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

A Piece of the Immunerdy *Pastel de Nata*- CDER Regulatory Stakeholders and their role in the Immunogenicity Review Process

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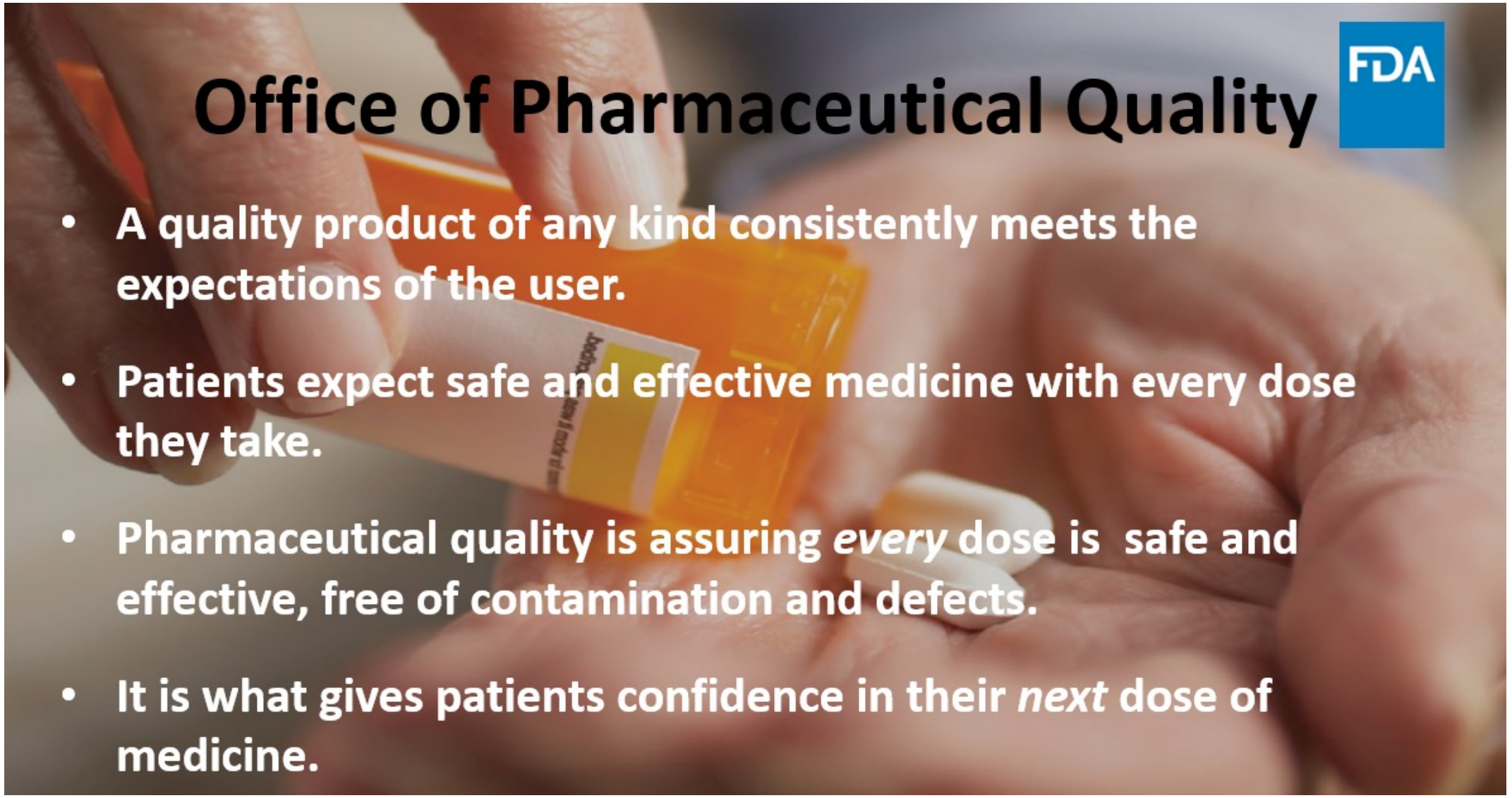
Disclaimer

- 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.


