How to Facilitate First Cycle Approvals – Recommendations and Expectations

FILL AMOUNT CONTROL FOR LIQUID AND SEMISOLID DOSAGE FORMS

Yaodong (Tony) Huang, Ph.D.
Quality Assessment Lead (Acting)
Branch VIII/Division of Process Assessment III
Office of Process and Facilities (OPF/OPQ/CDER/FDA)
DISCLAIMER

The views and opinions expressed in this presentation are those of the authors and do not necessarily represent official policy or position of the Food and Drug Administration.
Outline

• Review Team and OPF (Office of Process & Facility)
• Importance of Fill Amount Control
• Related Guiding Documents
• Recommendations for In-Process Control of Fill Amount for Some Drug Products
  – Injections (Liquids, lyophilized powder, sterile powder)
  – Topical and Ophthalmic Semi-solids
• Conclusions
• Acknowledgements
Review Team for ANDAs & OPF

OGD
- Regulatory Project Manager (RPM)
- Filing Reviewer
- Labeling Reviewer
- Bioequivalence Reviewer

IQA TEAM (OPQ)
- Regulatory Business Project Manager (RBPM)
- Application Technical Lead (ATL)
- Drug Product Reviewer (OLDP)
- Biopharmaceutics Reviewer (ONDP)
- Drug Substance Reviewer (ONDP)
- Process Reviewer (OPF)
- Facility Reviewer (OPF)
- Microbiology Reviewer (OPF)

Office of Process & Facility (OPF)
- Divisions of Process Assessment (DPA1, 2, 3)
- Division of Inspectational Assessment (DIA)
- Division of Microbiological Assessment (DMA)
Importance of Fill Amount

21 CFR 201.51 - Declaration of net quantity of contents

(g) The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large. 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. 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.

Observations and Challenges in ANDA Review

• Under-fill is rarely seen;
• Over-fill is very common;
• In-Process Controls on fill amount vary significantly among applicants;
• Lack of good understanding of related guidance;
• Large number of IRs come from this aspect and slow down approval.
Guidance on Fill Amount

- USP<1>: Injections and Implanted Drug Products – Product Quality Test
- USP<3>: Topical and Transdermal Drug Products – Product Quality Test
- USP<4>: Mucosal Drug Products – Product Quality Test
- USP<698>: Deliverable Volume (oral liquids)
- USP<755>: Minimum Fill
- USP<905>: Uniformity of Dosage Units
- USP<1151>: Pharmaceutical Dosage Forms
Injections from USP<1151>

Injections are not treated as a dosage form in this chapter.

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 Table 1 are usually sufficient to permit withdrawal and administration of the labeled volumes.

<table>
<thead>
<tr>
<th>Labeled Size</th>
<th>For Mobile Liquids</th>
<th>For Viscous Liquids</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mL</td>
<td>0.10 mL</td>
<td>0.12 mL</td>
</tr>
<tr>
<td>1.0 mL</td>
<td>0.10 mL</td>
<td>0.15 mL</td>
</tr>
<tr>
<td>2.0 mL</td>
<td>0.15 mL</td>
<td>0.25 mL</td>
</tr>
<tr>
<td>5.0 mL</td>
<td>0.30 mL</td>
<td>0.50 mL</td>
</tr>
<tr>
<td>10.0 mL</td>
<td>0.50 mL</td>
<td>0.70 mL</td>
</tr>
<tr>
<td>20.0 mL</td>
<td>0.60 mL</td>
<td>0.90 mL</td>
</tr>
<tr>
<td>30.0 mL</td>
<td>0.80 mL</td>
<td>1.20 mL</td>
</tr>
<tr>
<td>50.0 mL or more</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Guidance for Industry:

Refer to footnote #8: “While it is not possible to specify a quantitative volume of remaining drug product that would generally be considered significant, volumes remaining that could provide a second dose, or would encourage pooling for a second dose, would be considered excessive.”
Injections
- Solution, Emulsion, Suspension

- Small volume injections (label size < 100 mL)
- Single-use and Multiple-use
- In general,
  - Use [labeled size + recommended excess volume per USP<1151>] as the lower tolerance (action) limit is acceptable; for certain specific occasions, may require an extractable volume study to confirm;
  
  - If the lower tolerance (action) limit is set less than recommended volume, justification needs to be provided to demonstrate that withdrawal and administration of the labeled volume can be achieved;

  - Establish reasonable target fill volume and Upper (alert & action) limits based on common industry practice.
**Injections – cont’d**

