Ensuring Drug Product Content Meets Label Claim
Are you getting what you paid for?

CDR Leslie Ann Rivera Rosado, Ph.D.
Supervisory Regulatory Review Officer
Office of Product Quality Assessment III
Office of Pharmaceutical Quality
CDER | US FDA

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Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

Disclaimers

- The views and opinions expressed are those of the presenter based on her experience.
- The views and opinions expressed should not be used in place of regulations, published FDA guidance, or discussions with the Agency.

Outline

- Problem Statement
- Critical terminology
- Regulatory framework
- Regulatory expectations
- Challenges
- Key Takeaways

Problem Statement

- Inability to completely withdraw the intended full dose ("label claim") from the vial
  - Vial does not meet the declaration of net quantity of contents (21 CFR 201.51(g))
  - Under-dose patients
  - Use of additional vials to complete treatment
    - Increased contamination risk
- Excessive volume
  - Could lead to use as a partial dose or pooled to produce a second dose
    - Increased contamination risk

Goal: Ensure patients receive the intended dose as stated on the drug product label

Problem Statement

The proper net quantity of contents is important for proper dosing of the patient, to minimize medication errors, to avoid drug product contamination, and to limit drug product waste.

CRITICAL TERMINOLOGY

Throughout this presentation, ‘net quantity of contents (NQC)’, ‘net container content (NCC)’ and ‘label claim’ refer to the same regulatory concept as defined in 21 CFR 201.51(g)

Net quantity of contents (NQC) (21 CFR 201.51(g))
= Net Container Content (NCC) (used in MaPP 5019.1)
= Labeled vial fill sizes (used in MaPP 5019.1)
= Labeled quantity (used in USP <1>)
= Labeled size (used in USP <1151>)
= Label claim (used in USP <1151>, USP <905>)
= Labeled content or labeled dose

Definitions

- **NQC / NCC ("label claim"):** The term refers to the declaration of net quantity of contents as described in 21 CFR 201.51(g).
- The NQC shall appear as a distinct item on the label.
  - **Liquid drug product:** – the NQC will be expressed as a measure of **volume** (e.g., mL)
  - **Solid drug product:** – the NQC will be expressed as a measure of **weight** (e.g., mg)

[Interpretation: NQC is the deliverable amount of drug to the patient]

Definitions

- **Gross content (GC):**
  - **Liquid drug product:** the total volume (e.g., mL) of drug product filled into a vial including the excess volume
  - **Solid drug product:** the total amount (e.g., mg) of drug substance or protein content filled into a vial including the excess amount
  - **GC** is a drug product **quality control test** to ensure compliance with 21 CFR 201.51(g) for injectable drug products filled in vials.

Definitions

- **Deliverable volume**
  - Quantity in volume of a liquid drug product or a solid drug product following reconstitution/constitution that can be transferred from the original container, following the procedures outlined in USP General Chapter <697> *Container Content for Injections*.
  - a.k.a. *volume of injection in container* in USP <1>

REGULATORY FRAMEWORK

21 CFR 201.51 *Declaration of net quantity of contents*

(a): “The label of a prescription or insulin-containing drug in package form **shall bear a declaration of the net quantity of contents**.[…]

(d): “The declaration shall appear as a **distinct item** on the label…”

(e) “The declaration shall **accurately reveal the quantity** of drug in the package…”

(g) {excerpt}--Key Requirements:

- Declaration must express **accurate statement of package contents**
- **Reasonable variations** from manufacturing/distribution will be **recognized**
- For liquid injectables: declaration expresses **minimum quantity**
  - **Excess volume** must comply with USP standards
- For solid drugs: declaration expresses **accurate net weight**

21 CFR 201.51 *Declaration of net quantity of contents*

(a): "The label of a prescription or insulin-containing drug in package form **shall bear a**

Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry (2015)

"…the declaration of **net quantity of contents** on the label is considered to express the **minimum** quantity of contents and further requires that **variation above the stated measure must comply with the excess volumes set forth in USP**."

- For solid drugs: declaration expresses accurate net weight

21 CFR 211.101(a) *Charge-in of components*

"The batch shall be formulated with the **intent** to provide **not less than 100 percent** of the labeled or established amount of active ingredient."

Where do the MaPPs fit in?

