FDA'S INTEGRATED FACILITY EVALUATION PROCESSES – PREAPPROVAL COMPLIANCE PROGRAM

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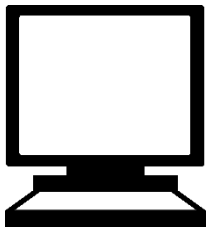
Pharmaceutical Quality

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



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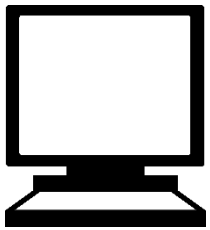



Drugs are no different.


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.


FDA
It is what gives patients confidence in their *next* dose of medicine.

Disclaimer

The comments expressed today are those of the presenter only and do not necessarily represent the official positions or policies of the FDA

Learning Objectives

- Interpret preapproval interactions in context of revised Preapproval Compliance Program

- Identify how quality related topics are addressed via an integrated approach

Preapproval Compliance Program: Scope

Preapproval facility evaluations and inspections support the assessment of marketing applications by ensuring that any establishment named in or referenced in support of an application can perform the proposed manufacturing operations in conformance with CGMP requirements and that data submitted in the application are accurate and complete.

Drivers for revision

- Align with CDER and ORA agreement defined in *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations*
- Allows for collaborative preapproval facility evaluation and inspections
- Provides for risk based strategies for scope of preapproval coverage
- Clarifies roles for efficient communication

References

- *Preapproval Inspection Compliance Program*
  PROGRAM: 7346.832 Implementation: 09/16/2019, replaces 5/12/2010 version - https://www.fda.gov/media/121512/download

- *FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations*

  https://www.fda.gov/drugs/pharmaceutical-quality-resources/integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept-operations

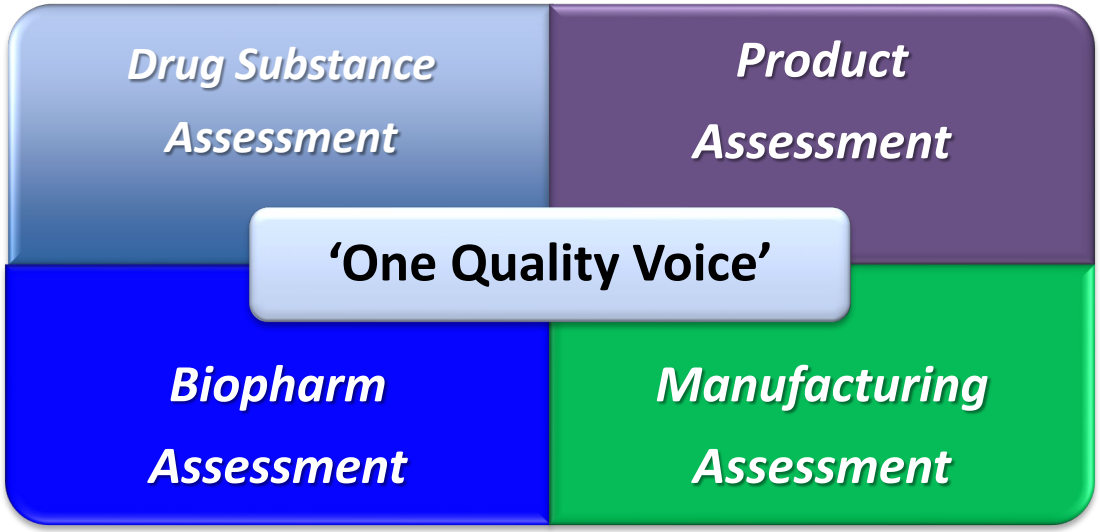
  https://www.fda.gov/drugs/pharmaceutical-quality-resources/questions-and-answers-integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept

Changes: Highlights

- Roles and responsibilities aligned with ORA and CDER ConOps and IQA review paradigm
- Clarifies and simplifies field reporting requirements
- Updates Program contacts
- Reinforces use of risk assessment within Integrated Quality Assessment framework to determine need for preapproval inspections (Attachment A)
- Establishes transparent communication pathways with timelines projected to meet User Fee Goal Dates