Office of Pharmaceutical Quality
FDA
• A quality product of any kind consistently meets the expectations of the user.
• 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.

Overview

- Immunogenicity Challenges for Regulators
- Immunogenicity Stakeholders at CDER
  - Role in the immunogenicity review process
- External Stakeholder engagement efforts

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

Product Immunogenicity results from complex interactions

Product Attributes + **Host Attributes** → **Immunologic Consequences**

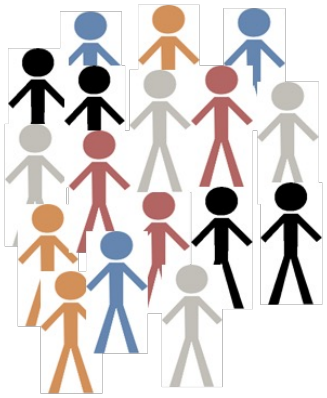
Drug Substance

- 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

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*

Acute

- **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**

Long-term

CDER Immunogenicity perspectives

- For CDER, the clinical concern is focused on detecting whether a drug or biologic induce an immune response (IR) in study subjects, and whether there is a relationship between anti-drug IRs and safety and/or efficacy of the product
  - Innate sentinel responses
    - Bioanalytical platforms still under development
  - Adaptive specific responses
    - T cell – anti-drug epitope responses (ADE)
      - Bioanalytical platforms still under development
    - **B cells – anti-drug antibody responses (ADA)**
      - **Bioanalytical platforms are well established, and their use is standard practice for biologics and some drugs**
      - **Tiered immunogenicity assessment**

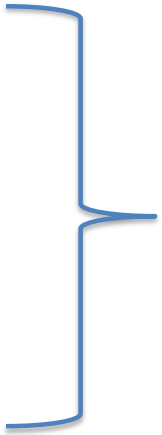
Challenges for CDER Immunogenicity Reviewers

Immunogenicity information is scattered throughout the eCTD in the regulatory filing

- 2.7.4 Summary of Clinical Safety
  - Summary of immunogenicity results
- 4.2.3 Toxicology
- 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

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



CDER Immunogenicity perspectives

- Assessment of the immunogenicity information submitted to the regulatory files requires an integrative multi-disciplinary review process:
  - OPQ
  - OCP
  - OND
  - OSIS
  - OTBB

CDER Immunogenicity Stakeholders

Office of Pharmaceutical Quality:

- Office of Product Quality Assessment III
  - 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
- Office of Product Quality Research
  - 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)

CDER Immunogenicity Stakeholders

Office of Clinical Pharmacology

- Provide feedback on clinical immunogenicity study design (e.g. ADA sampling plans and testing strategies)
- Collaborate with OPQ on immunogenicity assay review (e.g. drug tolerance)
- Review impact of immunogenicity on PK/PD and efficacy
- Review PK and biomarker PD assays

Office of New Drugs

- Pharm/Tox reviewers assess preclinical immunogenicity and Immunotoxicity Studies
- Clinical reviewers assess impact of immunogenicity on safety, including hypersensitivity and anaphylaxis

CDER Immunogenicity Stakeholders

- Office of Study Integrity and Surveillance (OSIS)
  - Perform inspections of bioanalytical sites including the ADA testing site(s)
  - Review responsibilities include auditing bioavailability/bioequivalence studies and non-clinical studies conducted under Good Laboratory Practice (GLP)
- Office of Therapeutic Biologics and Biosimilars
  - coordinates and supports all biosimilar and interchangeable product activities

CDER Integrative Immunogenicity Working Group (IIWG)

- Multidisciplinary regulatory membership (an *Immunerdy Paradise*)
  - Immunogenicity SMEs from OPQA III biologics and OPQR immunology
  - members from other CDER offices with strong immunogenicity interest
    - OSIS, OCP, OND, OTBB
  - Immunerdy Associates from other Centers
    - CBER, CVM, CDRH and CFSAN

CDER's Integrative Immunogenicity Working Group (IIWG)

