POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Allowable Excess Volume/Content in Injectable Drug and Biological Products

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PURPOSE

This MAPP describes the policies and procedures for the Office of Pharmaceutical Quality (OPQ) product quality assessors to ensure consistent assessment of excess **volumes**[1] in injectable[2] drug[3] products packaged into vials.[4]

This MAPP addresses both **liquid** as well as solid drug products that require reconstitution/constitution and describes the policies and procedures to be used by OPQ product quality assessors to ensure that the excess liquid or solids filled into vials for

[1] Terms defined in the glossary are bolded at first use.
[2] In this MAPP, injectable dosage forms include, but are not limited to, sterile solutions, suspensions, emulsions, and powders for solution and suspension (including liposomes).
[3] The term "drug" used throughout this MAPP refers to drugs, including biological products.
[4] The term "vial" used throughout this MAPP refers to both single-dose and multiple-dose vials, and ampule package types.

injectable drug products is sufficient to allow for withdrawal and administration of the **net container content** of the drug product.[5]

This MAPP also provides procedures for obtaining information in applications (e.g., justifications and documentation) in support of excess volumes for **single-dose and multiple-dose injectable drug products** submitted in new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs), and applicable supplements to these applications. The MAPP also includes expectations that should be communicated to NDA, BLA, and ANDA applicants, and investigational new drug (IND) sponsors as early as possible.

This MAPP is specific to vials and does not address injectable drug products in other packaging types (e.g., prefilled syringe package systems, cartridges for automatic injectors, and intravenous infusion bags) or noninjectable drug products, because there may be unique considerations for these packaging configurations.

BACKGROUND

This MAPP conveys 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). The guidance provides recommendations to industry on two topics:

(1) Allowable excess volumes of injectable drug products filled into vials, and

(2) Appropriate drug product net container content sizes (i.e., labeled vial fill sizes) for injectable drug products.[6]

Misuse of injectable drug products filled into vials, including unsafe handling and injection techniques, has led to drug product contamination and an increased risk of bloodborne illness transmission between patients. A factor that contributes to unsafe handling and injection practices by consumers and healthcare providers is an allowance for an excess volume in vials that results in leftover drug product that can be used as a partial or second dose.

If the contents of the vial do not allow delivery of the labeled dose, the healthcare provider or consumer would have to underdose or use additional vials to administer the

[5] In this MAPP, mg/mL is used as a common expression of concentration and strength. However, the principles of this MAPP apply to all units of concentration and expressions of strength for the injectable products that are in scope of this MAPP.

[6] A separate MAPP 5019.2 *Assessment of the Appropriate Net Container Content for Injectable Drug Products* is currently in development and will cover the assessment and documentation of net container content(s) for injectable drug products.

labeled dose. Vials containing insufficient volumes can also cause problems during patient administration.

POLICY

A. Net Container Content

(1) The Office of Pharmaceutical Quality (OPQ) quality assessor will:

a. Ensure that the minimum fill volume/content contains sufficient excess drug product to allow for withdrawal and administration of the net container content for a liquid drug product and a solid drug product following reconstitution/ constitution.[7] This applies to both single-dose and multiple-dose vials.

b. Ensure that the maximum fill volume for a liquid drug product or the total volume of a reconstituted solid drug product is not unreasonably large[8] such that it would allow a second dose to be withdrawn or would encourage pooling of one or more vials to produce a second dose. For both single-dose and multiple-dose vials, the maximum fill volume should not exceed the acceptance criterion for the **gross content** per vial.

c. Evaluate the minimum fill volume for a liquid drug product to ensure that each vial contains sufficient excess volume in accordance with the United States Pharmacopeia (USP) General Chapter <1151> *Pharmaceutical Dosage Forms* recommendations.[9]

d. Ensure that each vial of a liquid drug product meets the net container content (e.g., mL per vial) in the labeling. The net container content on the label will be met if the minimum fill volume conforms to USP General Chapter <697> *Container Content for Injections*.[10]

