Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Bill Harvey at 240-402-4180.

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

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Pharmaceutical Quality/Manufacturing Standards (CGMP)

Revision 1

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Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The last few decades have seen an increasing demand in various health care settings for solid oral dosage form drug products repackaged into unit-dose containers, which hold a quantity of drug for administration as a single dose. The increase in unit-dose repackaging has led to questions regarding stability studies and appropriate expiration dates for these repackaged products. This guidance describes the conditions under which FDA does not intend to take action regarding required stability studies for these repackaged products and the expiration date to assign under those conditions.[2]

This guidance addresses repackaging of prescription and over-the-counter solid oral dosage form drugs into unit-dose containers by commercial pharmaceutical repackaging firms that are required to register with FDA under section 510 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and to comply with current good manufacturing practice (CGMP) regulations in 21 CFR parts 210 and 211.[3]

The guidance does not address repackaging involving the following:

- Other dosage forms (e.g., sterile, liquid, topical).

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] This draft guidance replaces the draft guidance for industry *Expiration Dating of Unit-Dose Repackaged Drugs: Compliance Policy Guide* (2005). In addition, this draft guidance, once final, will supersede Compliance Policy Guide 480.200 *Expiration Dating of Unit-Dose Repackaged Drugs* (1995).

[3] As described in 21 CFR 207.3(a)(8), *manufacturing* or *processing* includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.

- Products repackaged by State-licensed pharmacies, Federal facilities, and outsourcing facilities as defined under section 503B of the FD&C Act.[4]

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 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

FDA's CGMP regulations for finished pharmaceuticals require that each drug product bear an expiration date determined by appropriate stability testing and that the date must be related to any storage conditions stated on the labeling, as determined by stability studies (§§ 211.137(a) and (b)).[5] The expiration date for a drug product packaged in a single-dose container should be placed on the primary container unless it is not feasible to do so.[6]

Samples used for stability testing must be in the same container-closure system as that in which the drug product is marketed (§ 211.166(a)(4)). This is to ensure the drug product's safety and efficacy over its intended shelf life and to ensure that data representing the marketed product are available in case quality issues arise during the drug product's intended shelf life.

United States Pharmacopeia (USP) General Chapter <7> *Labeling* states that "the label of an official drug product … shall bear an expiration date."[7] For unit-dose repackaged products, USP General Chapter <1178> *Good Repackaging Practices* recommends that the expiration date "not exceed (1) 6 months from the date of repackaging; or (2) the manufacturer's expiration date; or (3) 25% of the time between the date of repackaging and the expiration date shown on the manufacturer's bulk article container of the drug being repackaged, whichever is earlier."

III. POLICY

For solid oral dosage form drugs repackaged into unit-dose containers, FDA does not intend to take action regarding the requirements of §§ 211.137 and 211.166 (i.e., expiration dating determined by stability studies) if these products are assigned an expiration date that does not exceed (1) 6 months from the date of repackaging, or (2) 25 percent of the time between the date

[4] Repackaging by state-licensed pharmacies, Federal facilities, and outsourcing facilities is addressed by separate guidance. See, for example, guidance for industry *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities.* We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] Stability testing and stability studies are described in § 211.166.

[6] Under 21 CFR 201.17, when single-dose containers are packed in individual cartons, the expiration date may properly appear on the individual carton instead of the immediate product container.

[7] Here and elsewhere in this guidance, the USP version referenced is USP 39, 8/1/2016.

of repackaging and the expiration date on the container of the original manufacturer's product, whichever time period is shorter, and if the following conditions are met:

(1) The unit-dose container complies with Class A or Class B standards as described in USP General Chapter <671> *Containers—Performance Testing*, "Packaging System Classification for Single-Unit Containers and Unit-Dose Containers for Solid Oral Dosage Forms."

Under this condition, containers complying with the Class B standard are used only if (a) appropriate data on the moisture permeability of the Class B material and the moisture sensitivity of the drug product are available, and (b) a risk assessment of these data provides a high level of confidence that use of such containers will not compromise the quality of the product throughout the assigned expiration dating.[8]

(2) If the drug product is sensitive to light as indicated by the manufacturer (e.g., "Protect from light" on its labeling), the unit-dose repackaging container-closure system provides light protection equal to or greater than that of the drug product's original container-closure system.

(3) The drug product's original container has not been opened previously and the entire contents are repackaged in one operation.

(4) Repackaging and storage occur in an environment that is consistent with the conditions described in the original drug product's labeling. If temperature and humidity are not specified in the original labeling, the product should be maintained at "controlled room temperature" and in a "dry place" (as defined in USP <659> *Packaging and Storage Requirements*) during the repackaging process, including storage.

(5) The drug product's labeling does not caution against repackaging.[9]

In addition, FDA does not intend to take action regarding the requirements of §§ 211.137 and 211.166 for an expiration date exceeding the ones described above (i.e., (1) 6 months from the date of repackaging, or (2) 25 percent of the time between the date of repackaging and the expiration date on the container of the original manufacturer's product, whichever time period is shorter), provided the following:

(1) The above five conditions are met.

(2) Supportive data from appropriate studies, using an adequate number of samples, demonstrate that the container-closure system used for repackaging is at least as protective of the drug product as is the original packaging. Appropriate studies should

[8] Containers meeting USP <671> Class C and Class D standards do not meet condition (1).

[9] Directions in the package insert such as "Keep these tablets in the original container" and "Do not repackage" are examples of a caution against repackaging in the product's labeling.

be based on sound science and a risk-based assessment to ensure that product quality is maintained up to the expiration date.[10]

(3) The expiration date of the repackaged product does not exceed the original manufacturer's expiration date.

[10] Satisfactory comparison of container-closure systems is possible through several methods, e.g., testing for protection from moisture, oxygen, and light, as appropriate; comparing the properties of the original container-closure system to a new system by stress testing, which refers to product testing after storage under exaggerated conditions (e.g., high temperature and high humidity); degradation testing after storage under long-term or accelerated conditions.