Application Manufacturing Assessment

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Learning Objectives

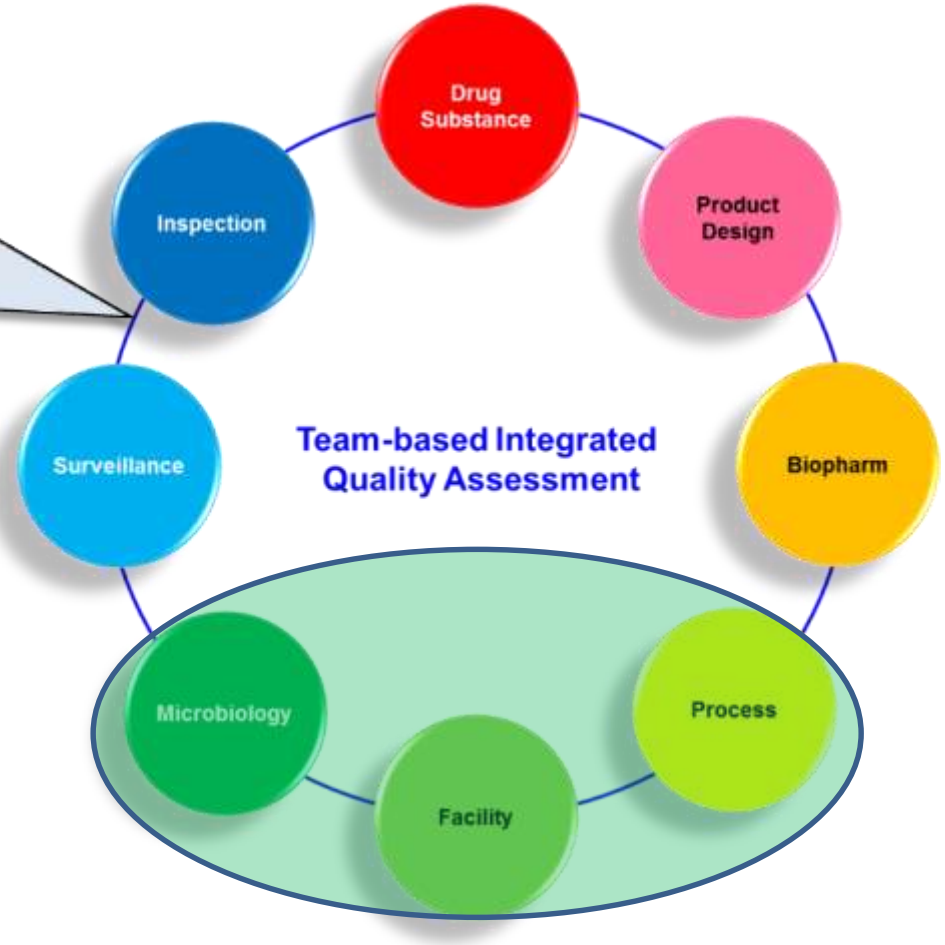
- Understand:
  - The goals of OPQ's Manufacturing Assessment
  - OPQ's general process for Manufacturing Assessment
  - Interactions with industry stakeholders regarding manufacturing issues

OMPA in Context

- FDA established OPQ to improve internal assessment of drug quality, and facilitate interactions with industry to improve drug product quality.
- OPQ integrates the assessment of drug applications across multiple quality expertise areas, leading to a more informed quality assessment.
- OPMA conducts application assessment in coordination with manufacturing facility evaluation and inspections to ensure that manufacturing will produce quality drugs for the patient.
- OPMA mission: to ensure that quality is built into manufacturing processes and facilities over the product lifecycle.