- Solution, Emulsion, Suspension

**Case 1: Label size = 10.0 mL per vial**

![Table](image)

**Case 2: Label size = 20.0 mL per vial**

Set target limit as 21.10 mL, ± 0.21 mL (1%) as control limit and ± 0.42 mL (2%) as tolerance limit

<table>
<thead>
<tr>
<th>Vial filling</th>
<th>Fill weight control</th>
<th>Target fill weight (g) = 21.10 mL x weight per mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency: once in 45 minutes</td>
<td>Target fill weight (g) = 21.10 mL x weight per mL</td>
<td></td>
</tr>
</tbody>
</table>

Control upper limit = 21.31 mL x weight per mL  
Control lower limit = 20.89 mL x weight per mL  
Tolerance upper limit = 21.52 mL x weight per mL  
Tolerance lower limit = 20.68 mL x weight per mL
Case 3: Viscous liquid, Label size = 10.0 mL

Proposed IPC:
The applicant proposes that higher fill volume (10.7 mL) will be as per USP recommended excess fill for viscous liquids and the lower fill volume (10.2 mL) will be based on the average residual volume in the vial for the 10 ml labeled size.

Supporting evidence:
The applicant performed extractable volume study in their Pharmaceutical development report. Data appeared to be acceptable, but no information regarding the testing procedure was provided.

Information request:
Please provide the gauge and length of the needle used for the extractable volume study.
Injections
– Lyophilized powder

➢ Prior to lyophilization, or at vial filling stage, do we have to include excess volume?

✓ Not necessarily, it depends on the actual drug substance content in RLD;
✓ We suggest you individually assay the fresh samples of RLD. Your generic drug’s range of variation should be in agreement with that of RLD;
✓ If the product is subject to degradation and fresh RLD samples cannot be obtained, then excess volume should be justified and USP<1151> may be used as reference.

➢ The finished product needs to comply with USP<905> - Weight Variation.
In general,

- No need to consider overfill to fulfill recommended excess volume per USP<1151>;

- Standard In-Process Weight Control is acceptable, and finished product needs to comply with USP<905>:
  - Single component, use weight variation;
  - Multiple components, use content uniformity;

- When an API loading is low (≤5.0%) in the drug product, stratified sampling needs to be considered for In-Process Control.
  - https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm#18
In general,

- Multiple-dose, imprecisely applied;
- USP<905> is not applicable;
- Maximum filled weight is not a concern;
- Needs to establish an IPC on fill weight so as to comply with USP<755> for the finished product.

However, USP<905> is applicable for topical dosage forms:

- Intended for systemic delivery;
- Where tight control of the dose is necessary to limit local irritation or undesired systemic exposure;
- Packaged in single-unit containers.
Topical Semi-Solid Case Study

Background:
The generic drug product is a gel packaged in single dose laminate tubes containing a nominal fill weight of 0.47 g, with a deliverable weight of 0.25 g; It uses containers of the same volumetric size and design as the RLD

In-Process Control on Fill Weight

<table>
<thead>
<tr>
<th>In-Process Test</th>
<th>Acceptance Criteria</th>
<th>Exhibit Batch #1</th>
<th>Exhibit Batch #2</th>
<th>Exhibit Batch #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fill Weight</td>
<td>Target: 0.47 g</td>
<td>Mean = 0.55g</td>
<td>Mean = 0.55g</td>
<td>Mean = 0.54g</td>
</tr>
<tr>
<td></td>
<td>SD = 0.03 g</td>
<td>SD = 0.03 g</td>
<td>SD = 0.02 g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reject Limits: 0.47 – 0.70 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min. = 0.48 g</td>
<td>Min. = 0.48 g</td>
<td>Min. = 0.49 g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max. = 0.68 g</td>
<td>Max. = 0.68 g</td>
<td>Max. = 0.63 g</td>
<td></td>
</tr>
</tbody>
</table>

IR#1
We acknowledge that you have proposed in-process control limit for target fill weight of the drug product as 0.47 g – 0.70 g. However, the fill weight of the upper limit, 0.70 g, has 48.9 % overfill of the labeled amount of 0.47 g. The upper limit seems too high and may result in significantly higher deliverable weight than what is indicated in the label. We recommend tightening the fill weight limit. In addition, we recommend that you perform deliverable weight test and demonstrate the result is comparable to RLD.
Applicant’s response