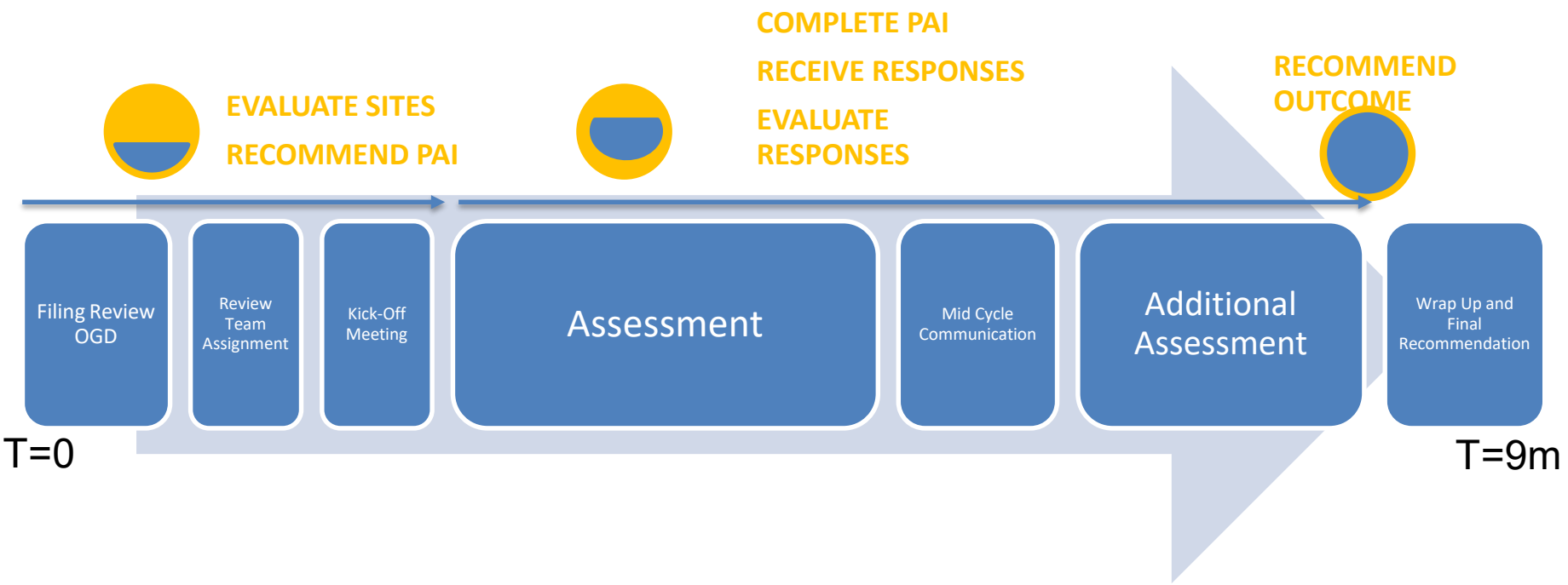
Integrated Quality Assessment (IQA) team

***Integrated Quality Assessment** = A team of experts performing a quality assessment of an application (NDA, BLA, ANDA) based on risk and knowledge management to arrive at a science-based approval recommendation from a pharmaceutical quality perspective.

