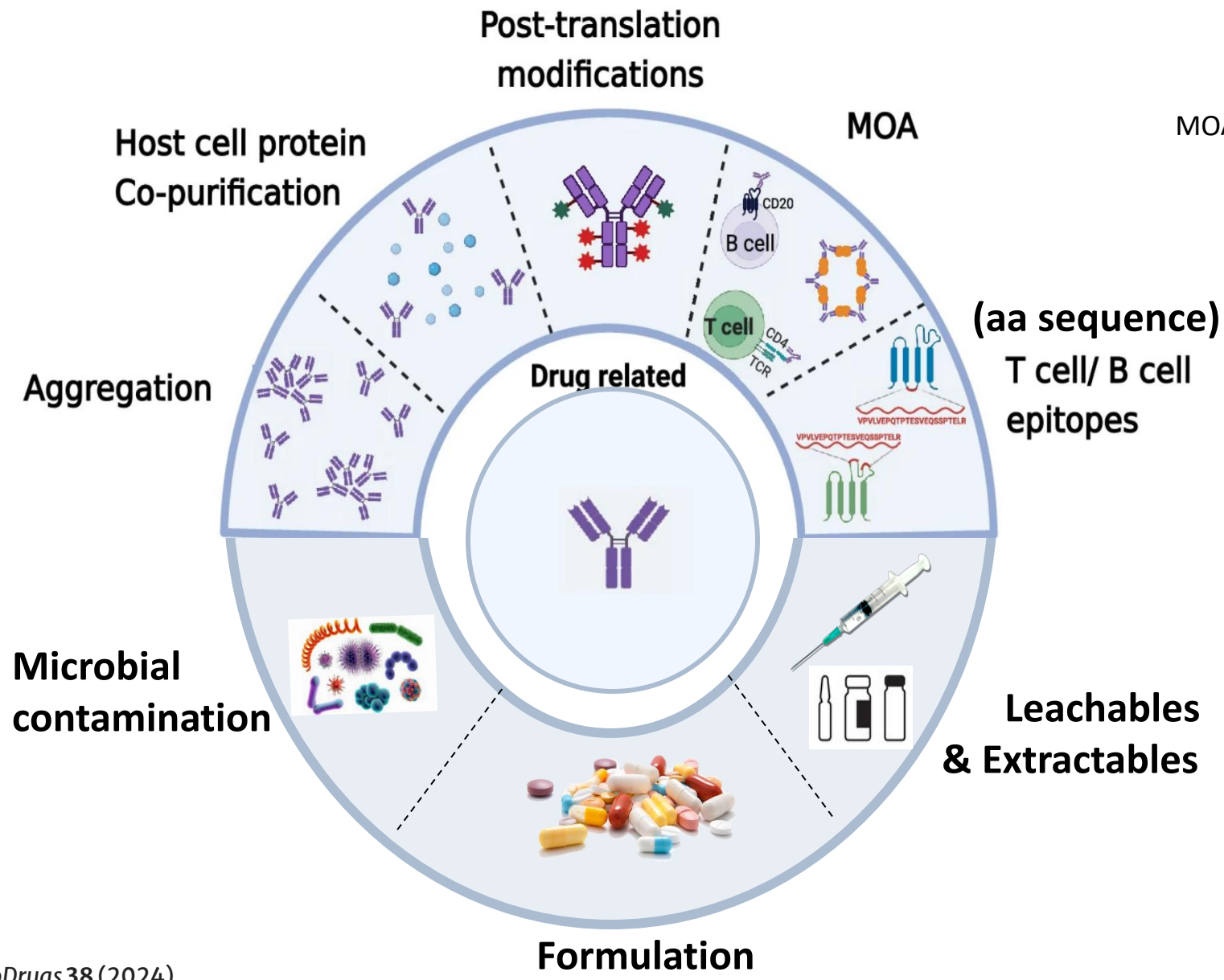
Office of Pharmaceutical Quality:

- Office of Product Quality Assessment III (OPQAIII)
  - Product quality for biologics and small molecule API (product quality related factors)
  - Collaborate in immunogenicity risk assessments for biologics with other CDER stakeholders (specific SMEs in the 4 biologics divisions)
  - Review Clinical Immunogenicity Assays for biologics under BLAs
    - Produce Immunogenicity risk assessment and Assay Review Memo
- Office of Product Quality Research (OPQR)
  - Review Clinical Immunogenicity Assays for peptides and drugs under NDAs
  - Collaborate in immunogenicity risk assessments for peptides and drugs under NDAs and ANDAs with other CDER stakeholders (specific SMEs in the divisions with immunology labs)
    - Produce Immunogenicity risk assessment and Assay Review Memo