Team-based Integrated Quality Assessment (IQA)

Inclusive of drug substance, drug product, manufacturing, and facilities, and maximizes each team member's expertise



Science- and Risk-Based approach that is patient-focused

Manufacturing Assessment in OPQ

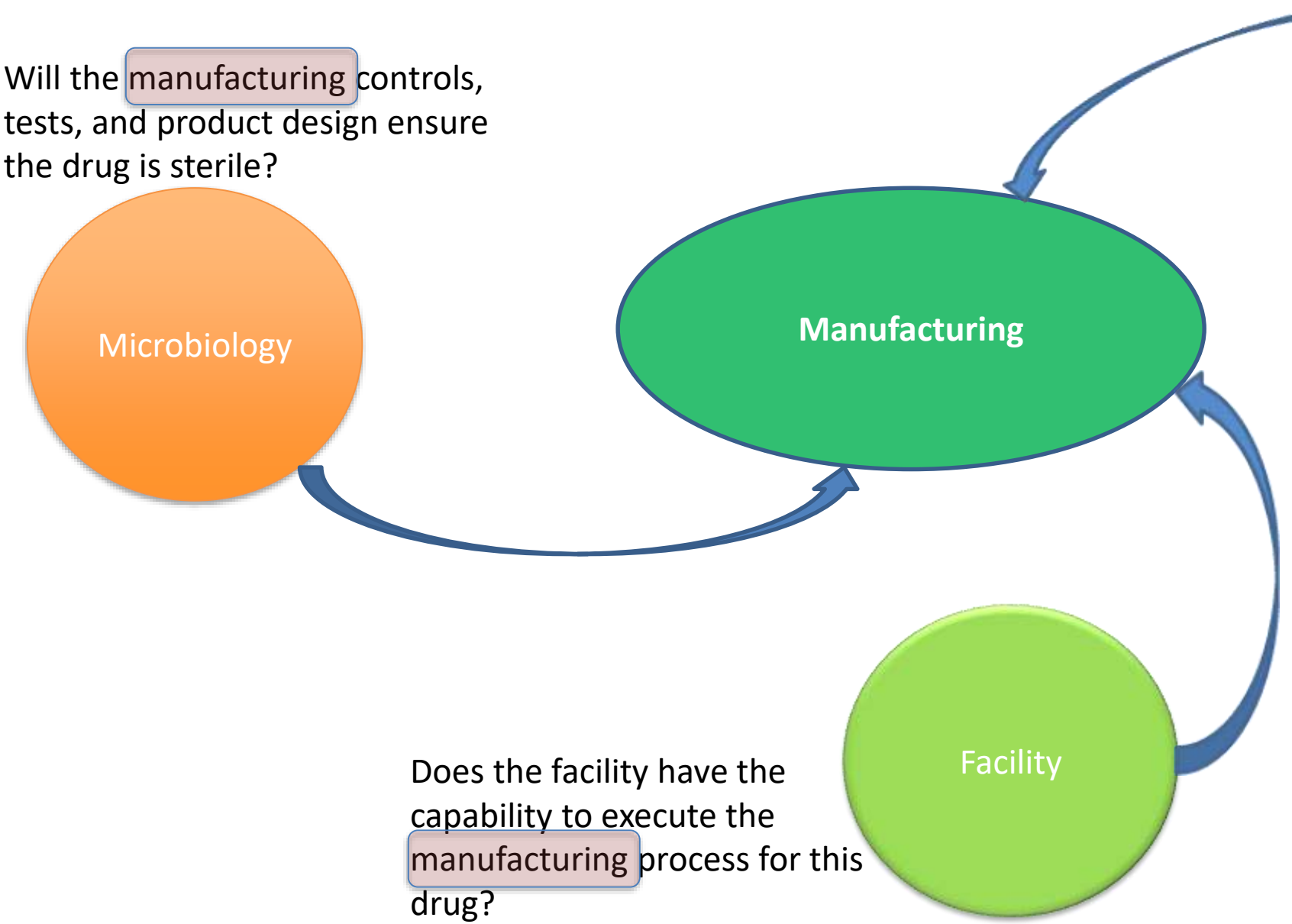
- Manufacturing is assessed in a cross functional, integrated quality assessment team.
  - This includes investigators from the Office of Regulatory Affairs when an inspection is indicated.
- CDER level manufacturing assessment primarily conducted by OPMA.
  - OPMA assessors participate as subject matter experts on Pre-approval inspection.
- Integration of assessment and inspection activities seeks to drive balance between oversight through the application and facilities.