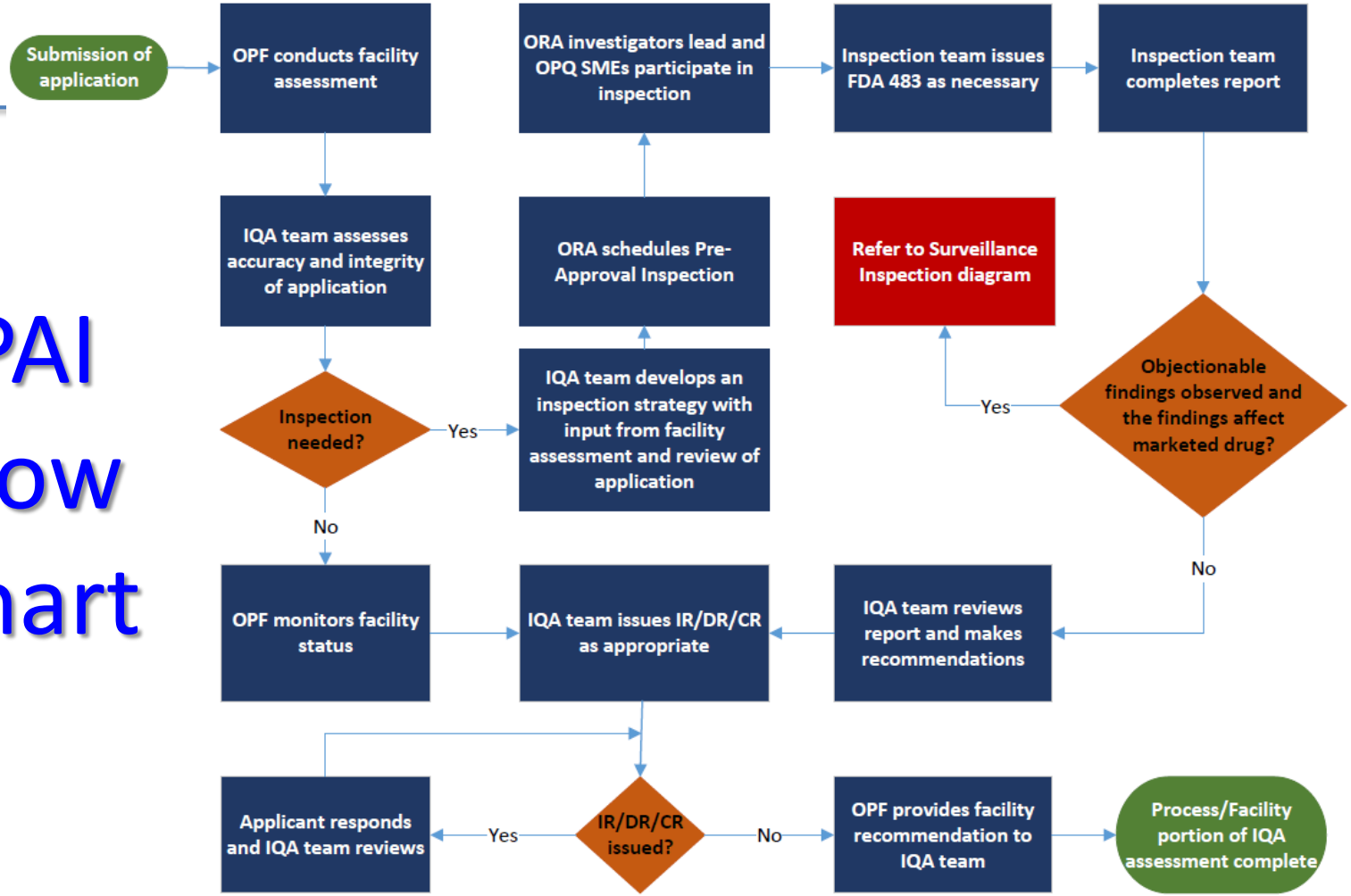


Participants from OPQ, OMQ, ORA

Timeline – coordinating inspection and reviews



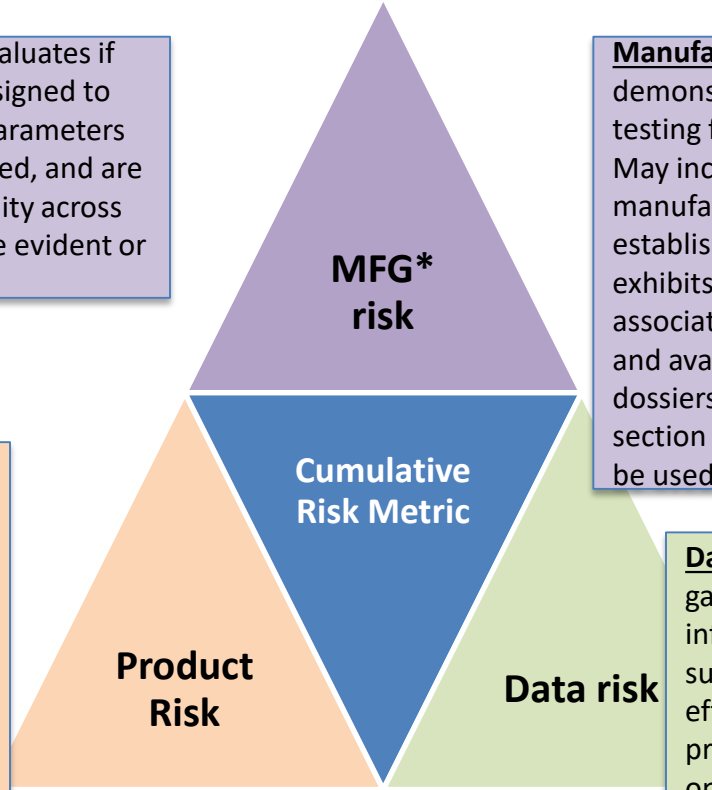
PAI flow chart



IQA- Cumulative Risk Assessment

Manufacturing process risk evaluates if process is established and designed to deliver CQAs. Critical process parameters have been identified, characterized, and are controlled. Controls on variability across scale and robust performance are evident or can be inferred.

Manufacturing facility risk evaluates demonstrated capabilities of manufacturing or testing facilities in context of proposed role. May include review of facility's recent manufacturing history through the evaluation of establishment inspection reports (EIRs) and exhibits, applicable field alert reports (FARs), associated recalls, regulatory/advisory actions, and available foreign regulatory reports. Site dossiers and responses to requests under section 704(a)(4)(A) of the FD&C Act may also be used.



Product Risk evaluates risk associated with a product's critical quality attributes (CQAs) in the specific product's context of use (e.g., therapeutic index, patient population, clinical benefit). Product design and understanding needs to support patient need and ensure quality can be maintained over shelf life.

