Integrated Manufacturing Assessment – Review Expectations

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Generic Drugs Forum 2021: Lifecycle of a Generic Drug– April 29, 2021

Learning Objectives

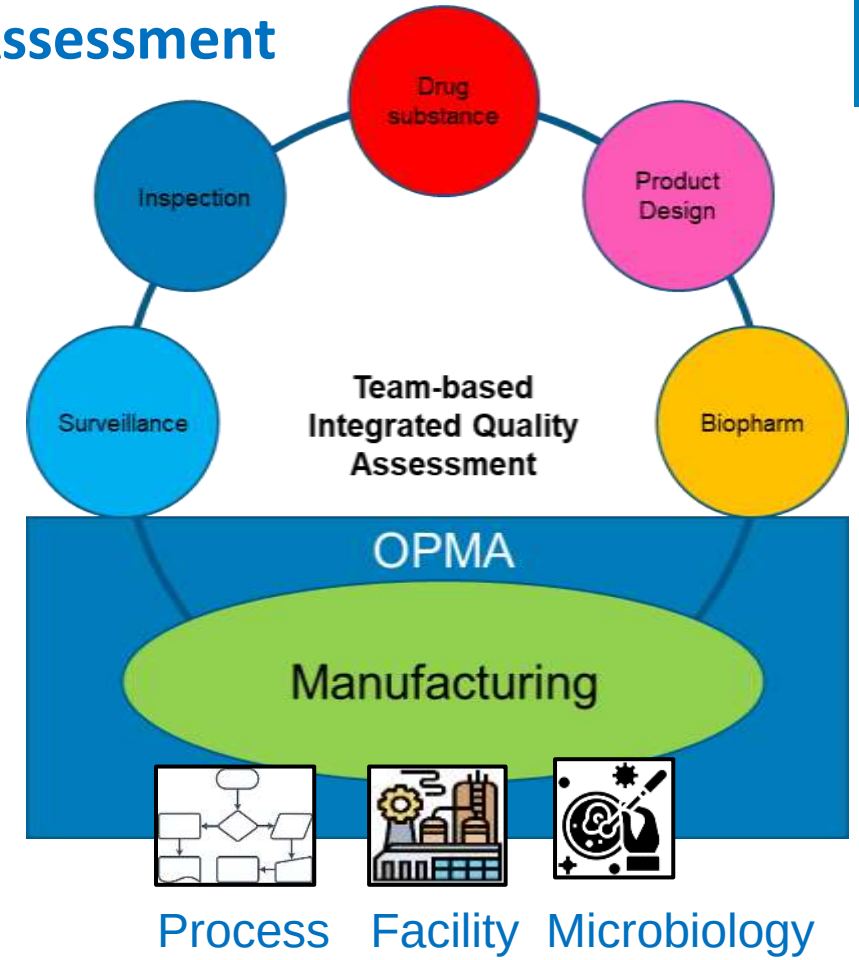
- Illustrate typical approaches to resolve common process deficiencies in generic applications

- Share tips to reduce review cycles via effective deficiency responses

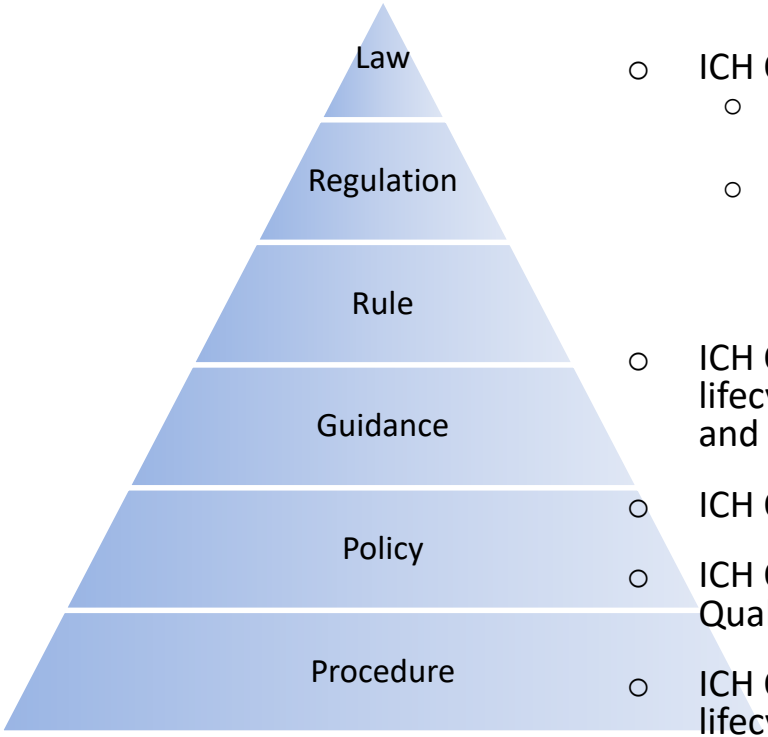
Integrated Manufacturing Assessment

Goal: Evaluate manufacturing and testing processes for proposed commercial product to ensure they are robustly designed and capable of delivering consistent product quality and performance over lifecycle.

