# Common Manufacturing Related Deficiencies for Liquid Drug Products

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# Learning Objectives

- Describe the typical liquid drug manufacturing unit operations
- Identify the common liquid drug manufacturing deficiencies
  - Manufacturing related risks and controls
  - Examples of common deficiencies and resolutions* (see disclaimer)

# Disclaimer

- The resolutions provided for the example deficiencies are related to the specific manufacturing conditions and are only for illustrative purposes. They should not be considered as the only accepted approaches. The firm should select an approach suitable for its respective application.

# Common Liquid Manufacturing Operations

- Dispensing & Mixing
- Filtration

  Particulate removal, bioburden reduction, sterile filtration
- Filling
- Lyophilization (if final product lyophilized)
- Stoppering and sealing

# Manufacturing Related Risks and Controls: Dispensing & Mixing

- Physicochemical characteristics of API and environmental controls

  Temperature, relative humidity, inert atmosphere, light protection, etc.

- Dispensing accuracy

  Amount of API adjusted by water content and residual solvents

- Bulk stability

  Contact surface compatibility, process time limits, bulk hold time limits established

- Bulk uniformity

  Controls on content homogeneity for suspension, emulsion, and gel

# Dispensing & Mixing Deficiencies

## Example:

According to your risk assessment, addition of API to low pH or high pH solution will cause degradation. However, in your proposed manufacturing process and process controls, there is no pH check on the bulk solution before addition of API. Provide additional in process control on pH before addition of API.

## Resolution:

The applicant added pH check as an additional in process control before addition of API.

# Dispensing & Mixing Deficiencies

## Example:

Your proposed total allowable storage time of the nano suspension final bulk in the stainless-steel  vessel is 24 hours till completion of sterile filtration. However, this time limit does not appear to be supported by the compatibility study, out of specification result on particle size distribution was observed on samples taken at 24-hour test point. Please explain the discrepancy and justify with data for the proposed hold time of 24 hours.

## Resolution:

Total hold time is shortened to 18 hours based on the actual processing times of the exhibit batches, and the existing acceptable 18-hour stability data.

# Dispensing & Mixing Deficiencies

## Example:

We acknowledge that you provided content uniformity data for only one engineering batch. Considering low drug load and that the drug product is a suspension, the risk of content non-homogeneity is high. Please include in-process tests for bulk uniformity (homogeneity) with samples taken from multiple locations in the bulk suspension.

## Resolution:

The applicant added in-process tests for bulk uniformity (homogeneity) with samples taken from multiple locations in the bulk suspension.

# Manufacturing Related Risks and Controls: Filtration

- Bulk stability

  Process duration supported by bulk stability study

- Process equipment-related adsorption

  Study to show no adsorption of API and excipients or propose adequate flushing

- Process equipment-related leachables (PERLs)
  - Process leachables have potential to affect safety and quality of the drug product
  - Risk of PERLs should be assessed based on drug product formulation and manufacturing conditions
  - Adequate mitigation strategies should be provided for any leachables above safety concern threshold

# Filtration Deficiencies

## Example:

You have provided a filter adsorption study by incubating the filter membrane with the drug product. This is inadequate. The adsorption study should be conducted using the entire filter unit including the cartridge as it is made of polymeric material and has contact with the bulk solution that exposes risk for adsorption.

## Resolution:

The applicant repeated the adsorption study using the entire filter unit (cartridge+ membrane).

# Filtration Deficiencies

## Example:

The drug product formulation contains a high level of solubilizer used to solubilize the API which may increase the risk of leachable impurities from polymeric manufacturing equipment (filters, tubing, etc.). Provide extractable studies on the individual equipment with appropriately selected model solvents and extractable study condition. Alternatively, a leachable study may be provided using the final drug product manufactured under the worst scenario conditions to demonstrate that the risk is mitigated.

## Resolution:

The applicant conducted the requested extractable studies.

# Manufacturing Related Risks and Controls: Filling

- Stability

  Total fill time and line interruption policy supported by bulk stability data

- Fill weight accuracy

  100% in-line fill weight check or a reasonable sampling plan

  At a minimum, samples should be taken for fill weight check from each filling needle at the beginning, middle and end of the filling process

- Fill volume range

  CDER MAPP 5019.1 Allowable Excess Volume/Content in Injectable Drug and Biological Products (effective 1/28/2022)

# Filling Deficiencies

Example:

Your proposed fill target is 20.60 mL with an action limit of deviation of 1.50% of the target volume. This means that the minimum fill volume is 20.29 mL (20.60x 98.5%=20.29mL), less than the excess fill volume recommended by USP<1151>. We refer you to CDER MAPP 5019.1 Allowable Excess Volume/Content in Injectable Drug and Biological Products. Revise your fill target and action limit accordingly or provide deliverable volume study data per USP<697> to justify your proposed minimum fill.

Resolution:

The applicant provided deliverable volume study using samples filled with minimum fill volume. The proposed minimum fill is supported.

# Filling Deficiencies

## Example:

We cannot locate your interruptions/restart policy of the filling line. Please specify what actions will be taken if interventions happen during the filling process and support with data.

## Resolution:

The applicant provided a description of the proposed restart policy including time limits on pauses and flush volume upon restart. The proposed restart policy is supported with data.

# Manufacturing Related Risks and Controls: Lyophilization

- Robustness of the lyophilization cycle parameters
  - Proceeding to secondary drying prematurely can lead to cake collapse or melt-back, end point of primary drying and secondary drying should be justified with data
  - Same applies to scale ups
- Drying uniformity

  Sampling plan should include vials in different locations of the lyophilization chamber

# Challenge Question #1

**After freeze drying cycle is completed for the exhibit batches, 10 vials were taken from each of the four corners and the middle position of each loaded shelf for drying uniformity study. The samples from each sampling point were tested for description (including structure, cake appearance), assay, related substances, reconstituted solution appearance, reconstitution time, water content, and pH of the reconstituted solution. Is the study adequate?**

A. Yes

B. No

# Challenge Question #2

**The tubing extractable study data shows total non-volatile residues (NVR) above the analytical evaluation threshold (AET). Which of the following steps are considered appropriate toward mitigation of risk of potential tubing leachables in the final drug product?**

A. Identification and quantitation of individual compounds from the total NVR

B. A leachable study that evaluated a few known tubing extractables in the final drug product.

C. A leachable study that evaluated identified compounds from the extractables studies, in the final drug product.

D. Both A and C

# Challenge Question #3

**Which of the following statements is true regarding fill volume control?**

A. The minimum fill volume must not be less than the excess fill volume recommended by USP <1151>.

B. MAPP 5019.1 describes the policies and procedures used by OPQ assessors to evaluate excess liquid or solids filled into vials for injectable drug products.

C. The proposed fill volume should be sufficient to allow the withdrawal and administration of the net container content of the drug product.

D. Both B and C

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