Risk-based Facility Assessment for Pre-Approval Inspection Determination

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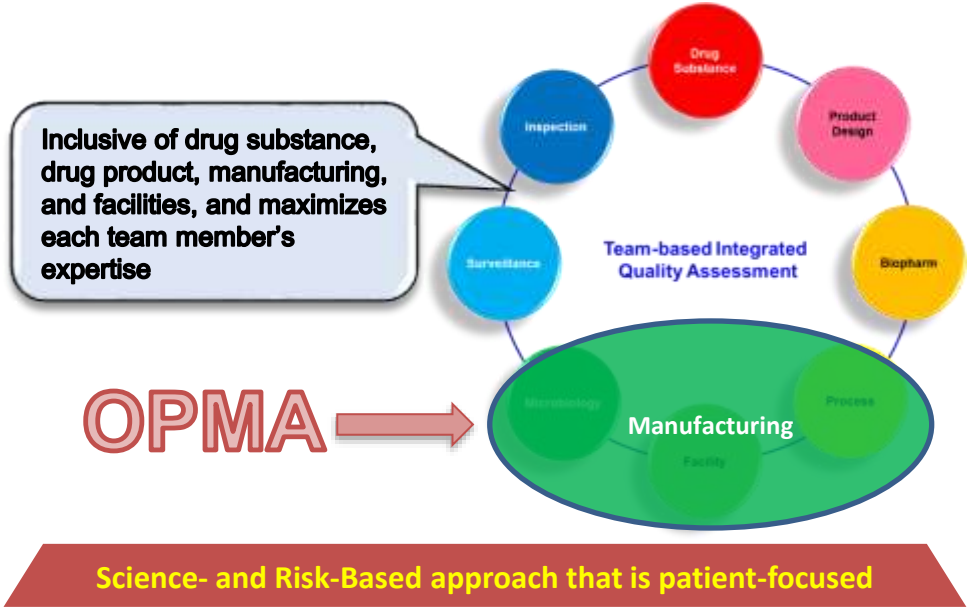
U.S. FOOD & DRUG ADMINISTRATION

Learning Objectives

- Learn how OPMA conducts risk-based integrated manufacturing assessment as a part of OPQ's quality assessment of applications
- Learn how OPMA utilizes FARs and BPDRs to support the risk-based determinations for pre-approval and pre-license inspections as a part of the integrated manufacturing assessment

Team-based Integrated Quality Assessment (IQA)



- Pre-marketing applications:
  - ❑ NDA
  - ❑ ANDA
  - ❑ BLA
- Post-marketing applications – (A)NDA, BLA supplements

OPMA's Role within the IQA Team

- Conducts scientific review and quality evaluation of the manufacturing process, microbiology and facilities for INDs, NDAs, ANDAs, BLAs, and supplements.
- Assessment focuses on manufacturing process, sterility assurance, and facilities.
- Determines need for pre/post-approval inspection or remote regulatory assessment to ensure that manufacturing is adequate to deliver quality products for the patient.

Integrated Manufacturing Assessment

Basic application information, drug substance, drug product, facilities list

Facilities risk assessment for all commercial drug substance and drug product manufacturing, testing, and primary packaging facilities

Initial risk for drug product manufacturing assessment include factors for drug product, drug substance, facilities, unit operations

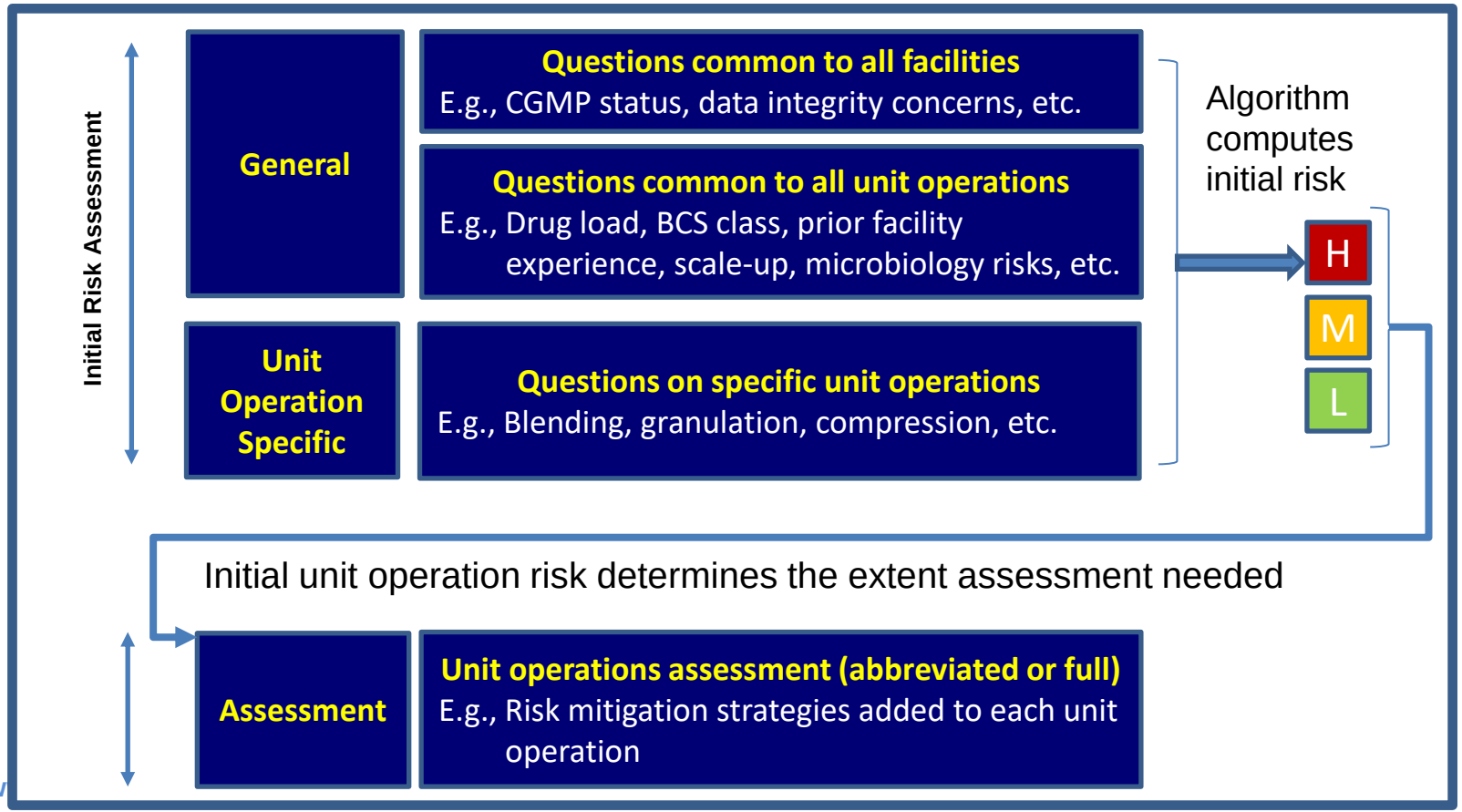
Each drug product unit operation assessment includes type, equipment, in-process controls, process parameters, design & development consideration, process development, scale up

