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

Guidance for Industry

DRAFT GUIDANCE

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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
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Contains Nonbinding Recommendations

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This guidance provides industry with the Food and Drug Administration's (FDA's) recommendations on the selection of appropriate package type terms and selection of appropriate discard statements[3] for injectable medical products for human use, packaged in multiple-dose, single-dose, and single-patient-use containers.[4] Specifically, this guidance provides FDA's revised definitions for single-dose and multiple-dose containers, and introduces the definition of a new package type term, "single-patient-use" container. Marketing applications for such products include: New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Biologics License Applications (BLAs), Premarket Approval Applications (PMAs), and Premarket Notifications under section 510(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only

[1] The term *container* in this guidance refers to all package types used for injectable medical products for human use. This guidance does not discuss all package type terms (e.g., *Pharmacy Bulk Package*). Please refer to United States Pharmacopeia (USP) General Chapter <659> *Packaging and Storage Requirements* for other package type terms.

[2] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biological Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Office of Combination Products in the Office of the Commissioner at the Food and Drug Administration.

[3] This guidance is intended to provide recommendations on the selection of discard information for drugs and drug containers, and certain combination products regulated as medical devices. It does not provide information on disposal instructions of drugs or devices. Discard information is a statement supported by appropriate data on when to stop using an injectable medical product. Disposal information is a statement on how to safely and appropriately destroy any unused injectable medical product.

[4] For the purpose of this guidance, the term *medical products* applies to human drug and biological products, and certain combination products regulated as medical devices.

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.

II. BACKGROUND

Unsafe injection practices, including the improper use of needles, syringes, and medication vials for more than one patient, threaten patient safety and have resulted in multiple blood borne bacterial and viral infection outbreaks. Bacterial infections have been transmitted to patients when single-dose containers were used improperly, the contents became contaminated and these contents were then administered to multiple patients. Failure to follow standard precautions and aseptic techniques has also been associated with several outbreaks of infections involving multiple-dose vials. Examples of such incidents with single-dose and multiple-dose vials are:

- From 1998 through 2008, patient to patient transmission of blood borne pathogens due to unsafe injection practices resulted in 33 outbreaks of viral hepatitis in nonhospital health care settings in the United States.[5]

- According to the Centers for Disease Control and Prevention (CDC), at least 26 incidents involving the improper use of single-dose medications in outpatient settings have occurred over a five year period resulting in the potential exposure of more than 95,000 patients to infectious diseases.[6]

- In 2002, 71 cases of hepatitis C virus (HCV) infection and 31 cases of hepatitis B virus (HBV) infection were attributed to unsafe needle/syringe practices in an Oklahoma pain clinic.[7]

- In 2008, an investigation of an HCV outbreak in Nevada revealed that reuse of syringes in multiple patients and use of single-use medication vials for multiple patients were the likely mechanisms by which HCV infections were transmitted.[8]

It is evident from the examples described above that single-dose containers, which are intended for use for a single patient, have been used for more than one patient in the past, and that this practice has contributed to many of these bacterial and viral infection outbreaks. Additionally, there is a concern that existing package type terms do not adequately convey that some

[5] Thompson, ND, et al. 2009, Nonhospital Health Care-Associated Hepatitis B and C Virus Transmission: United States, 1998-2008. Ann Int Med; 150:33-39.

[6] CDC: Injection Safety, 2012, CDC's position-protect patients against preventable harm from improper use of single-dose/single-use vials. Atlanta, GA: US Department of Health and Human Services. Available at: http://www.cdc.gov/injectionsafety/cdcposition-singleusevial.html.

[7] Comstock RD, et al. 2004, A Large Nosocomial Outbreak of Hepatitis C and Hepatitis B Among Patients Receiving Pain Remediation Treatments. ICHE; 25:576-583.

[8] CDC: 2007, Acute hepatitis C virus infections attributed to unsafe injection practices at an endoscopy clinic-Nevada. MMWR 2008; 57:513-7. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5719a2.htm.

containers (e.g., insulin pens) that provide multiple doses are intended for use for only a single patient.[9]

III. DISCUSSION

As part of its review of medical products, FDA clears or approves package type terms and discard statements as part of the labeling of injectable medical products. FDA believes that consistent use of correct package type terms and discard statements for injectable medical products for human use will promote their proper use and provide a foundation for educational efforts to reduce the transmission of blood borne pathogens. The following sections describe the appropriate package type terms for multiple-dose, single-dose, and single-patient-use injectable drug and biological products for human use and certain combination products regulated as medical devices for injection.