- Provide multi-disciplinary space to:
  - Develop and maintain risk-based frameworks for evaluating regulatory submission-specific immunogenicity risks
  - Provide scientific advice and bioanalytical method expertise to review programs evaluating INDs, BLAs, NDAs, and ANDAs with submission-specific immunogenicity concerns
  - Provide educational training on integrative immunogenicity risk assessment and bioanalytical method assessments to CDER regulatory stakeholders evaluating INDs, BLAs, NDAs, and ANDAs
  - Seminar series on novel Immunogenicity related technologies and cutting-edge topics from internal and external speakers
  - Establish connections with senior science council and CDER scientific centers of excellence to facilitate research on immunogenicity methodologies
  - Internally and externally communicate interdisciplinary submission-specific immunogenicity evaluations, as well as broader immunogenicity-related issues and initiatives

CDER Immunogenicity Review (IRC)

The IRC provides a multi-disciplinary policy 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

How do we facilitate CDER Immunogenicity Review Processes

- Proactively Engage External Stakeholders

Facilitating CDER immunogenicity review processes

Publishing Immunogenicity related guidances:

- Guidance (2014): Immunogenicity Assessment for Therapeutic Protein Products
  - 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 (2019): Considerations in Demonstrating Interchangeability to a Reference Product
  - Discusses immunogenicity studies required for interchangeability in context of 351(k) pathway
- **Guidance (2019): Immunogenicity Testing of Therapeutic Protein Products-Developing and Validating Assays for Anti-Drug Antibody Detection**
  - **Discusses the development and validation of immunogenicity assays**
- Guidance (2021): 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
- Draft Guidance (2022): Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Products
  - Discusses recommendations on immunogenicity labelling including new Immunogenicity Subsection under 12.6

Facilitating Immunogenicity Review Processes- Integrated Summaries of Immunogenicity

As per 2019 FDA Immunogenicity Assay Guidance section VIII. Documentation:

Recommend the creation a “living” integrated summary of immunogenicity (ISI) that sponsors would begin populating early in product development , and would update as clinical program progresses through IND stages into BLA and post-approval

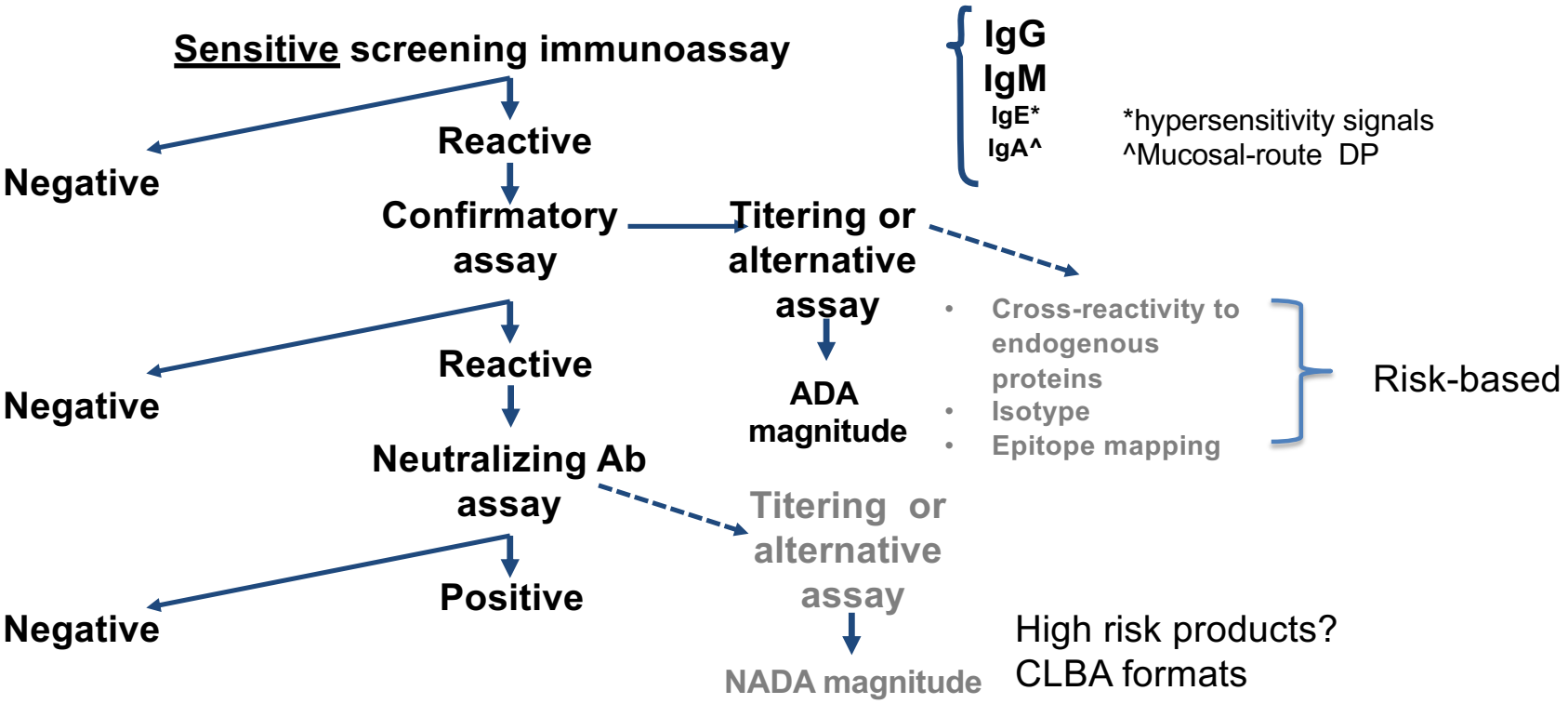
1. Immunogenicity risk assessment
2. Tiered bioanalytical strategy and assay validation summaries (with stage- appropriate information)
3. Clinical study design and detailed immunogenicity sampling plans
4. Clinical immunogenicity data analysis
5. Conclusions and Risk Evaluation and Mitigation Strategies (REMS)
   a) Include post-marketing/Life-Cycle management plans