Microbial assessment for drug product control

Executed and master batch records, yield, reconciliation, hold time, comparability protocol, process validation (if applicable)

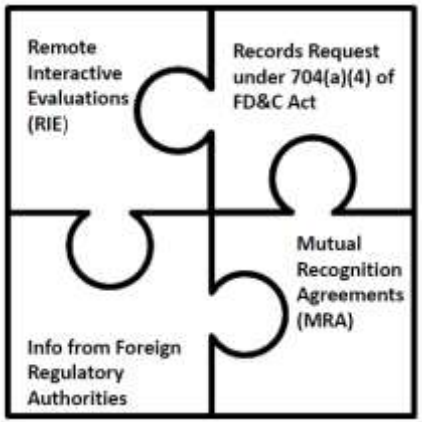
Assessment discipline summary and risk update table

KASA Manufacturing Risk Assessment & Control



Facility Risk Assessment Considerations

- OPMA considers the following high-level areas as a part of the pre-approval and pre-license decisions:
  - Product attributes and associated manufacturing risks, including scale-up
  - Manufacturing complexity pertaining to difficulty to execute or monitor state of control
  - Susceptibility of manufacturing process to contamination
  - Reported deviations and their resolutions
  - Quality surveillance intelligence



Use of Quality Surveillance Intelligence

- Current facility CGMP compliance status
- Prior inspection coverage and outcomes
- Other quality signals
  - Field Alert Reports
  - Biological Product Deviation Reports
  - Recall events
  - Confidential Informants

FAR/BPDR Considerations for Integrated Manufacturing Assessment

- Product quality defect signals, like FARs and BPDRs, can both generate and mitigate risks in the integrated manufacturing assessment
- Generating Risks:
  - Inadequacies in FARs/BPDRs with respect to timeliness and completeness
  - Trends and frequency of FARs/BPDRs in specific systems
  - FARs/BPDRs associated with similar products or processes
- Mitigating Risks:
  - Timely FAR/BPDR submission
  - Adequate/appropriate investigation, root cause determination, and CAPA implementation to prevent recurrence
  - Inclusion of continual improvement in CAPAs

FAR/BPDR Case Study

- Consumer complaints associated with potential packaging issues led to FARs
- CDER initially concerned about timeliness of FARs raising risks
- Initial FAR investigation could not duplicate the complaints
- Further analysis identified CAPAs and continual improvements to create a more robust packaging and visual inspection system
- While frequency of FARs remained consistent, the thoroughness of the investigations and continual improvements provided confidence in the facility's PQS.
- Pre-approval inspection was not requested for product packaged in the same configuration and same line.

Challenge Question

Which of the following statements is *NOT* true?

A. If I submit FARs and BPDRs, my facility may be subject to more frequent pre-approval or pre-license inspections.

B. Taking actions to minimize trends in FARs and BPDRs through continual improvement may not lead to pre-approval or pre-license inspections.

C. Submitting FARs and BPDRs late may increase the likelihood of pre-approval or pre-license inspections.

Summary

- FARs and BPDRs are an important source of surveillance intelligence to provide insight into the effectiveness of the pharmaceutical quality system to aid OPMA's risk-based integrated manufacturing assessment
- As shown in the case study, thorough, timely, and complete investigations and CAPAs can mitigate the need for pre-approval or pre-license inspections