



Bristol-Myers Squibb Company

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August 29, 2005

**Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852**

**Re: Docket No. 2005D-0174; Draft Guidance, Expiration Dating of Unit-Dose Repackaged
Drugs: Compliance Policy Guide; Federal Register Volume 70, Number 103, pages 30953-
30954 (May 31, 2005).**

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified global health care company, is pleased to have the opportunity to offer comments on the *draft guidance* entitled "*Expiration Dating of Unit-Dose Repackaged Drugs: Compliance Policy Guide*". Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. For this reason, we are interested in commenting on the *draft guidance*. Our comments are set forth below.

Summary of BMS Comments on Proposal

We commend the U.S. FDA for inviting comments on this draft guidance and for delaying final decision on the proposed revision in order to further study the expiration dating issue to determine the most scientifically sound approach. We are providing our comments on the draft guidance below.

Specific Comments (Items that Need Clarification & Recommended Actions)

1. BMS recommends that the Compliance Policy Guide Manual, Section 480.200 (CPG 7132b.11) not include the repackaging of LIQUID oral dosage form drug products.

Compatibility between a liquid oral dosage form drug product and the composition of a unit-dose container-closure system plays a major role in assuring the drugs' safety and efficacy over its intended shelf-life. Therefore, because of the substantial potential for adverse effect on the identity, strength, quality, purity, or potency of the drug product, we do not support repackagers assigning expiration dating without conducting stability, extractable and leachable studies for liquid oral dosage forms. The caution included on page 3 of the proposed draft guidance – that "liquid oral dosage forms should not be repackaged unless suitable materials are used and precautions are taken to prevent evaporation or solvent loss" – will not adequately protect product identity, strength, quality, purity, and potency in the absence of stability and extractable testing.

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According to the FDA guidance "Guidance for Industry, Changes to an Approved NDA or ANDA, April 2004, the majority of the primary packaging changes related to liquid (e.g., solutions, suspension, elixir) dosage forms are classified as Major Changes requiring prior approval before implementation. For prior approval submissions covering these types of packaging changes, in addition to the evaluation of extractables, stability studies covering both long-term and accelerated storage conditions would typically be included. Therefore, allowing the repackaging of liquid dosage forms into unit-dose containers should also require supportive stability data.

2. BMS also recommends that this section of the CPG include additional repackaging-related references of specific requirements that are already defined within the USP. Such references would clarify the conditions under which a repackager may assign an appropriate expiration dating period to repackaged solid oral dosage form drug products in unit-dose containers without conducting new stability studies on the repackaged drug products.

Therefore, in the draft Guidance, Section III Discussion, BMS recommends that FDA consider the following changes/additions to the 4 listed requirements.

Requirement No. 1

We believe the reference to USP General Chapter <1146> PACKAGING PRACTICE-REPACKAGING A SINGLE SOLID ORAL DRUG PRODUCT INTO A UNIT-DOSE CONTAINER, *Beyond-use Date*, should be added.

Requirement No. 2

We fully support this requirement being part of this guidance. The use of materials/processes that result in unit-dose containers that meet the Class A designation should provide a container-closure system with a higher moisture barrier.

Requirement No. 3

We fully support this requirement as stated.

Requirement No. 4

We fully support this requirement being part of this guidance. The majority of solid oral dosage form drug products in the U.S. are covered by CRT labeling supported by stability data generated at the ICH Zone II long-term storage condition of 25°C/60%RH. The defined controlled environment of not exceeding 75%RH at 23°C has approximately the same moisture load as the ICH Zone II storage condition and therefore, is an appropriate environment for the repackaging/storage of these unit-dose containers by the repackager.

We believe the reference to USP General Chapter <661> CONTAINERS, *Repacking into Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms, Storage*, should be added.

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Requirement No. 5

We support the addition of a requirement addressing reprocessing, specifically that covered under USP General Chapter <1146> PACKAGING PRACTICE-REPACKAGING A SINGLE SOLID ORAL DRUG PRODUCT INTO A UNIT-DOSE CONTAINER, *Minimum Requirements, Reprocessing*.

“Reprocessing of repackaged unit-dose containers (i.e., removing medication from one unit-dose container and placing it into another unit-dose container) shall not be done.”

Requirement No. 6

We support the addition of a requirement addressing special considerations, specifically that covered under USP General Chapter <1146> PACKAGING PRACTICE-REPACKAGING A SINGLE SOLID ORAL DRUG PRODUCT INTO A UNIT-DOSE CONTAINER, *Minimum Requirements, Special Considerations*.

“If a product is known to be oxygen sensitive or if it exhibits extreme moisture or light sensitivity (e.g., cold form foil), it shall not be repackaged. If a product is refrigerated, it shall not be repackaged unless proper environmental conditions and suitable materials are available.”

Requirement No. 7

We support the addition of a requirement addressing documentation, such as:

“Documentation must be on file to verify that all of the conditions listed above are met. Such supporting information should include, but not be limited to, records of the materials used for packaging, containers-permeation test results verifying the unit-dose container meets the Class A designation, and records of the controlled environment used during the repackaging operation and subsequent storage or repackaged products.”

BMS also supports adding a closing statement, such as:

“If any of these conditions are not met, the repackager must use expiration dates that are determined by appropriate stability testing as described in 21 CFR 211.166.”

BMS appreciates the opportunity to provide comment and respectfully requests that the FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



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