[7] For solid drug products, the minimum fill volume/content should be adjusted to provide not less than 100 percent of the net container content (e.g., mg per vial).
[8] While it is not possible to specify a quantitative volume of remaining drug product that would generally be considered unreasonably large, volumes remaining that could provide a second dose, or would encourage pooling for a second dose, would be considered unreasonably large.
[9] Typically, USP General Chapters titled with numbers above <1000> are considered informational and not requirements. However, in this case, because FDA's regulations, i.e., 21 CFR 201.51(g), specifically require adherence to the USP recommendations on this topic, the recommendations in USP General Chapter <1151> for excess volume of injectable drug products are considered requirements.
[10] USP General Chapters numbered below 1000 are requirements only if referenced in a USP/NF monograph or made applicable through USP General Notices for products with USP/NF monographs. Otherwise they are general recommendations. Alternative methods and procedures must be validated and demonstrated to be suitable for intended use (see 21 CFR 211.165(e) and 211.194(a)(2)). Specifically, this applies to references to USP General Chapters <697> and <905> throughout this MAPP.

e. Ensure that each vial of a solid drug product meets the net container content (e.g., mg per vial) in the labeling. The net container content on the label will be met if:

i. the total volume after reconstitution conforms to USP General Chapter <697> following the reconstitution/constitution procedure in the labeling; and,

ii. the labeled concentration following the reconstitution/constitution procedure as described in the labeling[11] is met when the vial is filled with the minimum fill (volume or weight) of the bulk drug product.

(2) The Office of Lifecycle Drug Products (OLDP) and the Office of Biotechnology Products (OBP) quality assessors will:

a. Follow this MAPP for applicable supplements to an NDA, ANDA, or BLA.

b. Ensure that the concentration of a liquid drug product and the reconstituted/ constituted concentration of a solid drug product for an ANDA are the same as that described in the labeling for the reference listed drug (RLD).[12]

c. Ensure that the strength for a 351(k) BLA drug product is the same as that of the reference product.[13]

B. Drug Product Concentration

The OPQ quality assessor will:

a. Ensure that, for liquid drug products, the bulk drug product is formulated to provide 100 percent of the labeled concentration (mg per mL)[14] prior to filling the vials.

b. Ensure that, for drug products supplied as a solid, the drug product filled into vials at the minimum fill amount will meet the labeled concentration (mg per mL)[12,15]

[11] 21 CFR 201.57(c)(3)(iv).
[12] 21 CFR 314.94(a)(6).
[13] 42 U.S.C. section 262(k)(2)(A)(i)(IV). For additional information about the Agency's current thinking on the implementation of this regulation see QA.I.12 in FDA draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Rev. 3)* (September 2021); when finalized, this guidance will reflect the Agency's current thinking on the topics therein.
[14] In general, 21 CFR part 211 applies to all finished pharmaceuticals unless a more specific product standard is established by USP. For compendial products, see USP General Notices, 4.10.20. Acceptance Criteria: An official product shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label. For noncompendial products, see 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.
[15] Information about the reconstitution instructions including the concentration following reconstitution/ constitution should appear on the container label as long as space permits and in the Dosage and Administration section of the labeling.

following reconstitution/constitution. The concentration should also be evaluated at the maximum fill amount to ensure that final drug concentration following reconstitution/constitution will not exceed assay or protein concentration limits.

C. Gross Content per Vial

The OPQ quality assessor will:

a. Ensure that the minimum fill volume/content is not less than the lower limit of the acceptance criterion for the gross content per vial.

b. Ensure that the maximum fill volume/content does not exceed the upper limit of the acceptance criterion for the gross content per vial.

c. Ensure that the upper limit of the acceptance criterion for the gross content for a single-dose or multiple-dose vial for a liquid drug product is not unreasonably large such that it may result in misuse of the leftover drug product as a partial or second dose.

d. Ensure that at the upper limit of the acceptance criterion for the gross content for a single-dose or multiple-dose vial for a solid drug product, the total volume following reconstitution/constitution is not unreasonably large such that it may result in misuse of the leftover drug product as a partial or second dose.

