

Applying CGMP to the Quality Assessment of the Application

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Learning Objectives

- Describe CGMPs relationship to Quality
- Explain quality expectations related to manufacturing Assessment in applications
- Describe the Impact of Pre-approval inspections findings to the manufacturing assessment
- Discuss outcomes
- Wrap up

What are CGMPs?

- **Regulatory basis-** Drugs and biologics including investigational products are required to be manufactured in accordance with CGMPs [§ 501(a)(2)(b) of the Federal Food, Drug and Cosmetic Act]

Is a drug adulterated?

FD&C Act

Finished drugs:
21 CFR 210, 211

API: ICH Q7

Is patient safety at risk?

High risk → Quick action

Identity?

Contamination?

Sterility concerns?

Sub- or super-potent?

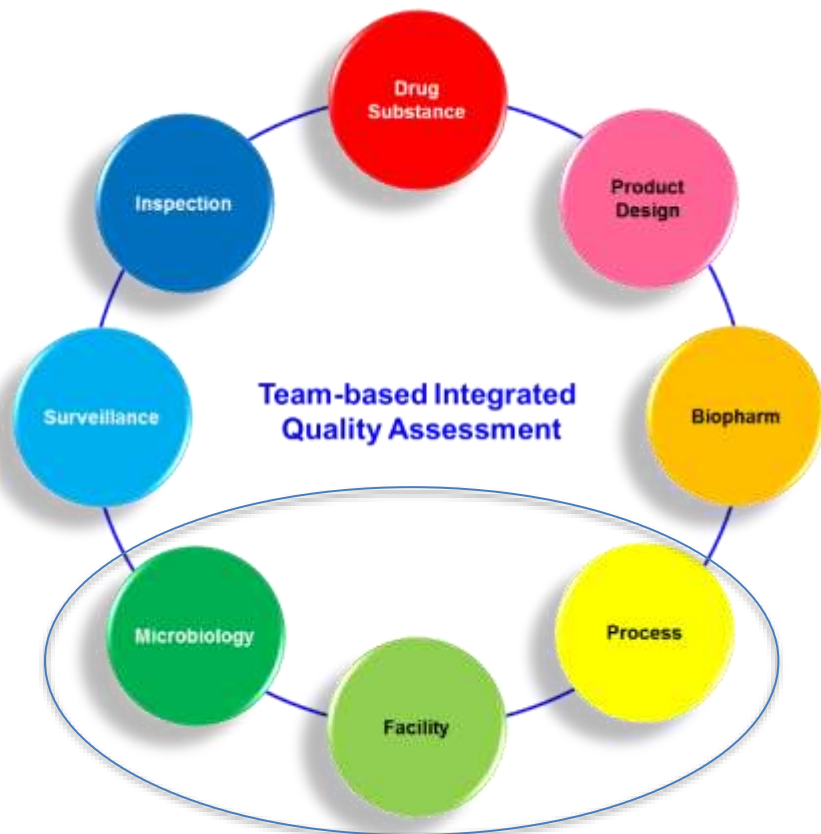
CGMP Principles

- Build QUALITY in - you cannot test or inspect quality into a product – it must first be there

BASIC PARADIGM:

- ‘Quality Assurance’: System to ensure control and consistency, validation as well as oversight
- Quality Control: Components, containers, and product meet specifications
- Documentation: If it’s not documented, it didn’t happen

One Quality Voice



- A team of experts performing a quality assessment of an application (NDA, BLA, ANDA) based on risk and knowledge management.
- The manufacturing assessment includes process, facility and micro in certain cases a single OPMA reviewer.
- The RBPM works with the scientific application team lead (ATL) to manage the review team and produce the overall recommendation.