Definitions

The package type terms "single-dose" container and "multiple-dose" container have been in use for a long time. To provide clarity on the intended use of these terms, the definitions are being revised as follows:

1. *Single-Dose Container:* A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/infusion. When space permits, a single-dose container is labeled as such and should include on the label appropriate discard statements. Examples of single-dose containers are vials, ampules, and prefilled syringes.

2. *Multiple-Dose Container:* A multiple-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that has met antimicrobial effectiveness testing requirements, or is excluded from such testing requirements by FDA regulation.[10] A multiple-dose container is intended to contain more than one dose of the

[9] In March 2009, in response to reports of improper use of insulin pens in hospitals, FDA issued a Safety Alert for health care professionals reminding them that insulin pens are meant for use on a single patient only and are not to be shared between patients. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm127783.htm.

[10] Antimicrobial effectiveness testing determines whether the product prevents microbial growth if contamination of the container occurs during patient use conditions. Some injectable chemical formulations may possess sufficient inherent antimicrobial effectiveness characteristics without the addition of a preservative, while other products rely on the addition of a preservative to meet this requirement. However, certain specially designed packaging and delivery systems permit the use of preservative-free injectable products for multiple patient uses. While most multiple dose biological products require a preservative, 21 CFR 610.15 provides for a few exceptions.

drug product. When space permits, a multiple-dose container is labeled as such. Multiple-dose containers are generally expected to contain 30 mL or less of medication.[11] The beyond-use date[12] for an opened or entered (e.g., needle-punctured) multiple-dose container is 28 days, unless otherwise specified by the manufacturer in the label.[13,14] An example of a multiple-dose container is a vial.

In the vast majority of cases, the package type terms "single-dose" and "multiple-dose" are properly used. However, in some unique situations, a package contains multiple doses of a medical product that is intended to be for use in a single patient. The medical product in this package type may not contain a preservative or be able to pass antimicrobial effectiveness if tested, yet this package type contains multiple doses. An example of this package type is a drug intended for intrathecal administration that is packaged in a patient-controlled analgesia cartridge. Because the package type is designed to administer multiple doses, the package type term "single-dose" is not appropriate. However, the package type term "multiple-dose" is also inappropriate because the package contents are not able to meet antimicrobial effectiveness testing requirements.

In other cases, the medical products in this package type do contain a preservative and are expected to pass antimicrobial effectiveness if tested, yet the intent is that the package is to be restricted to use by a single patient. In this scenario, referring to the package type as "multiple-dose" does not adequately convey the intent to restrict the use to a single patient. An example of such a product is an insulin pen that contains multiple doses of insulin for individual patient use.

In the past, the term "single-use" container has been used by FDA to describe a package type that contained multiple doses but was intended to be used in a single patient. Unfortunately, the term "single-use" was also inappropriately used as if it were interchangeable with the term "single-dose" which was not the Agency's original intent. To address this confusion regarding the terminology, the Agency is retiring the term "single-use" and a new package type term "single-patient-use" container, is being created to address the need for describing a package that contains multiple doses of an injectable medical product that is intended to be used in a single patient.

3. Single-Patient-Use Container: A single-patient-use container is a container of a sterile medication for parenteral administration (injection or infusion) that is intended to be used multiple times for a single patient. When space permits, a single-patient-use container is labeled as such and should include on the label appropriate discard

[11] United States Pharmacopeia-National Formulary (USP 38-NF 33) <1> INJECTIONS, *Packaging and Storage* in the version official until 4/30/2016. This information also appears in the version of <659> PACKAGING AND STORAGE REQUIREMENTS, *Injection Packaging* that will be official on 5/1/2016.

[12] Beyond-use date (BUD) is the date or time beyond which a product should not be used. See USP 38-NF 33 General Notices 10.40.100. This information appears in <7> LABELING, *Expiration Date and Beyond-Use Date* which will be official on 5/1/2016.