- ISIs are recommended for all new 351(a) and 351(k) BLA and certain NDA submissions.
  - section 5.3.5.3 Reports of Analysis of Data from More than One Study

Facilitating Immunogenicity Review Processes- Biopharmaceutical Industry Stakeholder Outreach

- CDER IIWG SMES (OPQ, OCP, OSIS, OND) externally communicate recommendations on immunogenicity-related issues and initiatives
  - FDA sponsored workshops on Immunogenicity Related Topics
  - Various Industry Associations Meetings and Immunogenicity Working groups
    - European Immunogenicity Platform
    - American Association of Pharmaceutical Scientists
    - Workshop on Recent Issues of Bioanalysis
    - European Bioanalytical Forum

Multi-Tiered ADA Testing Strategy



Encouraging the use of Harmonized Validation Template(s) with industry

- Allow for triage of immunogenicity assays
- Help with setting workload timelines
- Facilitate assessments by OPQ(A/R) and inspections by OSIS
- Standardize quality of validation reports
  - Common terminology of parameters
  - Common order for data presentation
  - Make immunogenicity assay reviews less time-consuming
- CDER IIWG SMES Participated in AAPS sponsored working groups with Industry stakeholders to produced specific White Papers

AAPS Journal White Papers

White Paper

Anti-drug Antibody Validation Testing and Reporting Harmonization

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Abstract Evolving immunogenicity assay performance expectations and a lack of harmonized anti-drug antibody validation testing and reporting tools have resulted in significant time spent by health authorities and sponsors on resolving filing queries. Following debate at the American Association of Pharmaceutical Sciences National Biotechnology