D. Quality Control Tests

The OPQ quality assessor will:

a. Ensure that the following tests are included in the drug product specification for a liquid drug product:

i. **Deliverable volume** (mL per vial) determined by USP General Chapter <697>

ii. Assay or protein concentration (e.g., mg per mL)

iii. Gross content in mL per vial of the drug product for NDAs, ANDAs, and BLAs.

iv. Uniformity of dosage units determined by USP General Chapter <905> *Uniformity of Dosage Units* for suspensions, emulsions, and injectable drug products where segregation may occur during the filling operation.[16,17]

b. Ensure that the following tests are included in the drug product specification for a solid drug product requiring reconstitution/constitution:

i. Uniformity of dosage units determined by USP General Chapter <905>[18]

ii. Net container content (mg per vial)[19]

iii. Gross content of the drug substance per vial (NDA/ANDAs), or gross content of the protein content per vial (BLAs)

iv. Following reconstitution/constitution according to the labeled instructions:

a) Deliverable volume (mL per vial) determined by USP General Chapter <697>

b) Assay or protein concentration (e.g., mg per mL)

RESPONSIBILITIES

Quality Assessor [20]

Deliverable Volume, Net Container Content, Assay or Protein Concentration, Gross Content per Vial, and Uniformity of Dosage Units

For NDAs, ANDAs, BLAs, and their applicable supplements, the evaluation of the deliverable volume, net container content, assay or protein concentration, content uniformity for liquid (suspensions, emulsions, and injectable drug products where segregation may occur during the filling operation) and solid drug products, and gross content per vial in the drug product specification will be performed by the quality assessors in Office of New Drug Products (ONDP), OLDP, and OBP.

[16] Content uniformity testing for suspensions and emulsions is performed in accordance with USP General Chapter <905>, Table 1, "Others".
[17] In order for 21 CFR 211.110(a) and 21 CFR 211.165(d) to be met, conformance of a sample to USP <905> is appropriate as an indicator of acceptable content uniformity for a batch only in the presence of a statistical sampling plan. Depending on the complexity of the dosage form, additional in-process controls may also be needed to ensure content uniformity. Also see USP General Notices, 3.10. for the applicability of a statistical sampling plan.
[18] See footnote 17.
[19] Refer to Policy section A(1)e for criteria to meet net container content for a solid drug product, which indicates that this term is expressed in weight per vial.
[20] See tables 1 and 2 in Attachment 1.

Manufacturing Process - Fill Amounts[21] and Bulk Concentration

(1) For original NDAs and ANDAs, the evaluation of the minimum and maximum fill amounts for liquid drug products and drug products requiring reconstitution/constitution is performed by Office of Pharmaceutical Manufacturing Assessment (OPMA). For ANDA and NDA supplements, the evaluation of the minimum and maximum fill amounts for liquid drug products and drug products requiring reconstitution/constitution is performed by OLDP with technical assistance from OPMA, as needed. For BLAs and their applicable supplements, this evaluation is performed by OBP.

(2) For original NDAs and ANDAs, the evaluation of the bulk drug product concentration prior to filling in vials is performed by OPMA. For ANDA and NDA supplements, the evaluation of the bulk drug product concentration prior to filling in vials is performed by OLDP with technical assistance from OPMA, as needed. For BLAs and their applicable supplements, this evaluation is performed by OBP.[22]

PROCEDURES

A. Net Container Content

(1) Liquid Drug Products

a. The ONDP, OLDP, and OBP quality assessor will:

Ensure that the volume of a liquid drug product meets the net container content (mL per vial) of the drug product. This includes evaluating data from USP General Chapter <697> testing to ensure that each container of an injection drug product contains sufficient excess volume to allow withdrawal and administration of the labeled quantity of drug.

b. The OPMA and OBP quality assessor will:

[21] In this MAPP, fill volume can also be determined by weight based on the density of the drug product. In some cases (e.g., formulations containing unique polymers) where the bulk density is defined as an established condition, the range of bulk density should ensure that all the limits of fill volume, as defined in this MAPP, are met.

