
Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products

Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**June 2015
Pharmaceutical Quality/CMC**

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1 **Allowable Excess Volume and Labeled Vial¹ Fill Size in Injectable**
2 **Drug and Biological Products**
3 **Guidance for Industry²**
4

5
6 This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on
7 this topic. It does not establish any rights for any person and is not binding on FDA or the public. You
8 can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.
9 To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the
10 title page.
11

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13
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15 **I. INTRODUCTION**
16

17 This guidance provides the pharmaceutical industry with the Center for Drug Evaluation and
18 Research's (CDER's) and the Center for Biologics Evaluation and Research's (CBER's) current
19 thinking on allowable excess volume and labeled vial fill size in injectable drug and biological
20 products. It replaces the draft of the same name that was published on March 14, 2014 (79 FR
21 14517). Specifically, the guidance clarifies the FDA regulatory requirements and
22 recommendations pertaining to allowable excess volume in injectable vials and describes when
23 justification is needed for a proposed excess volume in these injectable drug³ products. This
24 guidance also discusses the importance of appropriate fill volumes for injectable drug products
25 and recommends that labeled vial fill sizes be appropriate for the intended use and dosing of the
26 drug product.
27

28 This guidance addresses withdrawable volume and labeled vial fill size for injectable drug
29 products that are packaged in vials and ampules, including products that require reconstitution.
30 It does not address injectable drug products in other packaging types (e.g., prefilled syringe
31 package systems and intravenous infusion bags) or noninjectable products, because there may be
32 unique considerations for these packaging configurations. The recommendations in this
33 guidance apply to new drug applications (NDAs), abbreviated new drug applications (ANDAs),
34 biologics license applications (BLAs), as well as supplements or other changes to these
35 applications for new packaging or other changes that may affect the fill volume.
36

37 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
38 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
39 as recommendations, unless specific regulatory or statutory requirements are cited. The use of

¹ The term *vial* used throughout this guidance refers to both vial and ampule package types.

² This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in collaboration with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

³ The term *drug* used throughout this guidance refers to drugs, including biological drug products.

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40 the word *should* in Agency guidances means that something is suggested or recommended, but
41 not required.

42

43 **II. BACKGROUND**

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45 Injectable vial misuse, including unsafe handling and injection techniques, has led to vial
46 contamination and an increased risk of bloodborne illness transmission between patients.^{4,5}
47 Inappropriate excess volume and labeled vial fill sizes are two factors that may contribute to
48 unsafe handling and injection practices by consumers and health care providers. FDA has been
49 concerned about these issues and is publishing this guidance to clarify its regulatory
50 requirements and recommendations.

51

52 **III. OVERVIEW**

53

54 **A. Allowable Excess Volume**

55

56 The United States Pharmacopeia (USP) General Chapter <1> *Injections* provides that each
57 container of an injectable product is filled with a volume that slightly exceeds the content
58 indicated in the labeling.⁶ The excess volumes are meant to be sufficient to permit withdrawal
59 and administration of the labeled volumes. FDA regulations at 21 CFR 201.51(g) provide that
60 for drugs in ampules or vials that are intended for injection, the declaration of net quantity of
61 contents on the label is considered to express the minimum quantity of contents and further
62 requires that variation above the stated measure must comply with the excess volumes set forth
63 in USP. USP General Chapter <1151> *Pharmaceutical Dosage Forms* provides excess volume
64 recommendations for mobile and viscous liquids in a range of fill volumes, noting that the excess
65 volumes recommended are usually sufficient to permit withdrawal and administration of the
66 labeled volumes. Allowable excess volume may also be referred to as “overfill,” but should not
67 be confused with “overage,” which is addressed in a separate guidance.⁷ Generally, an applicant
68 should not declare the amount of overfill on the container label.

69

⁴ Perz J, Thompson N, Schaefer M, Patel P, 2010, US Outbreak Investigations Highlight the Need for Safe Injection Practices and Basic Infection Control, *Clinics in Liver Disease*, 14:137-151.

⁵ Centers for Disease Control and Prevention, Injection Safety, Safe Injection Practices to Prevent Transmission of Infections to Patients, *2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings* (http://www.cdc.gov/injectionsafety/IP07_standardPrecaution.html).

⁶ For a drug product for which there is an official USP drug product monograph, the product must comply with the standards set forth therein, including the standards set forth in General Chapter <1>, unless expressly excepted in that drug product monograph. See Federal Food, Drug, and Cosmetic Act, sections 501(b) (21 U.S.C. 351(b)) and 502(g) (21 U.S.C. 352(g)); USP 37-NF 32, General Notices and Requirements 2.10. Official Text. Thus, for an injectable drug product for which a USP monograph exists and incorporates General Chapter <1>, the provision regarding inclusion of a slight volume exceeding the labeled volume is a mandatory requirement; for injectable products without a USP monograph that incorporates General Chapter <1>, compliance with the slight excess volume provision is strongly recommended. USP has proposed moving the text discussing the container content from USP General Chapter <1> *Injections* to USP General Chapter <697> *Container Content for Injections*. These proposed changes are being considered for USP 38.

⁷ Overage is an amount of a drug substance in excess of the label claim. The use of an overage to compensate for degradation during manufacture or a product’s shelf life, or to extend the shelf life is generally discouraged. The use of an overage is discussed in section 2.2.2 of the [International Conference on Harmonisation \(ICH\), Guidance for Industry, Q8\(R2\) Pharmaceutical Development](#).

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70 FDA becomes concerned when the excess volume in a vial is greater or less than the USP
71 recommended amount without appropriate justification. Such excesses and deficiencies may
72 result in medication errors and may lead to misuse of leftover drug product or pooling of vials to
73 obtain a single dose.