The Slings and Arrows of Product Quality

Immunogenic or not immunogenic

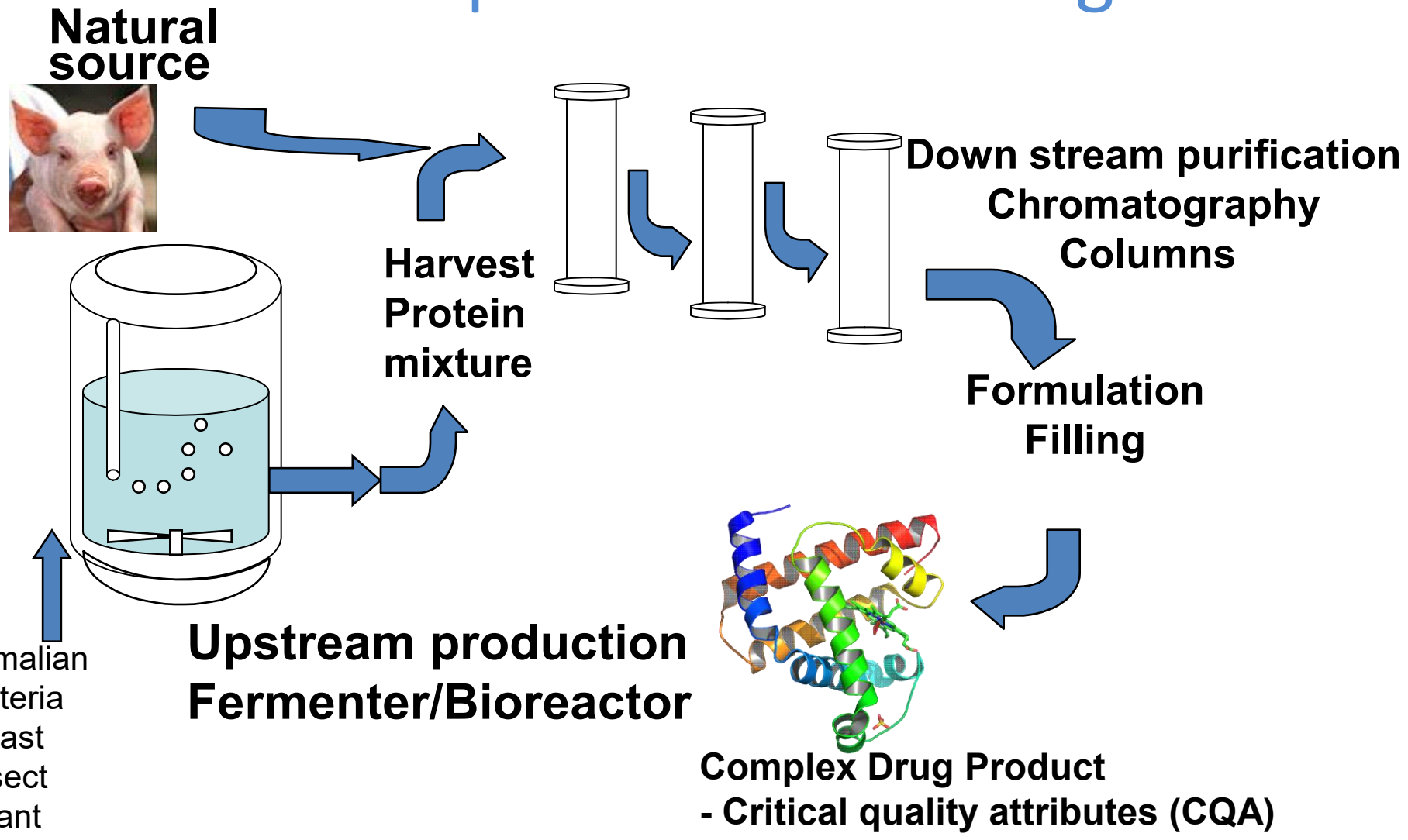
Product Quality-related risk factors: An OPQ Perspective



MOA- Mechanism of Action

Adapted from Harris CT & Cohen S. *BioDrugs* **38** (2024).