[22] See Attachment 1 for Tables 1 and 2 for assessor responsibilities for solutions, suspensions, or emulsions and reconstitution/constitution.

Evaluate the minimum fill volume to ensure that each vial of drug product contains sufficient excess volume in accordance with the USP General Chapter <1151>[23] recommendations and verified by withdrawal studies.[24]

i. If the excess volume does not meet USP General Chapter <1151>, confirm data from the withdrawal studies is submitted along with adequate justification to ensure that the net container content is met. Confirm the documentation of any necessary justification and data from studies performed is included in the appropriate sections of the eCTD: sections 3.2.P.1. *Description and Composition of the Drug Product* and 3.2.P.2.2.1. *Formulation Development*.

ii. Mobile liquids are not required to provide any evidence of viscosity. If viscosity is not claimed, the quality assessor can assume that the drug product is mobile and follow the excess volume recommendations for mobile liquids in USP General Chapter <1151>.

iii. If USP General Chapter <1151> excess volume for viscous liquids is used, confirm the applicant provides the results of viscosity measurements in the appropriate sections of the eCTD: 3.2.P.2. *Pharmaceutical Development.*

(2) Solid Drug Products

a. The ONDP, OLDP, and OBP quality assessor will:

Ensure that, following reconstitution/constitution of the drug product per the labeling instructions, the total reconstituted volume conforms to USP General Chapter <697>.

b. The OPMA and OBP quality assessor will:

i. Evaluate the minimum fill amounts of a solid drug product to ensure that each vial of drug product contains enough excess solid to allow for withdrawal and administration of the net container content of drug after reconstitution/ constitution following the labeled procedure.[25]

[23] If the labeling specifies the number of doses in a multiple-dose vial (e.g., 10 x 1 mL doses), the excess volume may be more than what is specified in USP General Chapter <1151>. The excess volume needed to withdraw the number of doses specified in the labeling should be verified by withdrawal studies.
[24] Development studies that correlate drug product fill volumes to the administrable volume, following a scientifically sound approach, which will ensure conformance with USP General Chapter <697> during batch release without an excessive volume in the vial that could provide a second dose, or would encourage pooling of two or more vials to produce a second dose.
[25] For a solid drug product, the assessment of the minimum and maximum fill volumes or weights of bulk product (i.e., solution or solid prior to filling) should confirm the applicant has accounted for assay or protein content variability of bulk product, if there is any.

ii. Confirm the documentation of the proposed excess volume after constitution/reconstitution, including any necessary justification and data from studies performed, is included in the appropriate sections of the eCTD: sections 3.2.P.1. *Description and Composition of the Drug Product*, 3.2.P.2.2.1. *Formulation Development*, 3.2.P.2.3. *Manufacturing Process Development*, 3.2.P.3.3. *Description of Manufacturing Process and Process Controls*, 3.2.P.3.4. *Controls of Critical Steps and Intermediates*, and 3.2.R. *Regional Information - Executed Batch Record*.

B. Assay or Protein Concentration

(1) Liquid Drug Products

a. The ONDP, OLDP, and OBP quality assessor will:

Ensure the drug product filled into vials will meet the concentration (mg/mL) on the label as determined by assay or protein concentration.

b. The OPMA and/or OBP quality assessor will:

Ensure that the concentration of the bulk solution is formulated with the intent to provide 100 percent of the labeled concentration (mg per mL determined by assay or protein concentration) prior to filling in the vials.[26]

(2) Solid Drug Products

a. The ONDP, OLDP, and OBP quality assessor will:

Ensure that after reconstitution/constitution, the drug product filled into vials at the minimum fill weight/volume represents the labeled concentration (e.g., mg/mL).

b. The OPMA and/or OBP quality assessor will:

Evaluate the maximum bulk solution concentration and maximum fill weight/volume to ensure that final drug concentration following reconstitution/ constitution will not exceed assay or protein concentration limits.