1. Delivered weight

<table>
<thead>
<tr>
<th>Description</th>
<th>Average delivered weight (g)</th>
<th>Average delivered of label claim %</th>
<th>Average fill weight (g)</th>
<th>Average fill of label claim %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLD product</td>
<td>0.21</td>
<td>83</td>
<td>0.48</td>
<td>103</td>
</tr>
<tr>
<td>ANDA product</td>
<td>0.28</td>
<td>112.8</td>
<td>0.55</td>
<td>116.1</td>
</tr>
</tbody>
</table>

2. Justification on upper limit

- PI indicates that the patient should squeeze *only enough gel* from the tube to cover the affected area onto a fingertip and then spread the gel evenly over *only the skin area to be treated*;
- Any excess fill weight will remain unused in the tube or will be washed away from a patient’s finger;
- The minimum fill test included in the drug product specification has the requirement for the average fill weight to be not less than the label claim *but has no requirement for the maximum allowed*. The fill weight range of 0.47 g - 0.70 g was designed to pass this requirement.

*Why does the applicant prefer to fill more in the tube?*
**Topical Semi-Solid – cont’d**

**Case Study**

<table>
<thead>
<tr>
<th>Product</th>
<th>Mean fill weight (g)</th>
<th>SD (σ)</th>
<th>3σ</th>
<th>Mean - 3σ</th>
<th>Mean</th>
<th>Mean + 3σ</th>
<th>Mean + 7σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhibit Batch #3</td>
<td>0.54</td>
<td>0.023</td>
<td>0.07</td>
<td>0.47</td>
<td>0.54</td>
<td>0.61</td>
<td>0.70</td>
</tr>
</tbody>
</table>

![Diagram of process average and ±3σ limits](image)
USP <755> Minimum fill

……Record the volume of the contents of each of the 10 containers. The average net content of the 10 containers is not less than the labeled amount, and *the net content of any single container is not less than 90% of the labeled amount* where the labeled amount is 60 g or 60 mL or less, or not less than 95% of the labeled amount where the labeled amount is more than 60 g or 60 mL but not more than 150 g or 150 mL. If this requirement is not met……

<table>
<thead>
<tr>
<th>Product</th>
<th>Mean fill weight (g)</th>
<th>SD (σ)</th>
<th>3σ</th>
<th>Mean - 3σ</th>
<th>Mean / Target</th>
<th>Mean + 3σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch in the future</td>
<td>0.023</td>
<td>0.07</td>
<td></td>
<td>0.43</td>
<td>0.50</td>
<td>0.57</td>
</tr>
</tbody>
</table>

### Lower limit

0.47 x 0.9 = 0.43 g
IR #2:

Patient safety needs to be considered in case of patient’s using maximum delivered amount from a tube. Therefore, your proposed fill weight range with an upper limit of 0.70 g is not adequately justified. We recommend that you establish an alert lower limit of the fill weight based on the requirement for the net content of any single container per USP<755>. Please use common industrial practice to establish a proper range for the fill weight and demonstrate the finished product is able to meet the requirements per USP<905>. Otherwise, please provide data to demonstrate that your product, with the maximum filled amount of 0.70 g/tube, has no additional adverse impact on patient safety compared with the RLD.
Conclusions

- Controls of fill amount for parenteral injections, including solution, emulsion, suspension, lyophilized powder for injection, and sterile powder for injection were discussed;
- Proper use of USP<1151> is critical to establish a suitable in-process fill range so as to avoid under-fill or over-fill;
- The in-process control of fill amount for topical and ophthalmic semisolids should ensure the finished product be able to meet USP<755>;
- For certain specific semisolids, the upper limit of fill amount can be critical and USP<905> applies;
- Appropriate in-process control would improve the drug product quality, help you cut the cost and facilitate more first round approvals. 😊😊😊
Acknowledgement

• Nallaperumal Chidambaram (OPF)
• Naiqi Ya (OPF)
• Robert Iser (OPF)
• Erin Kim (OPF)
• Sydney Choi (OPF)
• Kejun Chen (OPF)
• Richard Chang (OLDP)
Backup slides
# Topical Semi-Solid Case Study

<table>
<thead>
<tr>
<th>Product</th>
<th>Mean fill weight (g)</th>
<th>SD (σ)</th>
<th>3σ</th>
<th>Mean - 3σ</th>
<th>Mean</th>
<th>Mean + 3σ</th>
<th>Mean + 7σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhibit Batch #3</td>
<td>0.54</td>
<td>0.023</td>
<td>0.07</td>
<td>0.47</td>
<td>0.54</td>
<td>0.61</td>
<td>0.70</td>
</tr>
</tbody>
</table>

**This must be the right solution!**