Data Risk evaluates risks related to gaps in accuracy and integrity of the information from a site within submission (data support safety, efficacy, and quality of the drug product). Confirm that a facility's operations match those proposed in the application

** MFG= Manufacturing*

PAI Objectives

- Objective 1: Readiness for Commercial Manufacturing
  - Determine whether the establishment has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations. (Parts 1a to 1e)
- Objective 2: Conformance to Application
  - Verify that the formulation, manufacturing or processing methods; analytical (or examination) methods; and batch records are consistent with descriptions contained in the CMC section of the application. This may include CMC information relevant to exhibit batches, biobatches, other pivotal clinical batches, and the proposed commercial-scale process.
- Objective 3: Data Integrity Audit
  - Audit and verify raw data at the facility to authenticate the data submitted in the CMC section of the application as relevant, accurate, complete, and reliable for an IQA assessment.

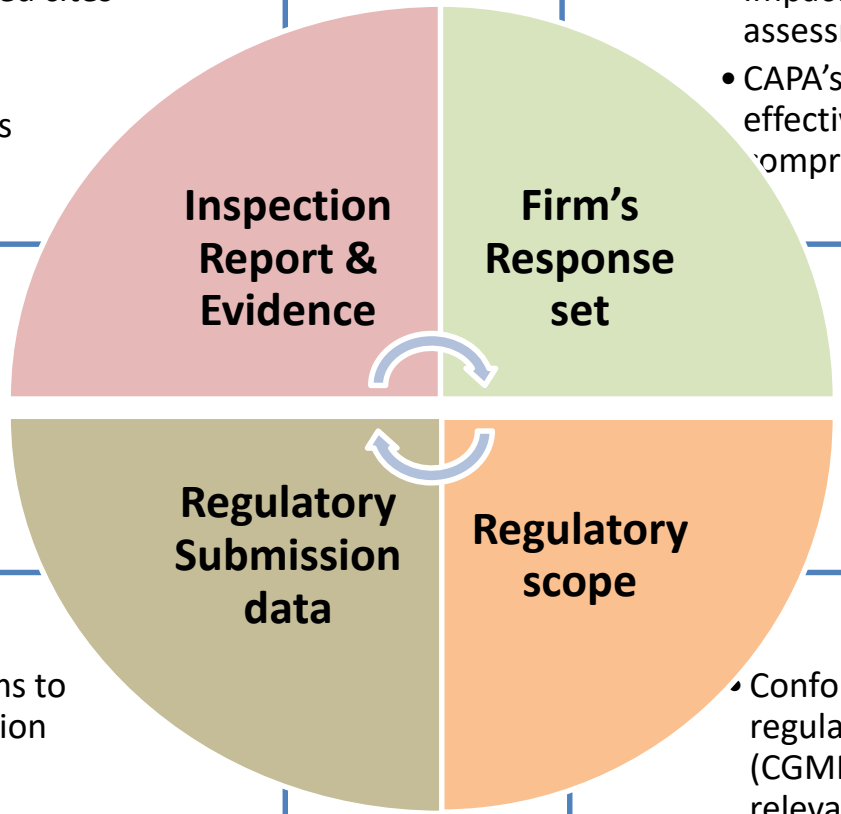
Before, during and after an inspection, field investigators communicate with CDER reviewers