Office of Pharmaceutical Manufacturing Assessment (OPMA) includes reviewers who evaluate Process, Facility and Microbiology aspects using a holistic risk-based approach.

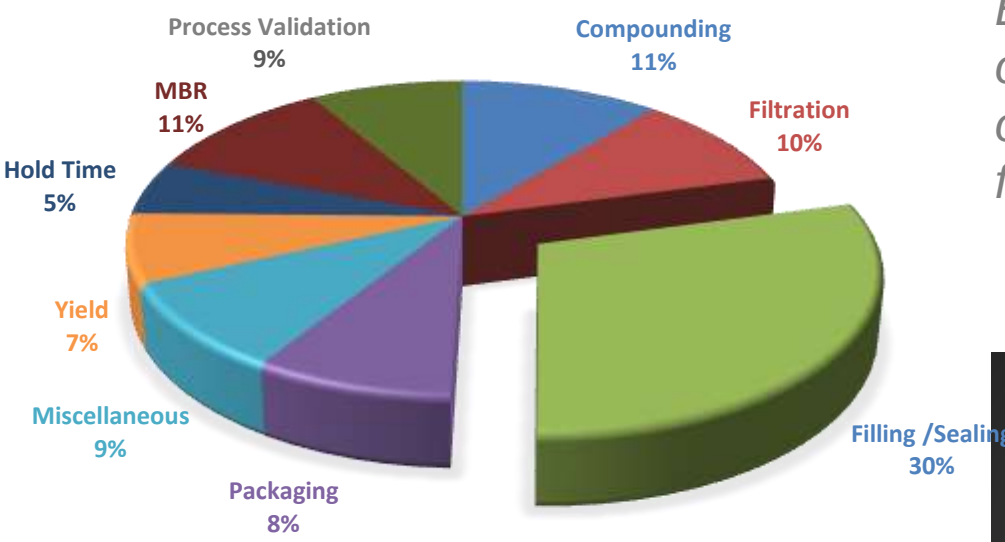


Regulatory Considerations

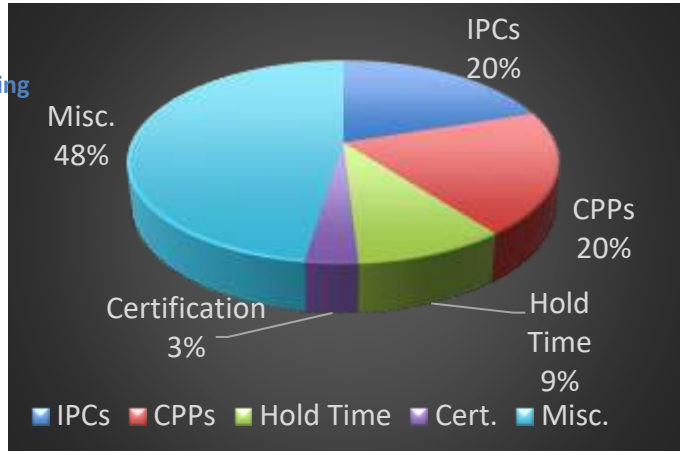


- ICH Quality Guideline (ICH Q8(R2), Q9, Q10, Q11, Q12 (draft)
  - science- and risk-based approaches for drug development and regulatory decisions.
  - assessment of Chemistry, Manufacturing and Controls (CMC) changes across the product lifecycle.
- ICH Q8(R2) and Q11 focus on early stages of the product lifecycle (i.e., product development, registration and launch) and emphasize product and process understanding.
- ICH Q9 emphasizes use of Quality Risk Management principles
- ICH Q10 provides insight into an effective Pharmaceutical Quality System
- ICH Q12 (draft) addresses the commercial phase of the product lifecycle (as described in ICH Q10).