74

75 **B. Labeled Vial Fill Size**

76

77 While dosing flexibility is necessary with injectable drug products, applicants should determine
78 the appropriate vial fill sizes during product development, considering how the vials are likely to
79 be used. For example, single-dose vials are designed for use in a single patient as a single
80 injection/infusion. However, even when appropriately labeled, single-dose vials that contain
81 significantly⁸ more drug than is required for a single dose may result in the misuse of the leftover
82 drug product. Similarly, the need to combine several single-dose vials for a single patient dose
83 may lead to medication errors and microbial contamination.

84

85 According to USP General Chapter <1>, multiple-dose vials have a maximum container volume
86 sufficient to permit the withdrawal of not more than a total of 30 mL, unless otherwise specified
87 in the USP drug product monograph.^{9,10} Setting a maximum volume in multiple-dose vials will
88 minimize vial septum punctures, which will reduce the risk of compromising vial integrity and
89 the potential for vial contamination.

90

91 **IV. DISCUSSION AND RECOMMENDATIONS**

92

93 With respect to allowable excess volume, the applicant of drugs in ampules or vials intended for
94 injection must follow the requirements in 21 CFR 201.51(g). The regulation requires an
95 applicant to comply with the excess volume recommendations prescribed by the USP.

96 Therefore, for drugs in ampules and vials intended for injection, the applicant must comply with
97 the excess volume recommendations that appear in USP General Chapter <1151>.¹¹ In the case
98 of drug products requiring reconstitution, the product should be designed to meet the label claim
99 and acceptable overfill, and allow for correct dosing. Deviations from the recommendations in
100 USP General Chapter <1151> with regard to excess volume should be justified.¹² FDA
101 recommends providing the justification by obtaining extractable content testing data, which is

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.

⁹ USP has proposed moving the text discussing the maximum container volume for multiple-dose vials from USP General Chapter <1> *Injections* to USP General Chapter <659> *Packaging and Storage Requirements*. These proposed changes are being considered for USP 38.

¹⁰ For products without a USP monograph, multiple-dose vials must have a maximum fill volume sufficient to permit the withdrawal of not more than 30 mL, unless justified in the application.

¹¹ Typically, USP General Chapters titled with numbers above <1000> are considered to be recommendations and not requirements, unless the chapter is cited in a product-specific monograph or another General Chapter titled with a number below <1000>. However, in this case, because FDA's regulations specifically require adherence to the USP recommendations on this topic, the recommendations in USP General Chapter <1151> are considered to be requirements.

¹² For example, for a drug product requiring reconstitution that is dosed based on body weight, it is important for the final concentration to be a whole number that allows for easy calculation and withdrawal of the appropriate dose. This consideration may be used to justify a slight deviation from the recommended overfill.

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102 described in USP General Chapter <1> under *Packaging, Determination of Volume of Injection*
103 *in Containers*, or other appropriately justified methods. A variety of approaches may be
104 considered acceptable for sample collection, for example:

- 106 • For BLAs: Lot release testing and/or collection from batches representative of the
107 commercial process, using appropriate sampling and methods.
- 108
- 109 • For NDAs and ANDAs: One or more batches representative of the commercial
110 process as part of the product development studies using appropriate sampling
111 and methods.
- 112

113 The applicant should provide data related to proposed excess volume in the following sections of
114 the application:¹³

- 116 • The excess volume included in a drug product should be described in the common
117 technical document (CTD) section 3.2.P.1, *Description and Composition of the*
118 *Drug Product*.
- 119
- 120 • The studies and justification (i.e., extractable volume testing, viscosity studies, fill
121 volume variability) should be described in CTD section 3.2.P.2.2.1, *Formulation*
122 *Development* and/or 3.2.P.2.3, *Manufacturing Process Development*.
- 123

124 FDA recommends that a drug product's vial fill size should be appropriate for the labeled use
125 and dosing of the product.¹⁴ FDA may request justification when there are questions about the
126 appropriateness of the proposed labeled vial fill sizes in an application. When deciding what is
127 appropriate, applicants should consider the following:

- 129 • Single-dose vials should not contain a significant¹⁵ volume beyond what would be
130 considered a usual or maximum dose for the expected use of the drug product.
- 131
- 132 • Consumers and/or health care providers should not be routinely required to use
133 more than one vial to administer a typical single dose of the drug product.
- 134
- 135 • Multiple-dose vials should contain no more than 30 mL of drug product except
136 under specific circumstances.¹⁶
- 137

138 For all application types, the applicant should communicate with FDA early in the drug
139 development process about the vial fill size and unique excess volume concerns. For example,

¹³ Guidance for Industry, *M4: The CTD – Quality Questions and Answers/Location Issues*

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073285.pdf>.

¹⁴ An ANDA that references a currently approved reference listed drug (RLD) is generally expected to have the same labeled vial fill size as the RLD. In the event of a suitability petition permitting a change in vial fill size, the basic principles of this guidance would be applied to the petitioned ANDA.

¹⁵ See footnote 8 for information on significant volumes.

¹⁶ Exceeding the 30mL multiple-dose vial limit may be justified if the usual dose of the drug product packaged in a multiple-dose vial is large, making the 30 mL limit impractical.

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140 applicants should consider such communications during the end of phase II meetings or other
141 communications for investigational new drug applications (INDs).

142
143 We recommend communicating with FDA as outlined in existing recommendations related to
144 communication with applicants, including the Guidance for Review Staff and Industry *Good*
145 *Review Management Principles and Practices for PDUFA Products*.¹⁷

¹⁷ See

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf>.

We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA
Drugs guidance Web page at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> and the CBER Web
page.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.