- CDER's Manual of Policies and Procedures (MaPPs) are federal directives and documentation of **internal policies and procedures**. MaPPs are required by law and made available to the public to make CDER a more **transparent** organization.
- MaPP 5019.1 and 5019.2 convey information related to OPQ's **implementation of the final guidance** for industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015).
  - (1) Allowable excess volumes of injectable drug products filled into vials
  - (2) Appropriate drug product net container content sizes (i.e., labeled vial fill sizes) for injectable drug products
- MaPPs are not directly enforceable against external parties.

REGULATORY EXPECTATIONS

Declaration of net quantity of contents (“label claim”)

21 CFR 201.51(g):
“…**liquid drug**… the declaration shall be considered to express the **minimum quantity**…”

21 CFR 201.51(g):
“ …**solid drug…** the declaration shall be considered to express the **accurate net weight**.

NDC 12345-123-12
WeBio
(examplemab-xxxx)
Injection

150 mg/5 mL
(50 mg/mL)

For intravenous Infusion only
Requires dilution prior to administration

Rx only
5 mL single-use vial
Discard unused portion

Declaration of NQC:
Total amount of content in the package

NDC 12345-123-12 Rx only
OurBio
(examplecept-xxxx)
For Injection

150 mg/vial

For intravenous Infusion only
Must reconstitute and dilute prior to use

Single-use vial. Discard unused portion

Liquid products in vials

"In the case of a **liquid drug** in ampules or vials, intended for injection, the declaration shall be considered to express the **minimum quantity** and the **variation above the stated measure shall comply with the excess volume prescribed by the National Formulary or the U.S. Pharmacopeia** for filling of ampules." [21 CFR 201.51]

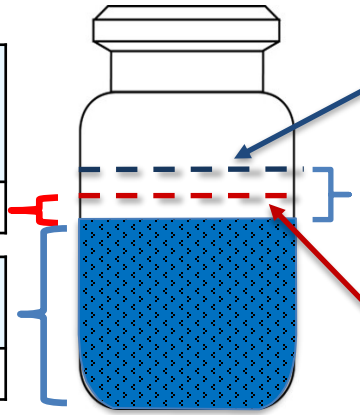
USP<1151>: Excess Volume in Injections

"Each container of an Injection is filled with a volume in slight excess of the labeled "size" or the volume that is to be withdrawn. The excess volumes recommended in the accompanying table are usually sufficient to permit withdrawal and administration of the labeled volumes."

Labeled Size	Recommended Excess Volume	
	For Mobile Liquids	For Viscous Liquids
0.5 mL	0.10 mL	0.12 mL
1.0 mL	0.10 mL	0.15 mL
2.0 mL	0.15 mL	0.25 mL
5.0 mL	0.30 mL	0.50 mL
10.0 mL	0.50 mL	0.70 mL
20.0 mL	0.60 mL	0.90 mL
30.0 mL	0.80 mL	1.20 mL
50.0 mL or more	2%	3%

Liquid products in vials

Recommended Excess Volume *(USP <1151>)*
0.10 mL
Net Quantity of Content
1 mL



Gross content (UL):
max fill volume.
Should be justified.

Overfill
(allowable excess volume)

Gross content (LL):
NQC + excess volume per USP <1151>
(or adequately justified excess volume)

- Protein concentration (x mg/mL ± adequately justified variation)
- Volume in container (USP<697>)
- Gross Content
- Data to demonstrate that the required volume for a dose can be delivered using recommended administration materials

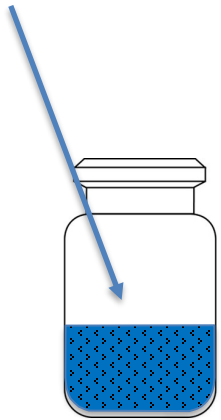
Lyophilized products in vials (1)

"In the case of a **solid drug** in ampules or vials, the declaration shall be considered to express the **accurate net weight**. Variations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary." [21 CFR 201.51]

"In the case of drug products requiring reconstitution, **the product should be designed to meet the label claim and acceptable overfill, and allow for correct dosing**."
Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for industry.

Total volume of the reconstituted solution should be determined experimentally to ensure proper dosing.