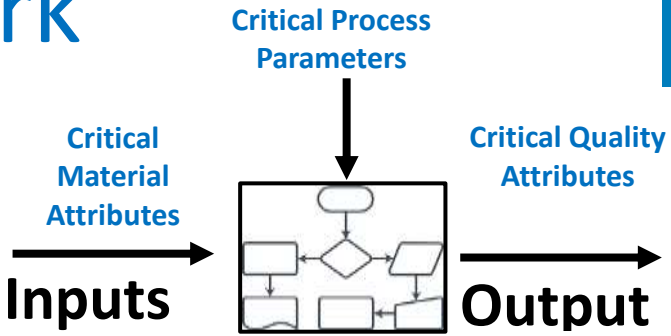
Liquid Dosage forms – deficiency trends



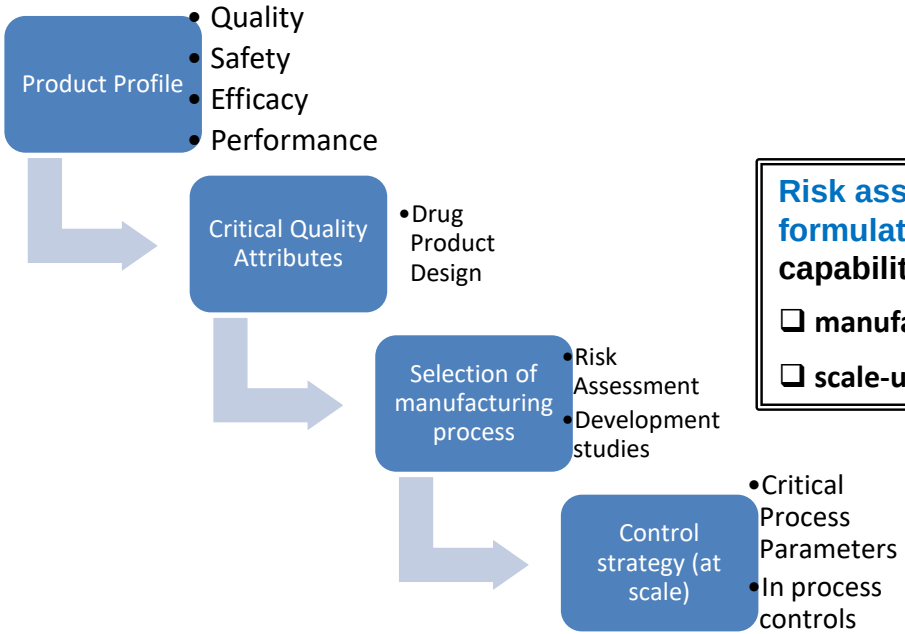
Example: First glance analysis of ANDA deficiencies issued over 18m for liquid dosage forms



Framework



$CQAs = f(CPP_a, CPP_b, \ldots CMA_{ds}, CMA_{ex}, \ldots)$



Risk assessment, development studies and justified material, formulation and process choices demonstrate and establish capability to

- ❑ **manufacture product with defined quality parameters over time**
- ❑ **scale-up to commercial and ensure comparable quality to the bio batch(es)**

Consider critical material attributes

Deficiency: A highly hygroscopic active is being dispensed. The amount dispensed does not account for purity of the active, which may be impacted by moisture increase during storage, handling or dispensing. Provide controls in place; additionally, revise your batch recipe to account for purity of active.

Considerations in Response:

- ❑ Multiple pronged approach may be appropriate including, adjusting for purity of active, test for water content at time of use.
- ❑ Additionally, environmental controls for humidity or an inert atmosphere during dispensing and repackaging may proposed.

Understand Criticality

Deficiency: Formulation for your lotion drug product contains 0.1% w/w active (BCS Class IV) dispersed into lotion base. Considering the low drug content, active suspended in the drug product and the scale-up risk, propose in process tests for viscosity, globule size and particle size distribution (three tier specification) with justification.

Considerations in Response:

- ❑ Explain if and how risk related to bulk manufacturing are managed via in-process controls. Rheological properties, such as viscosity can impact skin retention of the dosage form and drug delivery. Globule size consistency can impact performance of lotion. Monitoring changes in particle form, size, shape, habit, or aggregation during manufacturing process is important for ensuring the batch-to-batch
- ❑ Assessment of critical quality attributes at end of bulk manufacturing as well as homogeneity of such attributes across bulk are desired.

Explain ‘representativeness’

Deficiency: Compatibility studies do not include justification or comparison between the membrane filter used for filter compatibility and the proposed cartridge filter for commercial manufacturing. Provide comparisons which show that disc filter used during compatibility when soaked into bulk solution has surface area to volume ratio larger or equivalent to proposed cartridge filter when it holds volume to its capacity. Alternatively, you can conduct additional compatibility studies using the proposed cartridge filter. Filters used in the study should be autoclaved or otherwise treated in the same way as they would for routine production.

Considerations in Response:

- ❑ Development study report is provided; however clear and explicit information to correlate the tested filter with proposed commercial filter by calculating the surface area to volume ratio could be included. Additionally, report could include calculations which establish that study was conducted under worst-case conditions would support and allow for complete assessment.
- ❑ Alternative approaches are acceptable and would be reviewed.