Quality Expectations Related to Manufacturing

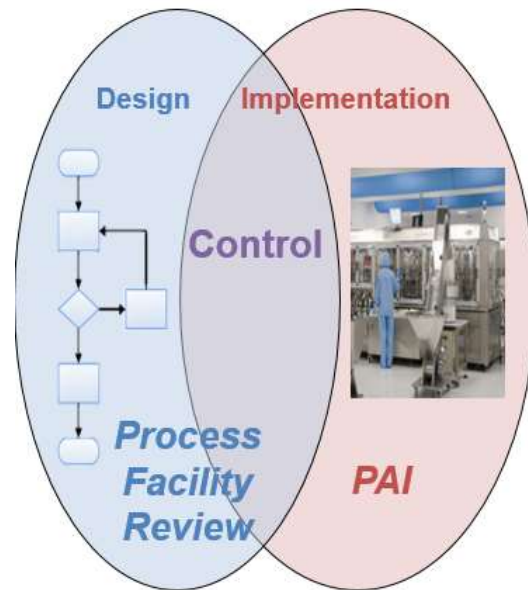


- The commercial manufacturing process can consistently produce a quality product over lifecycle
- Each manufacturing step should be adequately controlled to ensure the final drug product can meet all its quality attributes
- Facilities are capable of performing their stated functions and have documented procedures, data, and corrective actions to ensure product will meet quality requirements

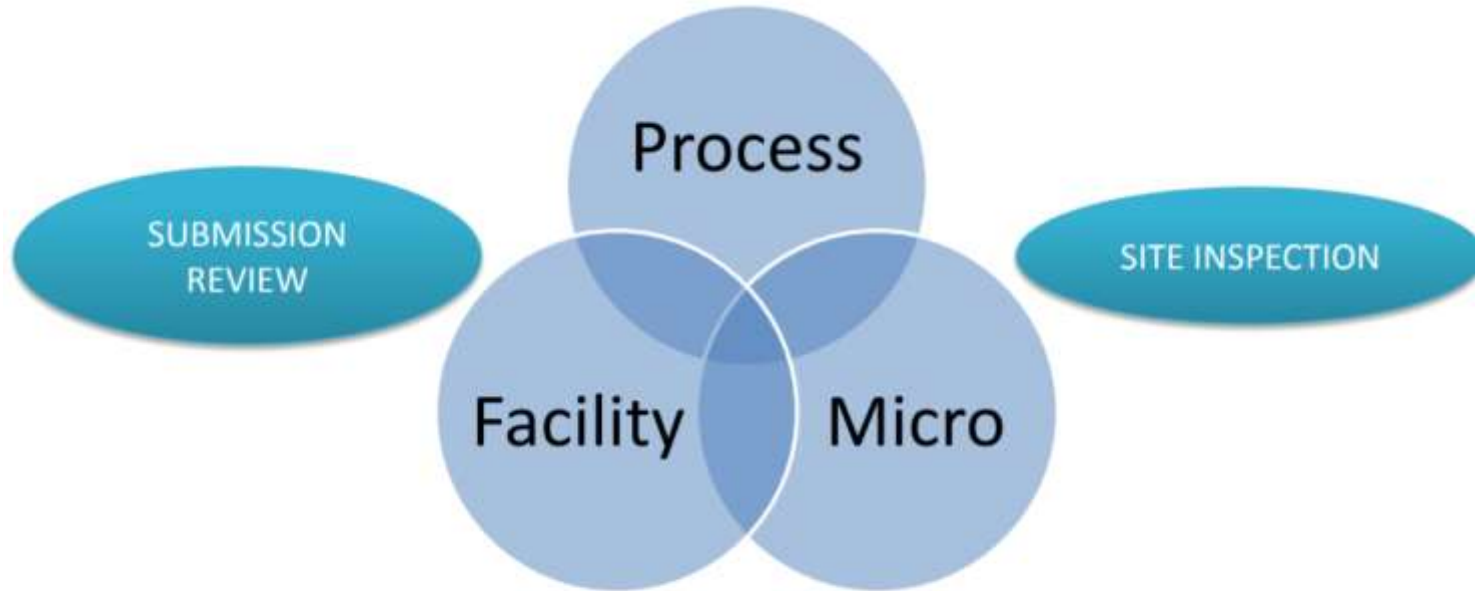


Quality Assessment- Manufacturing

- Review – Manufacturing is assessed in a cross functional, integrated quality assessment team.
- Inspection – Performed by FDA Investigator who has a focus on CGMP aspects of manufacturing that product. Investigator is part of the Integrated Quality Assessment team. OPMA assessors participate as subject matter expert on Pre approval inspections
- Integration of assessment and inspection activities seeks to drive balance between oversight through the application and facilities



Assessment and Inspections



Final decision depends on how well these questions are addressed:

- Potential sources of variability adequately identified?
- Scientific evidence supporting that the proposed process can consistently deliver quality product?
- Process works as intended and remains in control?

