MAPP 5019.1 Allowable Excess Volume/Content in Injectable Drug and Biological Products

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 3: Simple Injectables

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Learning Objectives

- Understand the concepts of net container content and gross content for injectable drug products
- Establish appropriate excess content filled into vials
- Establish gross content limits for finished drug products
- Establish in-process controls for bulk fills

Problem Statement for Injectable Drug Products Filled into Vials

- Insufficient volume causes problems during administration:
  - Need additional vials to deliver the labeled dose or under-dose the patient
- Excessive volume may pose:
  - Risk of contamination of the drug product, i.e., leftover drug product was pooled to produce a second dose.

Applicable Policy

- 21 CFR 201.51(g): The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package
  - For a liquid drug in ampules or vials, intended for injection, it shall be considered to express the minimum quantity and the variation above the stated measure shall comply with the excess volume prescribed by the NF/USP for filling of ampules
  - For a solid drug product in ampules or vials, it shall be considered to express the accurate net weight.
- USP <697> Container Content for Injections: Ensures sufficient excess in the vial to allow withdrawal of the labeled quantity of drug
- USP <1151> Pharmaceutical Dosage Forms: Includes excess volume recommendations for injections

Overview of MAPP 5019.1

- **Publication:** Posted on FDA's website on December 22, 2021, and was effective on January 28, 2022
- **Purpose:** To ensure that the excess liquid or solid filled into vials for injectable drug products is appropriate to **deliver the labeled content** of drug product and **avoid excessive overfill**
- **Scope:** Injectable Drug Products filled in vials and ampules, including those requiring constitution/reconstitution, for NDAs, BLAs, and ANDAs, and applicable supplements

MAPP Terms for Liquid Drug Products

- **Deliverable volume** (mL per vial) is the volume that can be withdrawn and delivered following procedures in USP General Chapter <697>
- **Net container content** (mL), i.e., labeled content, is the net quantity of contents that appears on the container label as a distinct item. It will be met if deliverable volume conforms to USP <697>
- **Gross content**: content of the drug product (i.e., mL) per vial including the excess volume:
  - Lower limit: ensure labeled content is delivered
  - Upper limit: avoid excessive overfill

MAPP Terms for Solid Drug Products Requiring Reconstitution

- **Net container content** (e.g., mg) is the labeled quantity of drug substance or protein content
- **Gross content**: content of drug substance or protein content (i.e., mg) per vial including the excess amount
  - Lower limit: ensure labeled content is delivered
  - Upper limit: excess fill does not exceed the upper limit of the assay/protein content specification
- Following reconstitution according to the labeled instructions
  - **Deliverable volume** (mL per vial) determined by USP <697>
  - **Assay or protein concentration** (e.g., mg per mL)

Gross Content – *cont.*

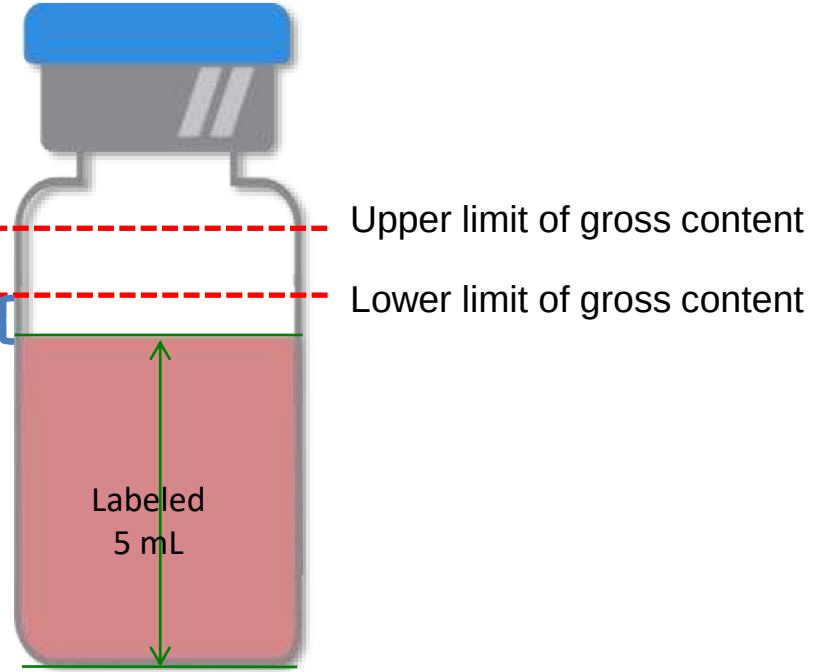
- Again, Gross Content is defined as the total content filled in a vial including the excess amount. We recommend that it be assessed at release as part of drug product specification.
- Minimum/maximum fill volume/content should be established based on the calculated gross content limits:
  - The minimum fill volume/content should not be less than the lower limit of the gross content
  - The maximum fill volume/content should not exceed the upper limit of the gross content