Examples of PAI findings on FDA 483

- ✓ PAI findings reflect differences from filed CMC description for bio-batch, or stability batches; proposed commercial batch record does not assure a reproducible manufacturing operation
- ✓ PAI points to difference from filed CMC description of formulations, processing principles, equipment used, or discrepancies in raw material lot reconciliation
- ✓ Missing data or unreliable data:
  - Data/information submitted potentially unreliable or misleading.
  - Unexplained or inappropriate gaps in a chromatographic or analytical sequence.
- ✓ A pattern of inappropriately disregarding test results; inadequate or lack of justification for not reporting data/information.
- ✓ Insufficiency, discrepancy, or failure of an analytical method validation program.
- ✓ Lack of suitability of the facility, equipment, or manufacturing operations intended for making the commercial API or finished product to the CGMP regulations.

In addition, Part V of Program includes a list of Withhold Reasons – minor edits to wording for 12 prior reasons; additional reason included - 13) Delaying, denying, limiting, or refusing a drug inspection

General Inspection Review Framework



- Supported cites
- Impact
- No new concerns

- Impact assessment
- CAPA's scientific effective, comprehensive

Consulted parties could include

- *IQA team*
- *ORA Compliance Branch*
- *Investigator*

Facility Adequate – Approve application

- *No 483's*
- *No actionable concerns in EIR and exhibits*
- *Adequate correction of the findings that led to the initial **withhold** recommendation;*