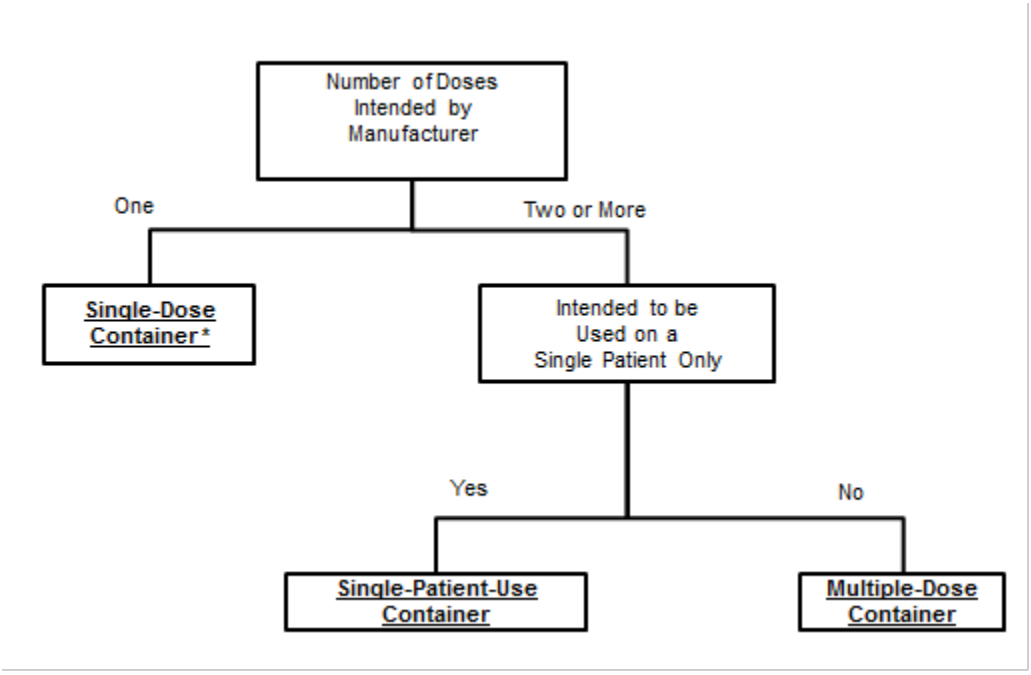
[13] See http://www.jointcommission.org/standards_information/jcfaqdetails.aspx?StandardsFaqId=434&ProgramId=47.

[14] Vaccines in multiple-dose vials should be used and disposed of according to their FDA approved product labeling. Unless a multiple-dose vial is labeled otherwise, vaccines supplied in multiple-dose vials may be used up to the date of expiry of the product. See also http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm.

statements. Examples of single-patient-use containers are patient controlled analgesia cartridges and certain pens for injection.

For multiple-dose and single-patient-use containers, the antimicrobial effectiveness testing results, if performed, will be used to support the labeled beyond-use date or discard instructions.

The following diagram illustrates how the appropriate package type term for an injectable medical product can be determined:



* Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose. For example, for a medical drug product that is dosed based on body weight, or due to the required overfill in vials and ampules, there may be excess amount constituting more than one dose in the container, which should be discarded. Please refer to FDA's guidance for industry on *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products*.[15] Furthermore, although dosed over an extended time period, infusion containers (large or small volume) are considered single-dose containers because they are designed for use with a single patient as a single infusion.

IV. LABELING REQUIREMENTS AND RECOMMENDATIONS

Applicants should determine the proper package type term ("single-dose," "multiple-dose," or "single-patient-use") for injectable medical products for human use and use only the correct term for the package type throughout the labeling. FDA recommends that the appropriate package

[15] 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.

type term will appear on all components of the labeling of injectable medical products for human use so the user will be able to easily identify the package type. This includes the container label and carton, and, where applicable, the prescribing information.[16]

The package type term "single-dose" is required to appear on the container labels of single-dose injectable medical products that have a United States Pharmacopeia (USP) monograph, when space permits (FD&C Act section 502(g) (21 U.S.C. 352(g)).[17] When space does not permit the "single-dose" term to appear on such products' container labels, then according to 21 CFR 201.10(i)(2), it must appear on the carton or other outer container or wrapper, if space permits, or in the prescribing information. In FDA's experience, there has always been sufficient space to include this information on the carton labeling.

When space permits, the appropriate package type term should appear on the container label of multiple-dose and single-patient-use injectable medical products, as well as single-dose injectable medical products that do not have a United States Pharmacopeia monograph. If there is insufficient space to include this information on the container label, the package type term should appear on the carton labeling where it will be easily visible.

When appropriate, the prescribing information for single-patient-use and single-dose injectable medical products should include a discard statement. The discard statement should also be included on the container and carton, when space permits. For example, single-dose container labeling should typically include the statement "Discard unused portion."