Biotechnology Process-complex manufacturing



Product Critical Quality Attributes (PCQA)

- Physical, chemical, biological, or microbiological characteristics of the biologic or drug that are important for safety and efficacy
  - defined, measured, and controlled through the manufacturing process.
- PCQA can impact:
  - Biological or enzymatic activity /mechanism-of-action (MOA)
  - Localization to target cells or tissues
  - Localization with the substrate
  - Half-life in blood stream or specific organ systems (e.g., gut)
  - Immunogenicity

Drug Mechanism of Action

Direct and indirect impact on the immune system

- Immunosuppressive
  - Drug may reduce immunogenicity to itself
  - May increase susceptibility to infections and/or incidence of malignancies

- Immunostimulatory
  - Drug may enhance immunogenicity to itself
  - Increase adverse reactions such as cytokine release syndrome

Impact of Molecular Structure and PTMS

- **Sequence Origin:** Foreign sequences, non-human regions, or even humanized sequences can contain T-cell epitopes.
- **Glycosylation:** Non-human glycoforms (e.g., alpha-gal, high-mannose from yeast) can act as neo-antigens and trigger an immune response (innate and adaptive). Glycans can also modulate epitope access.
- **Other Modifications:** Chemical modifications like oxidation or deamidation can create neo-epitopes or induce aggregation, breaking immune tolerance.

The Evolving Role of Impurities-Product- and Process-Related

- **Aggregates & Particulates:** Remain a primary concern. They can break B-cell tolerance and act as "danger signals." Minimizing their formation throughout the lifecycle is key.
- **Host Cell Proteins (HCPs):** Can be immunogenic, possess enzymatic activity, or act as adjuvants.
- **An OPQ Perspective:**
  - With advances in manufacturing, the impact of routine process-related impurities has been significantly reduced.
  - The concern has now shifted to managing risks during **Product lifecycle changes**—such as manufacturing scale-up or site transfers—where new or different impurity profiles can emerge.

Impact of Formulation and Container Closure

- **Formulation:** Excipients are chosen to maximize stability, but their degradation (e.g., polysorbates) can be a source of particles and risk.
- **Leachables & Extractables:** Chemicals leaching from container components can directly modify the protein, causing denaturation or aggregation. This must be evaluated for each specific product and storage condition.

Connecting Quality to Risk: The Foundational Recommendation

CQAs, Control Strategy, and the Integrated Summary of Immunogenicity (ISI)

- A **Critical Quality Attribute (CQA)** is a characteristic that must be controlled to ensure product quality.
- Sponsors must identify CQAs that impact immunogenicity and establish a robust **Control Strategy**.
- The **immunogenicity risk assessment (IRA)** and control strategy can be documented in the **Integrated Summary of Immunogenicity (ISI)**, a "living document" that evolves throughout development and is a key component of the BLA/NDA submission.

Beyond the Standard: The Potential for Tailored Bioanalytical Strategies

- The IRA should not just be seen as a “regulatory hurdle”; it should directly inform a **tailored, risk-based bioanalytical strategy**.
- A critique from pharma industry is that many programs still default to an intensive testing strategy for all molecules, regardless of risk.
- **Opportunities for a Smarter, Risk-Based Strategy:**
  - **Low-Risk Products:** An “event-driven" approach (bank samples, analyze only if clinical signals arise) may be possible with suitable scientific justification.
  - **High-Risk Products:** Front-load development of immunogenicity assays (e.g., domain specificity) and consider more frequent monitoring.
  - **Rethinking the NAb Assay:**
  - A standalone NAb assay may not always be the most relevant measure
  - An integrated analysis of PK/PD data in the presence of ADAs may provide more clinically meaningful evidence of neutralization.
  - **DISCUSS WITH REGULATORY AUTHORITIES**

Regulatory Recommendations

BLAs and NDAs (therapeutic peptides and oligos) with clinical trials

- Sponsors should provide an IRA and appropriate sampling plan, with clinical remediation measures as needed
- Sponsors should develop validated immunogenicity assays
  - Binding anti-drug antibody (BADA) assay
  - Neutralizing anti-drug antibody (NADA) assay*
- Phase dependent assay development and validation
  - Have assay validated prior to testing clinical phase 3 study samples

Summary & Key Takeaways

- From a CDER/OPQ perspective, proactive management of product quality is the most effective way to mitigate immunogenicity risk.
- A thorough understanding and control of CQAs—from structure to impurities—is a critical responsibility for the Sponsor.
- A robust IRA could lead to a more tailored bioanalytical plan, moving beyond a one-size-fits-all approach to one that can truly reflect the product's specific risk profile.
- We acknowledge the inherent uncertainties in this field and encourage a continued dialogue between industry and regulators.

Acknowledgements

- Susan Kirshner, Division Director (retired), DPQAXV, OPQA III
- Daniela Verthelyi, Division Director (retired), DPQRIV, OPQR
- Amy Rosenberg, Division Director (retired), DTP/DBBR3, OBP
- Montse Puig, Supervisory Biologist, former OBP/OPQR (Industry)

- CDER Integrative Immunogenicity Working Group
  - Current IFFs Davinna Ligons, Mohan Manangeeswaran and Harold Dickensheets
  - Former IFFs Steve Bowen, Haoheng Yan, Brian Janelsins (Industry)