C. Gross Content per Vial

Liquid Drug Products and Solid Drug Products Requiring Reconstitution/Constitution

[26] In accordance with 21 CFR 211.110(b), in-process testing for concentration should be performed considering product attributes, failure mode potential, and the control strategy. Exception(s) may be allowed for low-risk liquid drug products for which the concentration is solely affected by the addition of the ingredients and there is no risk of the concentration changing downstream in the manufacturing operation (e.g., filtration).

a. The ONDP, OLDP, and OBP quality assessor will:

Ensure the lower and upper limits of the gross content specification consider the excess amount in order to deliver the net container content and limit leftover drug product that can be used as a partial or second dose,[27] respectively. The lower and upper limits can be calculated using the following formulas:

Liquid drug product

- Net container content + required excess volume per USP <1151> (mL) = lower limit of the acceptance criterion of gross content test

- Maximum fill volume (mL) = upper limit of the acceptance criterion of gross content test

Solid drug product

- Labeled concentration (mg/mL) after reconstitution/constitution x total volume after reconstitution/constitution = lower limit of the acceptance criterion of gross content test.

- Labeled concentration (mg/mL) after reconstitution/constitution x upper limit of assay or protein specification (e.g., 110%) x total volume after reconstitution/constitution = upper limit of the acceptance criterion of gross content test.

b. The OPMA and OBP quality assessor will:

i. Ensure that the minimum fill volume/content should not be less than the lower limit of the acceptance criterion for the gross content per vial.

ii. Ensure that the maximum fill volume/content should not exceed the upper limit of the acceptance criterion for the gross content per vial.

iii. Communicate with the applicant to mitigate the risks, as applicable, if the maximum fill volume/content is considered excessive.

c. The ONDP, OLDP, and OBP quality assessor will:

[27] Maximum fill volume for a liquid drug product and reconstituted volume for a solid drug product should be determined by the quality assessor in ONDP, OLDP, OBP, and, if appropriate, the Office of Surveillance and Epidemiology (OSE). OPMA should provide guidance on manufacturing limitations for NDA/ANDAs, as needed.

i. Ensure that the upper limit of the acceptance criterion for gross content[28] for a single-dose vial for a liquid drug product should not be unreasonably large, which would allow a second dose or would encourage pooling of one or more vials to produce a second dose.

ii. Ensure that the total volume of the reconstituted drug product for a single-dose vial for a solid drug product should not be unreasonably large, which would allow a second dose or would encourage pooling of one or more vials to produce a second dose.

iii. Ensure that the maximum fill volume for a multiple dose vial for a liquid drug product or following reconstitution/constitution of a solid drug product should not be unreasonably large.

D. Uniformity of Dosage Units

Liquid Drug Products and Solid Drug Products Requiring Reconstitution/Constitution

The ONDP, OLDP, and OBP quality assessor will:

a. Ensure the liquid drug product supplied as a suspension, emulsion, or injectable drug product where segregation may occur during the filling operation conforms to USP General Chapter <905>.

b. Ensure the solid drug product conforms to USP General Chapter <905>.

E. Communication with Applicants and IND Sponsors

The ONDP, OBP, and OLDP quality assessor will communicate the following to NDA, ANDA, and BLA applicants as soon as possible, IND sponsors for products intended to be submitted as an NDA or 351(a) BLA as early as reasonable but no later than phase 2; if applicable, to IND sponsors for products intended to be submitted as 351(k) BLAs no later than initiation of a comparative clinical study:

a. The net container content expectations:

i. For an injectable drug product filled as a liquid, to conform to deliverable volume by USP General Chapter <697>.

ii. For a solid drug product following reconstitution/constitution, to conform to deliverable volume by USP General Chapter <697> and to meet the labeled concentration at the minimum fill (volume or weight) of the drug product.