Multiple-dose containers do not normally have a discard statement because the beyond-use date is assumed to be 28 days for an opened or entered (e.g., needle-punctured) multiple-dose container, unless otherwise indicated.[18] If the beyond-use date is other than 28 days for a product in a multiple-dose container, an appropriate discard statement (supported by appropriate data) should be included on the container label, carton labeling, and in the prescribing information. Examples of statements that might appear on multiple-dose containers include:

- "Discard within XX hours after opening or after assembly" or
- "After first use, refrigerate or keep at a temperature not greater than XX for XX days."

The Agency recommends that applicants make the necessary labeling changes to follow its recommendations within two years of the publication of the final version of this guidance. All submissions (annual reports and supplements) should clearly identify the change(s) being made. In addition, a supplement submission to follow the recommendations in the guidance should be

[16] Examples of sections within the prescribing information for drug products where the package type term may appear include, but are not limited to: DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING (21 CFR 201.56 and 201.57).

[17] 21 U.S.C. section 352(g); The following statement "A single-dose container is labeled as such…." appears in United States Pharmacopeia-National Formulary (USP 38-NF 33), <7> *Labeling* which becomes official on 5/1/2015 and <659> *Packaging and Storage Requirements* in the version that will be official on 5/1/2016.

[18] See footnote 14.

identified as "Labeling Changes to Follow the Package Type Term Guidance." For approved applications, changes made to labeling to follow the recommendations in this guidance should be submitted to the FDA as described below:[19]

A. Change from "single-use" to "single-dose" package type term

For a drug product that was designed and otherwise labeled for use with a single patient as a single injection/infusion, a change from the package type term "single-use" to "single-dose" to accurately reflect the package type should be submitted in an annual report. See 21 CFR 314.70(d)(2)(x); 21 CFR 314.94(a)(8)(iv) and 21 CFR 601.12(f)(3)(i)(A).[20]

B. All other changes to a package type term

ALL other changes to a package type term, including a change from the package type term "single-use" to "single-patient-use," as well as a change from "multiple-dose" to "single-patient-use" should be submitted as a "Prior Approval Supplement" (PAS) for NDAs and BLAs only. See 21 CFR 314.70(b)(2)(v)(A); and 21 CFR 601.12(f)(1).

After FDA approval of a PAS for an NDA, the holders of any ANDAs that relied upon the NDA as the reference listed drug (RLD) would be required to submit conforming labeling revisions. See 21 CFR 314.94(a)(8)(iv) and 21 CFR 314.150(b)(10). FDA is specifically requesting that these conforming labeling revisions be submitted in a "Changes Being Effected" (CBE-0) supplement. See 21 CFR 314.70(c)(6)(iii)(E). If approval of the NDA for the RLD has been withdrawn, the corresponding ANDA holders for specific drug product(s) should contact the Agency.

C. Changes made to add a package type term to the container/carton labeling (and, in some cases, the prescribing information) when no package type is included (or listed)

1. If the prescribing information already includes the appropriate assigned package type but the container/carton labeling lacks the designation for some reason other than lack of space, NDA, BLA and ANDA holders may submit the addition of the package type term to the container/carton labeling in an annual report under 21 CFR 314.70(d)(2)(x), and 21 CFR 601.12(f)(3)(i)(A), as long as the package type term being added to the container/carton labeling is the same correct term that has already been included in the approved prescribing information. The same procedure applies if the container/carton labeling includes the appropriate assigned package type but the prescribing information lacks the designation.

[19] This information is specific for NDAs, ANDAs, and BLAs. For information related to PMAs and 510(k)s, please contact CDRH.

[20] This discussion of potential regulatory pathways for submission assumes that the change in package type term from "single-use" to "single-dose" is the only change being made to the labeling. Other changes may require submission of a supplement.

2. If neither the container/carton nor the prescribing information has a package type term listed, NDA and BLA holders should submit a PAS to add the appropriate term to the container/carton and prescribing information, see 21 CFR 314.70(b)(2)(v)(A) and 21 CFR 601.12(f)(1). After FDA approval of the PAS for the NDA RLD, corresponding ANDA holders would be required to submit conforming labeling revisions. See 21 CFR 314.94(a)(8)(iv) and 21 CFR 314.150(b)(10). FDA is specifically requesting that these conforming labeling revisions be submitted in a CBE-0 supplement. See 21 CFR 314.70(c)(6)(iii)(E). If approval of the NDA for the RLD has been withdrawn, the corresponding ANDA holders should contact the Agency.

D. Any other proposed changes

For any other proposed changes regarding package type terms, please contact the Agency.