Manufacturing Assessment Evolution

- OPF: Three discipline assessments across process, facility, microbiology.
- OMPA: Component elements (process, facility, microbiology) coalesce into a holistic manufacturing assessment.
- Primarily an elevation in thought process aiming for more sophisticated assessment.
- Driven by:
  - Expanded assessor capabilities
  - Enhanced assessment and inspection processes
  - Revised policies and programs
  - Enriched collaboration between assessors and inspectors

OPF -> OPMA Evolution

Will the manufacturing controls, tests, and product design ensure the drug is sterile?



Is the manufacturing process designed and controlled to consistently deliver adequate drug?

Does the facility have the capability to execute the manufacturing process for this drug?

Manufacturing Assessment Goals

- OPMA assesses the potential for manufacturing to impact product quality attributes.
- Direct involvement with application assessment and facility evaluation leads to a better understanding of how the manufacturing process is designed and actually executed.
- Familiarity with process design and development experience drives effective inspections.
- Leads to a better balance between risk identification and risk mitigation.
  - Risk can be measured in the context of an end-to-end control strategy.
  - Mitigation can be driven by the process and implementation at the facilities.
- Higher confidence that quality is built into the manufacturing processes, controls, and facility operations.

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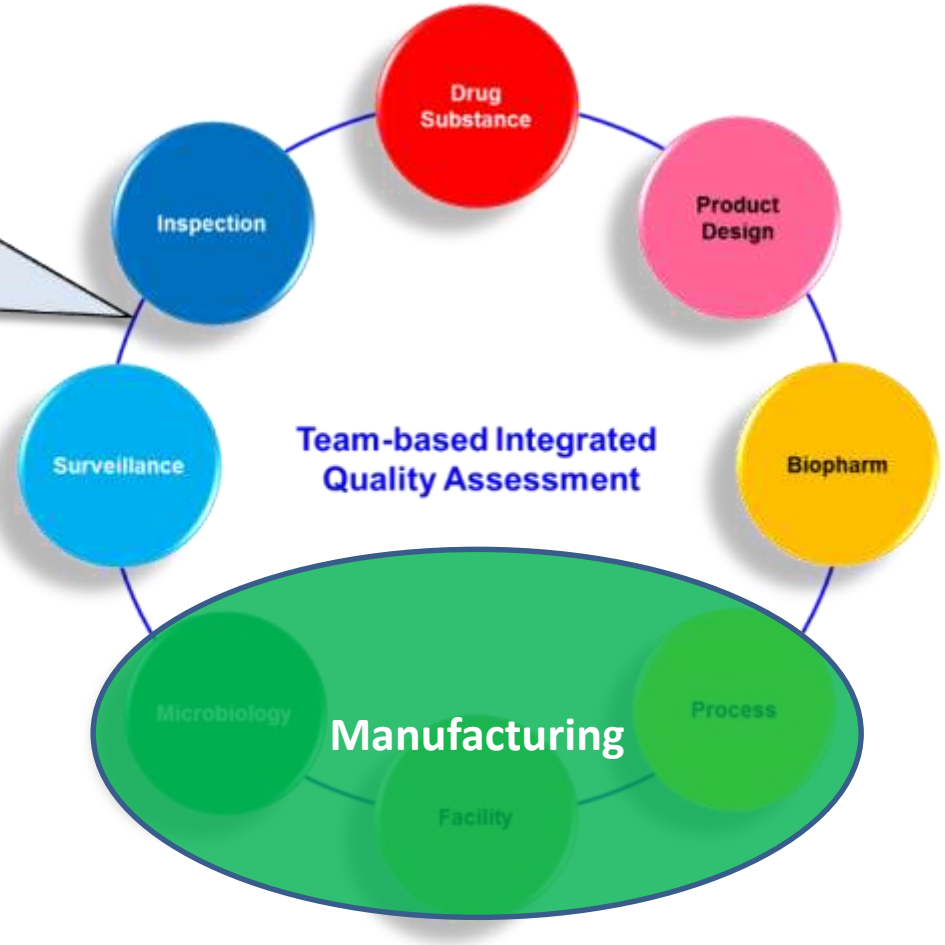