Manufacturing Assessment- Reviewer's perspective



Information Sources

- Have all potential sources of variability been considered, evaluated, assessed and mitigated?
- What scientific evidence supporting that process is capable of consistently delivering quality product?
- What demonstrates that process works as intended and remains in control?
- Submissions to agency (preIND meetings all the way to supplements)
- On-site Assessments (Preoperational visits, Inspectional assessments - Pre or Post approval or Surveillance)
- Information gathered through quality reporting (FARS, DPQR, BPDRs)

Manufacturing Assessment- Reviewer's perspective



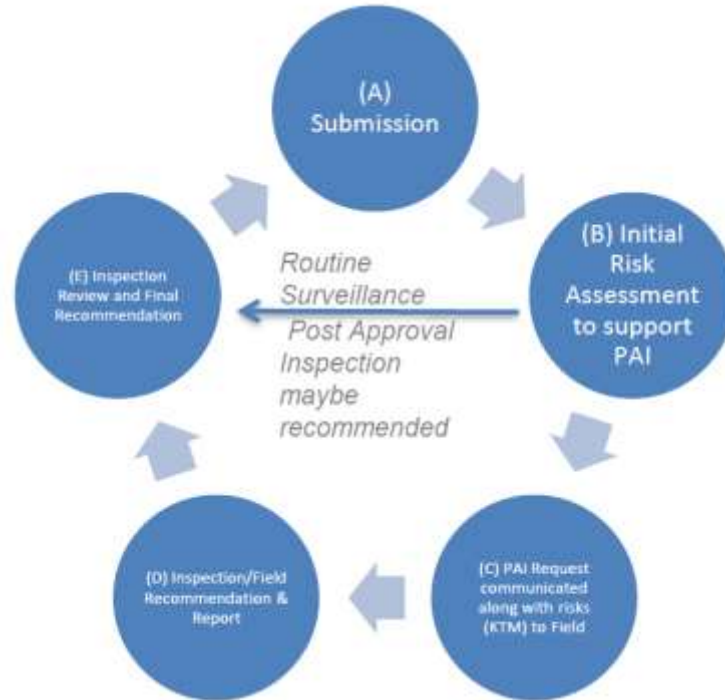
Manufacturing Assessor will conduct *both* the process and facility quality assessment, and participate on a PAI (if warranted):

- Conduct an objective risk assessment on the identified facilities and proposed commercial process designed to promote consistent risk-based assessment and initial PAI decisions
- Make a final determination on the need for a PAI after detailed and holistic risk assessment at early stage in the assessment cycle
- Evaluate process and product risks and mitigation strategies with the knowledge of site CGMP compliance and manufacturing history
- Potential to decrease the occurrence of PAI requests late in the assessment cycle when additional concerns may have been identified during the Process Assessment
- Streamline communication between Process and Facility assessments to other members of the IQA and inspection teams

Quality Assessment- PAI

Prerequisite:

Sites must be CGMP compliant to support an approval recommendation



Objectives of Preapproval Inspection Program (CP 7346.832)



- Specific to Application
- Assure applications are not approved if the applicant has not demonstrated ability to operate with integrity and in compliance with CGMPs
- Assure:
 1. Readiness for manufacturing
 2. Adherence to application commitments
 3. Authenticity and accuracy of data submitted in applications

Negative findings can result in non-approval of application.

Surveillance vs. PAI Process

- Surveillance inspection of manufacturing sites
 - Quality systems
 - Actual conditions and practices
 - Analytical methods
- Pre-Approval inspections are product specific and often cover more – such as an evaluation of:
 - Product development documentation
 - Bio/clinical batch manufacturing
 - Proposed manufacturing process, operational procedures, and batch records
 - Analytical method development
 - Data integrity (supporting application)

Impact of Pre-Approval Inspections (based on actual inspections)



- Identify firms not capable of manufacturing products, for example:
 - Renovation of facility, or equipment not installed
 - Full scale process validation studies were attempted prior to the PAI, demonstrate that the process is not under control and establishment is not making appropriate changes
 - Lack of appropriate controls to ensure quality
 - Multiple batch failures not reported in application

Impact of Pre-Approval Inspections (based on actual inspections)



- Identify lack of conformance to application and data integrity issues, for example:
 - Falsified data (complete fabrication of sterility testing, environmental monitoring, WFI testing, biological indicators for sterilization, bioburden samples, endotoxin testing, media fills)- CGMP issue as well
 - QA approval of incomplete and/or erroneous laboratory data
 - Changes in specification (widening) not reported to application
 - Testing into compliance; repeat testing until passing results, deletion of initial results

PAI Outcomes

The inspection is one part of the assessment process

- Lead investigator will make a recommendation at the conclusion of the inspection.