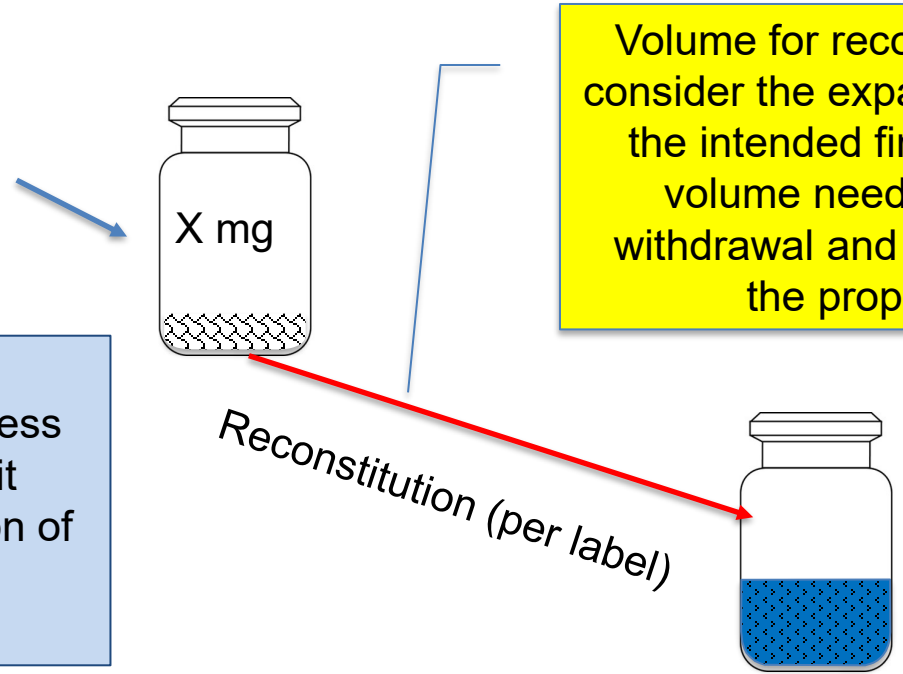
- Content Uniformity (USP<905>)
- Protein concentration after reconstitution
- Volume in container (USP<697>) after reconstitution
- Gross Content
- Data to demonstrate that the required volume for a dose can be delivered using recommended administration materials after reconstitution



Lyophilized products in vials (2)

Gross content:
the total amount of drug substance or protein content filled into a vial including the excess amount

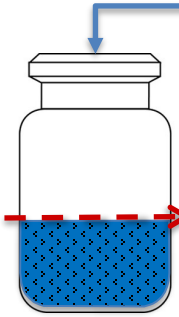
Data should be provided to justify that the proposed excess amount is adequate to permit withdrawal and administration of the NQC/ label claim (in mg) after reconstitution



Volume for reconstitution should consider the expansion volume and the intended final reconstituted volume needed to allow for withdrawal and administration of the proper dosing.

Lyophilized products in vials (3)

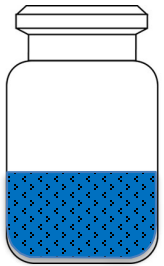
Fill amount contains sufficient excess drug product to allow for withdrawal and administration of the NQC/label claim for a solid drug product after reconstitution/constitution.



Max. Fill Vol
Target Fill Vol.
Min. Fill Vol

Lyophilization

Reconstitution (per label)



Min and Max fill volume should allow drug product to meet the final protein concentration specification after reconstitution at release and during stability

Challenges

- Meeting the declaration of net quantity of content (NQC)/Label claim
  - the preparation and administration instructions say to "~~withdraw the entire content of the vial~~" vs. "withdraw *x* mL from the vial"
    - Best practice: state the volume needed to administer the intended dose
      - for lyophilized products the prescribing information (PI) includes the name and amount of diluent, resultant concentration after reconstitution, and volume needed to administer the intended dose
  - using different preparation and administration materials. (e.g., syringe and needle vs. vial adapter)
  - human factor considerations

Challenges

- The “intended dose” was not met during product/clinical development
  - i.e., at marketing application submission, deliverable volume/dose studies show that the amount of drug that can be withdrawn following the preparation and administration instructions does not meet the expected NQC
  - Results in updating the label/labeling to state the correct NQC
  - Could complicate analysis of clinical data
  - Best Practice: Design your final product to meet your proposed intended dose (NQC/label claim) early in development.

Key Takeaways

- The product should be designed to ensure that the net quantity of content/label claim can be withdrawn and administered to the patient
  - Considerations
    - Manufacturing process: e.g., batch formulation, min/max fill volume, equipment capabilities, gross content, expansion volume for lyophilized products, container closure system
    - Preparation and administration instructions: e.g., proposed administration materials, hold-up volume
- Data and justification for the proposed excess volume/excess amount should be provided in the application
  - (e.g., product development studies, deliverable dose/volume studies, human factor studies, QC testing results, manufacturing data)
- Gross content specification ensures compliance with 21 CFR 201.51(g)

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