[28] OPMA can provide feedback to OLDP/ONDP on the upper limit of the gross content specification from a manufacturing perspective.

iii. For liquid drug product or their applicable supplements, to meet the USP General Chapter <1151> recommendations.

b. The recommendations regarding in-process testing for bulk assay or protein concentration.

c. For liquid drug products supplied as a suspension emulsion or injectable drug product, where segregation may occur during the filling operations, to conform to uniformity of dosage units by USP General Chapter <905>.

d. For solid drug product, to conform to uniformity of dosage units by USP General Chapter <905>.

e. The tests listed in table 3 in Attachment 2 should be included in the drug product specification.

REFERENCES

1. 21 CFR 201.51(g) Declaration of net quantity of contents
2. 21 CFR 201.57(c)(3)(iv) 2 Dosage and administration
3. 21 CFR 314.94(a)(6) Route of administration, dosage form, and strength
4. 42 U.S. Code section 262(k)(2)(A)(i)(IV) Licensure of biological products as biosimilar or interchangeable
5. 21 CFR 211.101(a) Charge-in of components
6. 21 CFR 211.165(e) Testing and release for distribution
7. 21 CFR 211.194(a)(2) Laboratory records
8. 21 CFR 211.110(a) and (b) Sampling and testing of in-process materials and drug products
9. 21 CFR 211.165(d) Testing and release for distribution
10. USP General Chapter <1> *Injections and Implanted Drug Products (Parenterals) – Product Quality Tests*
11. USP General Chapter <659> *Packaging and Storage Requirements*
12. USP General Chapter <697> *Container Content for Injections*
13. USP General Chapter <905> *Uniformity of Dosage Units*
14. USP General Chapter <911> *Viscosity – Capillary Methods*
15. USP General Chapter <1151> *Pharmaceutical Dosage Forms*
16. USP General Notices and Requirements, 3. CONFORMANCE TO STANDARDS, 3.10. Applicability of Standards
17. USP General Notices, 4.10.20. Acceptance Criteria
18. USP General Notices 6.30. Alternative and Harmonized Methods and Procedures
19. FDA guidance for industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable drug and Biological Products* (June 2015)
20. FDA guidance for industry *Good ANDA Submission Practices* (September 2018)

21. FDA guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products* (April 2005)
22. FDA guidance for industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018)
23. FDA guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Rev. 3)* (September 2021)
24. MAPP 5019.2 *Assessment of the Appropriate Labeled Content for Injectable Drug Products* (in development)

DEFINITIONS

Deliverable volume: Refers to the 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*.

Gross content: The term refers to: (1) for a liquid drug product, the total volume (e.g., mL) of drug product filled into a vial including the excess volume, and (2) for a solid drug product, the total amount (e.g., mg) of drug substance or protein content filled into a vial including the excess amount.

Liquid: Refers to solutions (including those products that are filled as solutions and are manipulated to form a different dosage form prior to administration, i.e., foams, suspensions, or emulsions).

Net container content: (a.k.a. labeled vial fill sizes) The term refers to net quantity of contents as described in 21 CFR 201.51(g). The net container content shall appear as a distinct item on the label. For injectable drug products that are marketed as: 1) liquids – the net container content will be expressed as a measure of volume (e.g., mL); 2) solids – the net container content will be expressed as a measure of weight (e.g., mg).

Single-dose and multiple-dose injectable drug products: For the definition of single dose and multiple-dose (aka multi-dose), see FDA guidance for industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) and the United States Pharmacopeia (USP) General Chapter <659> *Packaging and Storage Requirements*.

