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

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

**July 2020
Pharmaceutical Quality/Manufacturing Standards (CGMP)**

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This guidance represents 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 office 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 circumstances under which FDA generally does not intend to take action regarding required stability studies for these repackaged products and appropriate expiration dates under those circumstances.

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 211.²

The guidance does not address repackaging involving the following:

- Other dosage forms (e.g., liquid dosage forms³).

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 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.

³ Liquid dosage forms are excluded from this guidance because they are substantially more susceptible to degradation than solid dosage forms. For example, their components, including active ingredients, are more likely to interact with each other, light, reactive gases, and the primary container-closure system. See guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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- 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.

For unit-dose repackaged products, United States Pharmacopeia (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."⁷

III. POLICY

At this time and based on our current understanding of the risks involved, for solid oral dosage form drugs repackaged into unit-dose containers, FDA generally does not intend to take action regarding nonconformance with the requirements of §§ 211.137 and 211.166 (i.e., expiration dating determined by stability studies) if these products are assigned, and labeled with, an expiration date that does not exceed (1) 6 months from the date of repackaging, or (2) 25 percent

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* (January 2017).

⁵ Expiration dating requirements are in § 211.137, which exempts certain drugs (homeopathic and some over-the-counter drugs) from bearing an expiration date on the label. 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 42-NF 37 (NF=National Formulary).

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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, and if all the following circumstances are present:

- (1) The unit-dose container complies with Class A or Class B standards as described in USP General Chapter <671> *Containers—Performance Testing*.

Repackagers should use containers complying with the Class B standard 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 them with 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 generally does not intend to take action regarding nonconformance with 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 that:

- (1) The above five circumstances are present.
- (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 must be

⁸ Containers meeting USP <671> Class C and Class D standards do not fit the circumstances described in (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.

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based on sound science¹⁰ and should be supported by a risk-based assessment to ensure that product quality is maintained up to the expiration date.¹¹

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

¹⁰ 21 CFR 211.166(a) requires that sample size and approach be statistically based and “reliable, meaningful, and specific test methods” be used for stability testing; and §§ 211.160(a) and (b) require “scientifically sound and appropriate” test methods and sampling plans, among other requirements.

¹¹ 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. Approaches such as those described in ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003) (e.g., bracketing or matrixing) may be used, if justified.