Science- and Risk-Based approach that is patient-focused

Manufacturing assessment is multifaceted

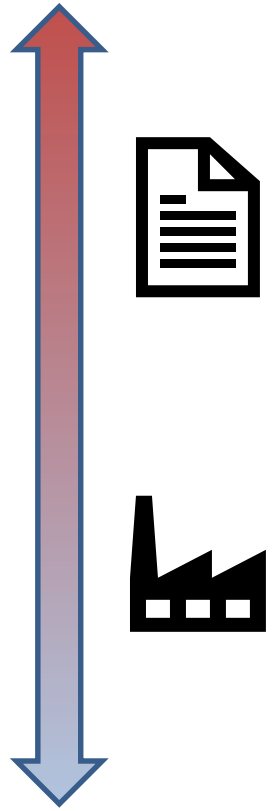
- Initial risk identification and assessment
  - Product: understanding the risks associated with a product's critical quality attributes (CQAs) in the specific product's context of use (e.g., therapeutic index, patient population, clinical benefit).
  - Process: understanding the impact of the process on the product's CQAs.
  - Facility: understanding the demonstrated capabilities of the manufacturing facilities related to the proposals in the marketing application.
- Determination of strategies to further assess risk
  - Information requests to the applicant
  - Inspection at the listed facilities

Manufacturing assessment is multifaceted

- Risk mitigation and evaluation
  - Send information requests and evaluate process design and control strategy.
  - Conduct inspection, and evaluate facility capabilities and responses to relevant inspection observations.
- Final risk assessment
  - Drives the recommendation for approval or complete response action.
- Lifecycle considerations
  - Post approval commitments
  - Post approval or Surveillance inspections
- Follow up communication
  - Post action meetings with applicants
  - Post complete response action letters to facilities

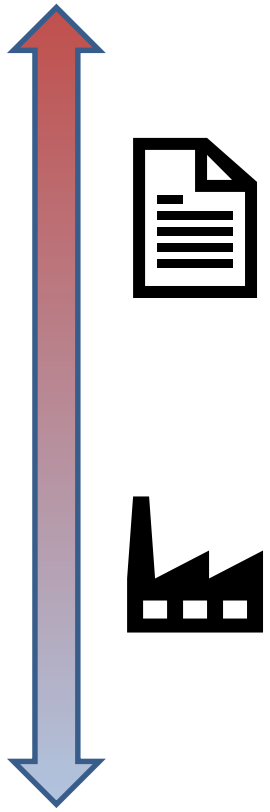
Assessment Across a Spectrum

- To ensure blend uniformity, assess many facets of manufacturing e.g.:
  - Material attributes (e.g. particle size distribution)
  - Order of addition
  - Blending process parameters
  - In process controls and measurements
  - Blender design, qualification, operation, and maintenance
  - Operator training
  - Batch record instructions
  - Quality unit response to deviations



Assessment Across a Spectrum

- To ensure a product is sterile, assess many facets of manufacturing e.g.:
  - Sterility test methods
  - Preservative concentration and uniformity
  - Compounding unit operation execution
  - Sterilizing filter effectiveness and compatibility
  - Media fills
  - Aseptic operations
  - Facility design
  - Operator training
  - Laboratory operations and controls
  - Sterility testing results
  - Quality unit decisions



Identification and resolution of issues

- A single manufacturing issue may be best communicated by an information request to the applicant or a 483 to the facility.
  - Does the submission need to be updated?
  - Does the facility need to implement a corrective or prevent action?
- Both may be appropriate if the application and the facility have a shared issue that requires resolution.
- Ensures that the right ‘owner’ is taking responsibility to resolve a concern.
- Ensures that
  - the application is accurate.
  - manufacturing, after all elements are considered, will deliver quality product.