Volume: Refers to liquid in the vial as packaged or liquid in the vial after reconstitution/constitution.

EFFECTIVE DATE

This MAPP is effective on January 28, 2022.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
7/18/2012	N/A	Interim MAPP
1/28/2022	Rev 1	Revised and updated to a Standard MAPP

ATTACHMENT 1

Table 1: Quality assessor responsibilities for injectable drug products that are solutions, suspensions, or emulsions

OPQ Office	Deliverable volume (mL per vial) by USP <697> testing[29]	Assay or protein concentration (mg per mL)	Gross content of drug product (mL per vial)[30]	Bulk concentration prior to filling (mg per mL)[31]	Uniformity of Dosage Units by USP <905> testing[32]	USP <1151> compliance	Minimum and maximum fill volume
ONDP	X	X	X		X		
OLDP	X	X	X	X[33]	X		X[34]
OBP	X	X	X	X	X	X	X
OPMA				X		X	X

Table 2: Quality assessor responsibilities for injectable drug products that require reconstitution/constitution

OPQ Office	Net container content (mg per vial)	Labeled concentration after reconstitution/ constitution (mg per mL)	Gross content of drug substance or protein content (e.g., mg per vial)	Bulk concentration prior to filling (mg per mL)[35]	Uniformity of Dosage Units by USP <905> testing	Deliverable volume by USP <697> testing after reconstitution/ constitution	Minimum and maximum fill amounts
ONDP	X	X	X		X	X	

[29] Compliance with this test will assure net container content is met.
[30] OPMA can provide feedback to OLDP/ONDP on the upper limit of the gross content specification from a manufacturing perspective.
[31] See footnote 26 regarding in-process testing of the bulk concentration.
[32] Applies to suspensions, emulsions, and injectable drug products where segregation may occur during the filling operation.
[33] For ANDA and NDA supplements, the evaluation of the bulk concentration prior to filling for liquid drug products is performed by OLDP/DPMA with technical assistance from OPMA, as needed.
[34] For ANDA and NDA supplements, the evaluation of the minimum and maximum fill volume for liquid drug products is performed by OLDP/DPMA with technical assistance from OPMA, as needed.
[35] In-process testing for bulk concentration should be performed to adjust fill volume/content to meet net container content requirements after reconstitution of the drug product. Alternate controls to an in-process bulk concentration or protein content test may be acceptable if the applicant can demonstrate through process and product knowledge, and the totality of controls employed, that compliance with 21 CFR 201.51(g) can be achieved.

OPQ Office	Net container content (mg per vial)	Labeled concentration after reconstitution/ constitution (mg per mL)	Gross content of drug substance or protein content (e.g., mg per vial)	Bulk concentration prior to filling (mg per mL)[35]	Uniformity of Dosage Units by USP <905> testing	Deliverable volume by USP <697> testing after reconstitution/ constitution	Minimum and maximum fill amounts
OLDP	X	X	X	X[36]	X	X	X[37]
OBP	X	X	X	X	X	X	X
OPMA				X			X

[36] For ANDA and NDA supplements, the evaluation of the bulk concentration prior to filling for drug products requiring reconstitution/constitution is performed by OLDP/DPMA with technical assistance from OPMA, as needed.

[37] For ANDA and NDA supplements, the evaluation of the minimum and maximum fill volume for drug products requiring reconstitution/constitution is performed by OLDP/DPMA with technical assistance from OPMA, as needed.

ATTACHMENT 2

Table 3: Drug product tests for liquid and solid drug products requiring reconstitution/constitution

Tests	**Liquid drug product (solutions, suspensions, and emulsions)**	**Solid drug products**
Container Content by USP <697>	X	X (after reconstitution/ constitution)
Assay or Protein Concentration	X	X (after reconstitution/ constitution)
Gross Content per vial	X	X
Uniformity of Dosage Units by USP <905>	X (for suspensions, emulsions, and injectable drug products where segregation may occur during the filling operation)	X