Explain ‘representativeness’

Deficiency: Please establish hold time for each intermediate based on actual data from exhibit batches or hold study results at representative condition of your production in terms of the size of the bulk intermediate containers and storage environment condition based on physical, chemical, and microbiological test/assessment results.

Considerations in Response:

- ❑ Assessment of representative conditions with appropriate level of sampling and testing to support proposed holding conditions is desired.

Challenge Question #1

Your product contains 45% organic solvent. You receive an information request seeking extractable and leachable studies to support suitability of manufacturing contact surfaces.

Your response could include

A) Studies per principles outlined in USP<1663>, USP<1664> that demonstrate formulation contacting surfaces are not reactive, additive or absorptive

B) Cleaning protocols for equipment prior to each use

C) Data to show impurities in your finished drug product are within acceptance limits

D) Certification from organic solvent vendor that it is suitable for pharmaceutical use (USP/NF grade)

Identify sources of variability

Deficiency: You propose a 10x scale up; Section 3.2.P.3.3 identifies commercial equipment. It includes a footnote stating “equivalent validated equipment” may be used for key equipment such as blending, granulation and drying. Indicate if the operating principal, design characteristics as well of materials of construction will differ.

Considerations in Response:

- ❑ Elaborate whether there is a change in principle, design or contact materials.
- ❑ Address whether development studies exist that assess impact of equipment variation on process parameters.
- ❑ Comment on available scientific data and rationale that will be used to implement change.

References: *Guidance for Industry: SUPAC Manufacturing Equipment Addendum, Dec 2014 (Draft)*

Establish equipment capability

Deficiency: The filling speed used for all three exhibit batches (50 vials/min) does not reflect those proposed for the commercial batches (25-200 vials/min). Provide data to support that the fill weight range can be met with accuracy across the proposed commercial fill speeds and across the entire filling duration.

Considerations in Response:

- ❑ Provide development studies that assess impact of process parameters ranges to deliver proposed fill weight (CQA).
- ❑ Refer to FDA's validation guidance for expectations around equipment qualification and process performance qualification (PPQ). Equipment qualification/requalification is expected to verify that the equipment operation can meet process requirements across all anticipated operation stages (e.g., speed and accuracy of filling operation during startup, interventions, stoppages).
- ❑ Based on product characteristics and risk, additional assurance of fill weight being met over the entire filling duration, would be verified during validation studies. The enhanced in-process sampling plan for validation batches could be submitted in 3.2.P.3.4.

Reference: Guidance for Industry: Process Validation: General Principles and Practices, Jan 2011

Process Validation

Considerations: Process validation protocols and reports are submitted in the application.

Comment:

- Process validation reports that relate to manufacture (not sterility assurance) are not reviewed or assessed.
- Process validation batches are expected to be manufactured with process parameters, sampling plans and in-process controls that are finalized based on review considerations.
- The batches reflect the intended commercial manufacturing operation and upon finalization of validation activities and application approval may be marketed.

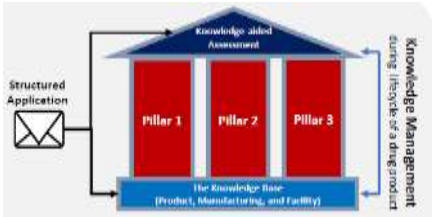
Reference: Guidance for Industry: Process Validation: General Principles and Practices, Jan 2011

Tips to minimize review cycles

- Submit complete and relevant information
- Include consistent information (e.g. between modules in eCTD)
- Understand and meet regulatory expectations
- Consider feedback and if possible, apply learnings across submissions.

Initiatives within Agency

- Teams
  - Effective collaboration between multi-disciplinary teams that continue to maintain interaction across multiple applications
- Tools
  - Informatics used across applications for knowledge management and structured review including compiling facility capabilities
- Training
  - Single reviewer (process and facility) with relevant standardized training
  - Subject matter experts included as needed



Summary

- Common deficiencies are resolvable with due attention to detail and inclusion of information and justification supported by science and risk-based analysis.
- Avenues for clarification and discussion with Agency are available. (e.g. Mid Cycle telecons for complex ANDA review issues).
- A submission that demonstrates thorough understanding of product, process and implementation risks allows for robust product quality management.

Challenge Question #2

A reference to support your process validation efforts prior to market launch would be:

A. Quality Agreement with contract manufacturer

B. Preapproval Inspection Compliance Program

C. Guidance for Industry: Process Validation: General Principles and Practices, Jan 2011

D. USP Monograph for Drug Product

Acknowledgements

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U.S. FOOD & DRUG ADMINISTRATION

Questions?

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Closing Thought

Yes, together we can…
ensure safe and
effective medicines are
available!


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