Recommend Approval

- Indicates that the inspection found no significant issues
- Response to observations is important

Recommend Withholding of Approval

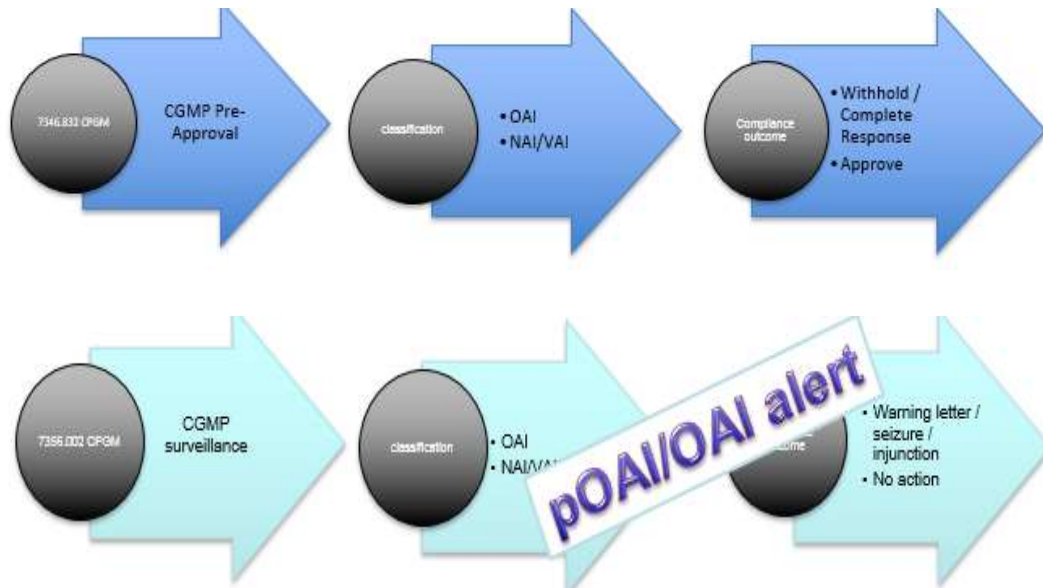
- Investigators observed that the site is not CGMP compliant, information in CMC is not consistent with site records, or information submitted is not accurate and complete.
- Response to observations is ***critical***

OND or OGD makes the ultimate decision on whether to approve or withhold.

PAI Outcomes

Facility recommendations in pending applications are dependent on:

1. The PAI recommendation of approve or withhold.
2. The CGMP inspection PAC* classification and resulting profile
 - ✓ Firms are “profiled” based on inspectional findings by updating their profile classes in eNSpect.



Overall Facility recommendation may be affected by either one, or both.

* Program Assignment code

CGMP compliance - Application Assessment



- When systemic CGMP deviations are found by inspections or during assessment, that implicate the reliability of data generated by a manufacturer, agency assesses the impact to data generated for application products and takes appropriate action for those pending approval.
- Is data submitted in applications to FDA reliable and truthful?
- Can we be confident the drugs will have meet their labeled and purported quality requirements?



Challenge Question



During the PAI of a facility it was observed that the stability studies were performed on samples packaged in amber glass bottles. As per the submission, applicant has proposed container closure system (LDPE bags) to store the finished DP ABC. The recommendation for the submission:

- A. Approve
- B. Withhold

Our Common Goal is Drug Product Quality



- Integrated Quality Assessment is the cornerstone of modern FDA quality oversight for human drugs
- PAIs provide valuable assurance that products approved will meet quality standards in conformance with CGMPs
- Let us communicate, collaborate, and work together to deliver a high quality product that meets the patient's needs

Acknowledgement



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