Guidance for Industry

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

DRAFT GUIDANCE

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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)

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Contains Nonbinding Recommendations

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance provides the pharmaceutical industry with the Center for Drug Evaluation and Research's (CDER's) and the Center for Biologics Evaluation and Research's (CBER's) current thinking on allowable excess volume and labeled vial fill size in injectable drug and biological products. Specifically, the draft guidance clarifies the FDA regulatory requirements and recommendations pertaining to allowable excess volume in injectable vials and describes when justification is needed for a proposed excess volume in these injectable drug[3] products. This guidance also discusses the importance of appropriate packaging sizes for injectable drug products and recommends that labeled vial fill sizes be appropriate for the intended use and dosing of the drug product.

This guidance addresses fill and packaging issues for injectable drug products that are packaged in vials and ampules, including products that require reconstitution. It does not address injectable drug products in other packaging types (e.g., prefilled syringe package systems and intravenous infusion bags) or noninjectable products, because there may be unique considerations for these packaging configurations. The recommendations in this guidance apply to new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), as well as new packaging supplements to these existing applications submitted to CDER and CBER.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) in collaboration with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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

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

II. BACKGROUND

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

III. OVERVIEW

A. Allowable Excess Volume

The United States Pharmacopeia (USP) General Chapter <1> *Injections* provides that each container of an injectable product is filled with a volume that slightly exceeds the content indicated in the labeling.[6] The excess volumes are meant to be sufficient to permit withdrawal and administration of the labeled volumes. FDA regulations at 21 CFR 201.51(g) provide that for drugs in ampules or vials that are intended for injection, 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. USP General Chapter <1151> *Pharmaceutical Dosage Forms* provides excess volume recommendations for mobile and viscous liquids in a range of container sizes, noting that the excess volumes recommended are usually sufficient to permit withdrawal and administration of the labeled volumes. Allowable excess volume may also be referred to as "overfill," but should not be confused with "overage," which is addressed in a separate guidance.[7] Generally, a sponsor should not declare the amount of overfill on the container label.

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

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[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 36-NF 31, 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.

[7] Overage refers to the use of an excess of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend the shelf life, and it is generally discouraged. This is described and discussed in the International Conference on Harmonisation (ICH), Guidance for Industry, *Q8(R2) Pharmaceutical Development.*

B. Labeled Vial Fill Size

While dosing flexibility is necessary with injectable drug products, sponsors should determine the appropriate packaging sizes during product development, considering how the vials are likely to be used. For example, single-dose vials are designed for use in a single patient as a single injection/infusion. However, even when appropriately labeled, single-dose vials that contain significantly[8] more drug than is required for a single dose may result in the misuse of the leftover drug product. Similarly, the need to combine several single-dose vials for a single patient dose may lead to medication errors and microbial contamination.

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

IV. DISCUSSION

With respect to allowable excess volume, the sponsor/applicant of drugs in ampules or vials, intended for injection, must follow the requirements in 21 CFR 201.51(g). The regulation requires a sponsor/applicant to comply with the excess volume recommendations prescribed by the USP. Specifically, for drugs in ampules and vials, intended for injection, a sponsor/applicant must comply with the excess volume recommendations that appear in USP General Chapter <1151>. Deviations from the recommendations in USP General Chapter <1151> with regard to excess volume should be justified. FDA recommends providing the justification by obtaining extractable content testing data, which is described in USP General Chapter <1> under *Packaging*, *Determination of Volume of Injection in Containers*, or other appropriately justified methods. A variety of approaches may be considered acceptable for sample collection, for example:

- For BLAs: Lot release testing and/or collection from validation lots, using appropriate sampling and methods.

- For NDAs and ANDAs: One or more exhibit batches as part of the product development studies using appropriate sampling and methods.

The applicant should provide data related to proposed excess volume in the following sections of the application:[10]

[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 37.

[10] Guidance for Industry, *M4: The CTD – Quality Questions and Answers/Location Issues*.

- The excess volume included in a drug product should be described in the common technical document (CTD) section 3.2.P.1, *Description and Composition of the Drug Product*.

- The studies and justification (i.e., extractable volume testing, viscosity studies) should be described in CTD section 3.2.P.2.2.1, *Formulation Development*.

With regard to a drug product's vial fill size, FDA recommends that it should be appropriate for the labeled use and dosing of the product.[11] FDA may request justification when there are questions about the appropriateness of the proposed labeled vial fill sizes in an application. When deciding what is appropriate, applicants should consider the following:

- Single-dose vials should not contain a significant[12] volume beyond what would be considered a usual or maximum dose for the expected use of the drug product.

- Consumers and/or health care providers should not be routinely required to use more than one vial to administer a typical single dose of the drug product.

- Multiple-dose vials should contain no more than 30 mL of drug product except under specific circumstances.[13]

For all application types, the applicant should communicate with FDA early in the drug development process about the vial fill size and unique excess volume concerns. For example, applicants should consider such communications during the end of phase II meetings or other communications for investigational new drug applications (INDs).

We recommend communicating with FDA as outlined in existing recommendations related to communication with sponsors/applicants, including the Guidance for Review Staff and Industry *Good Review Management Principles and Practices for PDUFA Products*.[14]

[11] 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.

[12] See footnote 8 for information on significant volumes.

[13] 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.

[14] 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.