FDA Compliance Program 7346.832: Preapproval Inspections

Latest revision effective on September 16, 2019.

Addressing Quality-Related Topics via an Integrated Approach

Quality Topic	Integrated Approach		
	IQA Team Assessment Before PAI →	**PAI** →	**IQA Team Assessment After PAI**
Manufacturing and control of finished product • Comparison of pilot-scale batches and proposed commercial-scale batches	The IQA team assesses the process design's overall development, including a review of manufactured batches (e.g., biobatch; pilot-scale, exhibit, or commercial-scale batch), proposed commercial manufacturing information, and available test data. The IQA team also determines if differences between pilot- and commercial-scale batch processes could adversely impact product quality. The IQA team communicates to the inspection team risks and concerns relevant to product/process development and commercial scale-up challenges. Product/process development facilities are not routinely inspected, unless specifically requested by the IQA team.	The inspection team evaluates the facility for conformance with CGMPs, the objectives of this compliance program, and the risks and concerns identified by the IQA team. The inspection team compares the firm's development and scale-up studies (e.g., scale-up from the biobatch, or pivotal batches, to a larger interim or full-scale batch) with the proposed commercial process and reports significant manufacturing process changes (including control strategy) and differences in equipment operating principles.	ORA provides the IQA team with its initial facility recommendation. The IQA team assesses the inspection findings and their impact on the drug product control strategy to make the quality recommendation. If the inspection findings indicate differences between pilot-scale and proposed commercial-scale manufacturing that could adversely impact product quality, CDER, on behalf of the IQA team, may communicate with the applicant or inspected facility, as appropriate. The IQA team may request that the applicant perform additional studies to support the application and the proposed control strategy at the commercial site.
	For example:		
	The IQA team requests inspection of any facility involved in the development of the drug product, including exhibit batches, if it differs from the commercial facility. →	The inspection team finds that exhibit batches were not manufactured under CGMP or as indicated in the application, which raises a concern about product quality. The inspection team includes its observations on Form FDA 483. →	The IQA team uses the finding of differences between pilot- and commercial-scale batch manufacturing methods to request that the applicant update the application with study data to ensure drug quality for the commercial-scale batches.

Resultant Confidence

- “Was the drug made correctly?”
  - E.g. exhibit batches, executed manufacturing process, development scale, facilities, etc…
- “Will the drug be made correctly?”
  - E.g. proposed commercial process, commercial facility capability, quality oversight, etc…

- Result of holistic manufacturing assessment that balances application evaluation and facility evaluation / inspection.

Conclusion

- Manufacturing assessment approach aligns with the ‘real world.’
  - Manufacturers simultaneously and holistically implement processes, controls, facility CGMPs, and sterility assurance practices when making drugs.
- Manufacturing assessment considers multiple quality elements that must work in balance.
- Balanced assessment provides confidence that drugs will be consistently produced to meet quality requirements and patient needs.

Knowledge Check

- Manufacturing Assessment is:
  - A) focused on information submitted in the application
  - B) limited to manufacturing facilities and inspections
  - C) integrates assessments of submission information and facilities

Knowledge Check

- An information request and a 483 item about the same manufacturing issue indicates:

  A) The FDA is confused

  B) Resolution of the issue requires information to be submitted to the application and corrections to CGMP operations at the facility

Helpful Documents

- Integration of 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
- FDA Compliance Program 7346.832: Preapproval inspections
  - https://www.fda.gov/media/121512/download
- Process Validation: General Principles and Practices
  - https://www.fda.gov/media/71021/download