WHITE PAPER

Neutralizing Antibody Validation Testing and Reporting Harmonization

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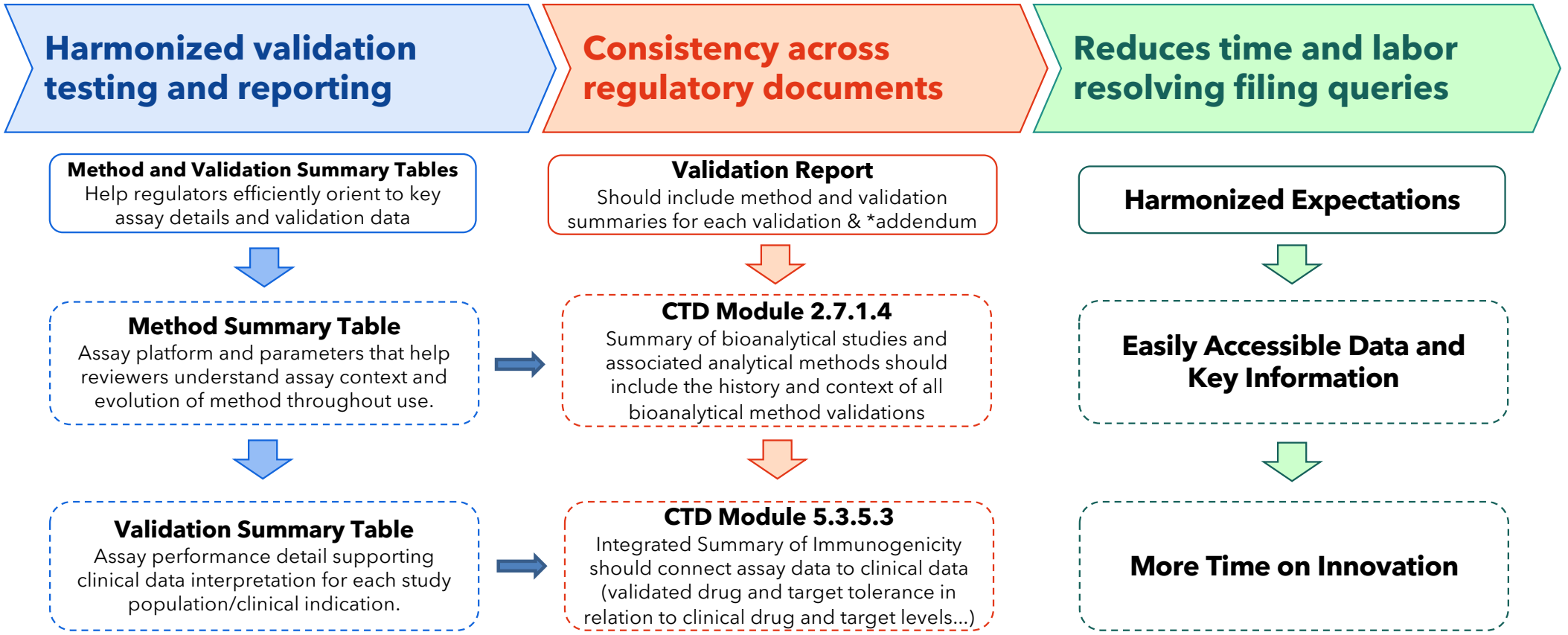
Abstract
Evolving immunogenicity assay performance expectations and a lack of harmonized neutralizing antibody validation testing and reporting tools have resulted in significant time spent by health authorities and sponsors on resolving filing queries. A team of experts within the American Association of Pharmaceutical Scientists' Therapeutic Product Immunogenicity Community across industry and the Food and Drug Administration addressed challenges unique to cell-based and non-cell-based neutralizing antibody assays. Harmonization of validation expectations and data reporting will facilitate filings to health authorities and are described in this manuscript. This team provides validation testing and reporting strategies and tools for the following assessments: (1) format selection; (2) cut point; (3) assay acceptance criteria; (4) control precision; (5) sensitivity including positive control selection and performance tracking; (6) negative control selection; (7) selectivity/specificity including matrix interference, hemolysis, lipemia, bilirubin, concomitant medications, and structurally similar analytes; (8) drug tolerance; (9) target tolerance; (10) sample stability; and (11) assay robustness.

Schematic representing harmonization recommendation



*Addendum can include partial validation, cross-validation, in-study cut point and any other testing included following the initial validation

Summary

- CDER Integrative Immunogenicity Review processes involve multiple internal stakeholders
  - OND, OCP, OPQ, OSIS
- CDER Immunogenicity stakeholder outreach efforts are intended to facilitate CDER Immunogenicity review processes
  - Publishing of immunogenicity-related guidances
  - Participation in industry sponsored meetings to communicate bioanalytical/immunogenicity recommendations
  - Participation in AAPS Assay validation harmonization white papers

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