- Conforms to application

- Conforms to regulations (CGMP's) & relevant CPGM

Inspectional outcomes – Facility Inadequate scenarios

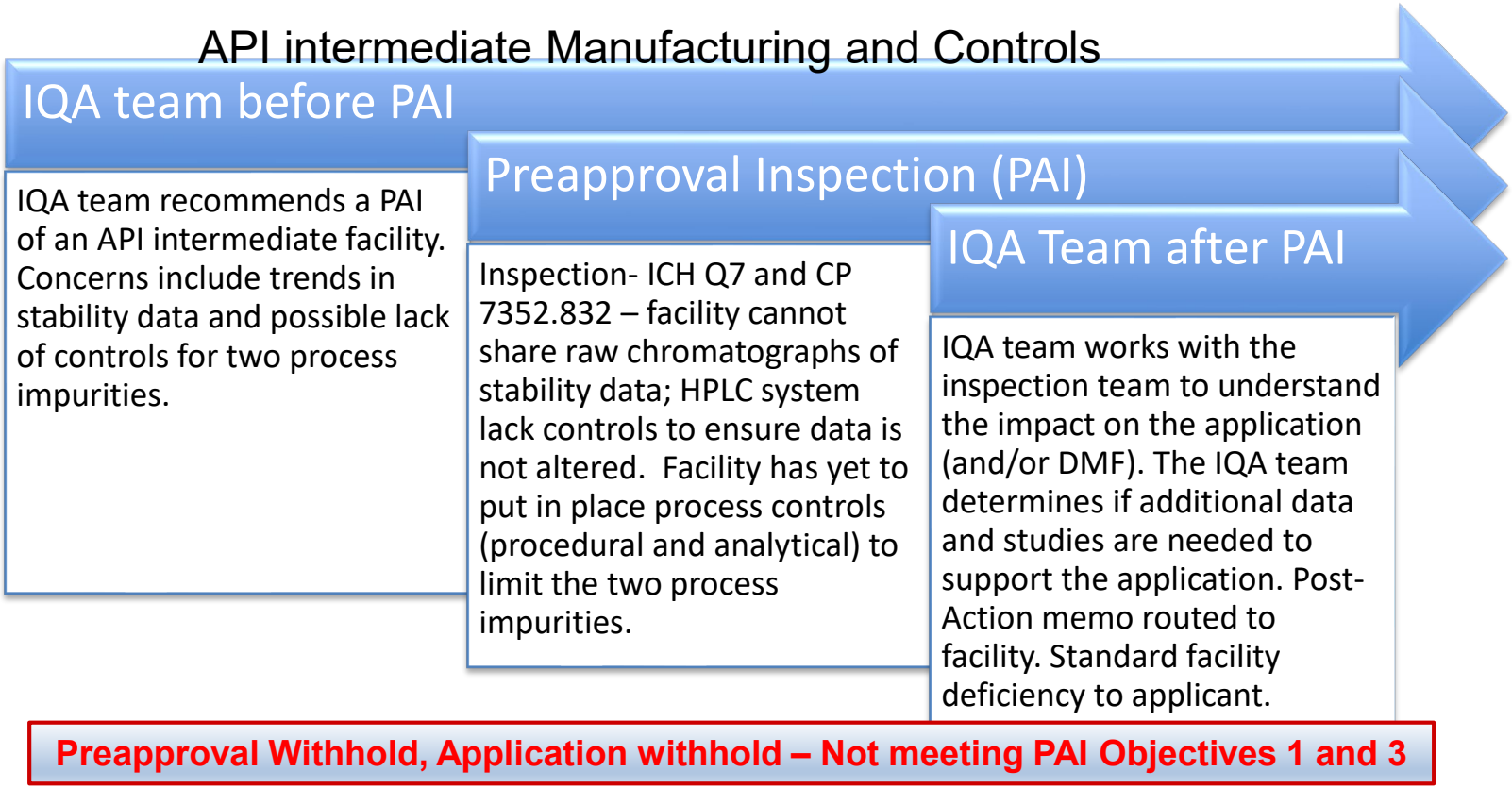
CGMP Withhold, Application withhold

- Deficiencies and findings for inspectional coverage under compliance program 7356.002
- Potential OAI status (pOAI) during ORA review to consider recommending an advisory or enforcement action
- Office of Compliance reviews ORA's recommendation for appropriate action
- When PAI results in a ORA withhold for an establishment that does not market FDA regulated products, a warning letter is not usually the appropriate regulatory action

Preapproval Withhold, Application withhold

- Product specific deficiencies noted
- Responses and CAPA's proposes/implemented do not provide assurance that Preapproval objectives can be met
- Responses not available within reasonable time frame deferred to next assessment cycle for application
- If necessary, Post Action Memorandum maybe routed to facility after application action with outstanding concerns
- Applicant to address application deficiencies while assuring that facility has resolved compliance as well as product specific deficiencies

Addressing Quality-Related Topics via an Integrated Approach



Addressing Quality-Related Topics via an Integrated Approach

CMC: Finished product test methods and acceptance criteria

IQA team before PAI

IQA team recommends a PAI for ER tablet manufacturer due to specific risks and concerns regarding test methods (e.g., suitability and validation data) and acceptance criteria (e.g., adequacy and verification of submitted data).

Preapproval Inspection (PAI)

Inspection team reviews method suitability, validation and related data and reports. Inspection team finds dissolution data that were not submitted to the application and includes its observations on Form FDA 483.

IQA Team after PAI

IQA team and inspection team review 483 responses collectively. The IQA team, which is responsible for recommending approval of the dissolution specification, uses the findings about the additional data to request that the applicant update the application with a revised dissolution specification.

Preapproval Initial Withhold overturned. Acceptable following review of Responses to 483 and update to application. Application approved.

Conclusions

- FDA communications about quality issues vary because, depending on the facility inspected and the specific quality topic, the responsibility for resolving FDA concerns resides with either the applicant or the inspected facility.

- Revised Preapproval Program takes a step forward towards timely, consistent, efficient, and transparent facility evaluations, inspections, and regulatory decision-making for marketing applications.

Acknowledgements

- Ying Zhang
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- Christina Capacci-Daniels

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- Questions, comments:
  - CDER-OPQ-Inquiries@fda.hhs.gov


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