Liquid Single Dose Case Study

Label: 500 mg per 5 mL (100 mg/mL), 5 mL (net container content)

Max. Fill Vol.	Discourage pooling	≤ 5.8 mL
Min. Fill Vol.	5 mLs + 0.3 mL	≥ 5.3 mL

Labeled Content/ net container content	Recommended Excess Volume (<1151>)
5.0 mL	0.30 mL



Relevant DP and IP Specifications

Drug Product (DP) Specifications

A. Deliverable volume:	NLT 5.0 mL/vial
B. Assay:	90 to 110 mg/mL
Narrow therapeutic	95 to 105 mg/mL
C. Gross content:	5.3 to 5.8 mL/vial

In-Process (IP) Specifications

A. Minimum fill volume:	≥ 5.3 mL/vial
B. Maximum fill volume:	≤ 5.8 mL/vial
C. In-process assay* (if applicable):	per 21 CFR 211.110(b)

**21 CFR 211.101(a) "The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient"*

Lyophilized Single Dose Case Study

From the Label

400 mg (i.e., net container content) lyophilized cake in single-dose vial.
Reconstitute with 20 mL WFI to give a reconstituted solution of 20 mg/mL.

From Experimental Development Studies

Reconstituted volume = 21.4 mL (20 mL WFI + 1.4 mL volume of expansion)
Note: The 1.4 mL excess volume satisfies USP <1151>

Equation to Determine mg of API per Vial to Achieve Labeled Concentration

$$\frac{\text{x mg of API per vial}}{\text{21.4 mL reconstituted volume}} = \text{20 mg/mL reconstituted solution}$$

Determining Gross Content Limits

Equation from Previous Slide

$$\frac{\text{x mg of API per vial}}{\text{21.4 mL reconstituted volume}} = \text{20 mg/mL reconstituted solution}$$

Gross Content Specification Lower Limit (100% of Labeled Concentration)

x = (20 mg/mL reconstituted solution) x 21.4 mL

x = **428 mg** of API per vial.

Gross Content Specification Upper Limit (110% of Labeled Concentration)

y = (22 mg/mL reconstituted solution) x 21.4 mL

y = **471 mg** of API per vial.

Establishing In-process Fill Volumes

- Recommended approaches:
  - Adjust fill volumes based on actual bulk conc.

    Gross content: 428 – 471 mg

    Target bulk conc. = 40 mg/mL

    Actual bulk conc. result = 39.6 mg/mL (i.e., 99% of target)

    In-process Specifications

    A. Minimum fill volume: **≥ 10.8 mL/vial**
    B. Maximum fill volume: **≤ 11.9 mL/vial**

  - Use a set fill volumes based on acceptable variability in the bulk conc.

    Bulk concentration variability, e.g., 97-103%

    In-process Specifications

    A. Minimum fill volume: **≥ 11.0 mL/vial**
    B. Maximum fill volume: **≤ 11.4 mL/vial**

Challenge Question #1

For an injectable ANDA application received after January 28, 2022, which of the following is applicable in terms of excess volume during assessment?

A. MAPP 5019.1 but not 21 CFR 201.51(g)

B. 21 CFR 201.51(g) but not MAPP 5019.1

C. Neither 21 CFR 201.51(g) nor MAPP 5019.1

D. Both 21 CFR 201.51(g) and MAPP 5019.1

Challenge Question #2

Which of the following is the drug product quality control test to ensure the maximum fill is not unreasonably large that results in leftover drug product to be used as a partial or second dose?

A. Net container content

B. Gross content

C. Min and max fill volume/weight

D. All of the above

Summary

- **Excess volume/content** should be appropriate to deliver the net container content of drug product or drug substance, and avoid excessive overfill
- **Net container content** is the net quantity of contents as described in 21 CFR 201.51(g). The declaration shall appear as a distinct item on the label and, in the case of large volume parenterals, may be embossed on the glass.
- **Gross content** is the total content of the drug product or drug substance per vial, including the excess amount. It is part of drug product specification assessed at release, to ensure compliance with 21 CFR 201.51(g) for injectable drug products filled in vials.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