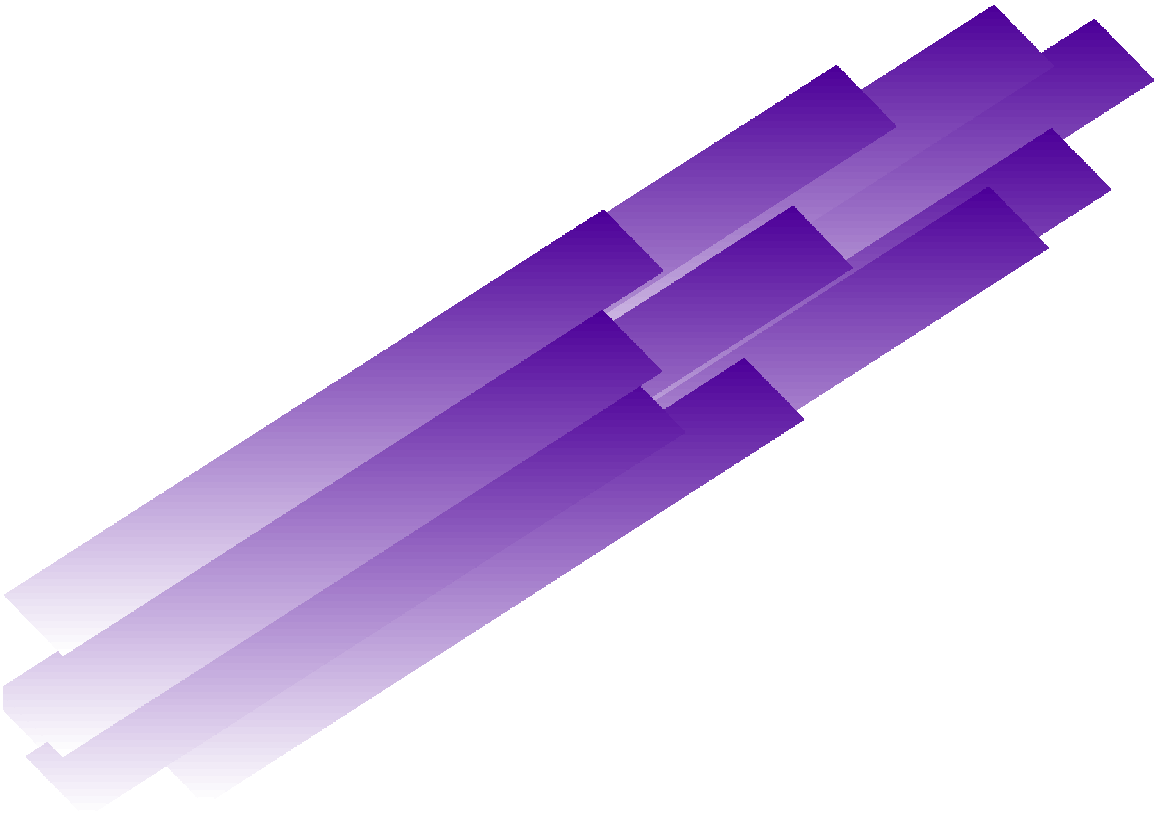
Guidance for Industry

Expiration Dating and Stability Testing of Solid Oral Dosage Form Drugs Containing Iron



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 1997

CP 2

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I. INTRODUCTION

This guidance describes how manufacturers and packagers affected by the final rule that published in the *Federal Register* (62 FR 2218) on January 15, 1997, requiring label warning statements and unit-dose packaging for solid oral drug products that contain 30 milligrams (mg) or more of iron per dosage unit, may meet stability and expiration dating requirements.

II. BACKGROUND

The Federal Food, Drug, and Cosmetic Act requires that manufacturers establish controls for the manufacture, processing, packing, and holding of drug products to ensure their safety, identity, strength, quality, and purity (§ 501(a)(2)(B)). Requirements for these controls, also known as current good manufacturing practices (CGMPs), are established and monitored by the FDA.

As part of the CGMP regulations, the FDA requires that drug products bear an expiration date determined by appropriate stability testing (21 CFR 211.137 and 211.166). The stability of drug products needs to be evaluated over time in the same container-closure system in which the drug product is marketed. In some cases, accelerated stability studies can be used to support tentative expiration dates in the event that full shelf life studies are not available. When a firm changes the packaging of a drug product (e.g., from a bottle to unit-dose), stability testing must be performed on the product in its new packaging, and expiration dating must reflect the results of the new stability testing.

To address the hazards of acute iron poisonings, including deaths, in children less than 6 years of age resulting from accidental overdose of iron-containing products, the FDA recently revised its requirements for the labeling and packaging of iron products. On January 15, 1997, the Agency published in the *Federal Register* (62 FR 2218) a final rule (the iron regulations) requiring label warning statements and unit-dose packaging for solid oral drug products that contain 30 mg or more of iron per dosage unit (21 CFR 310.518). The iron regulations were issued based, in part, on the Agency's conclusion that the likelihood of accidental overdose and serious injury to young

[1]This guidance has been prepared by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on expiration dating for solid oral drug products containing 30 mg or more of iron. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

children would be reduced significantly through the use of unit-dose packaging because such packaging would limit the number of doses a child may ingest if the child gains access to the product. The iron regulations are effective July 15, 1997.

Iron-containing supplements and drug products have certain special qualities, including (1) they generally are not a consumer's only source of the labeled ingredients, and (2) they frequently contain sufficient quantities of each ingredient that even if specifications are not met, consumers are still getting an adequate amount of the ingredients, at least as determined by U.S. Recommended Daily Allowances.

III. DISCUSSION

To meet the requirements of the iron regulations, manufacturers and packagers must determine an appropriate expiration date for the drug products in unit-dose packages. Accelerated stability testing may be impractical because drug products containing iron, especially multivitamin products, often do not perform well under the artificially stressful conditions of accelerated studies. As a result, real-time stability testing may be the only method to determine an appropriate expiration date. However, the final iron regulations were published only six months before they were to take effect; therefore, there may be insufficient time for some manufacturers of solid oral drug products containing 30 mg or more of iron per dosage unit to perform real-time stability testing on their products. To minimize the burden faced by those manufacturers who have made good faith efforts to comply with the stability testing requirements but were unable to do so, the FDA advises that, for a limited period of time, it does not intend to object if a manufacturer or packager fails to comply with §§ 211.137 and 211.166 under the following circumstances:

A. The firm sets an expiration date for tablets and capsule drug products packaged in unit-dose packaging based on the following: (1) the expiration period does not exceed 75 percent of the expiration dating period of the smallest version (usually the least stable) of the previously accepted product package and (2) the expiration period for the unit-dose container does not exceed 18 months.

B. The firm maintains appropriate stability data that support the expiration dating period used on the smallest version of the previously accepted product package.

C. The solid oral dosage form product put into unit-dose packaging is manufactured and formulated in the same manner as the product put into the previously accepted packaging.

D. The unit-dose packaging complies with either the Class A or Class B standard described in *USP 23*, under "Single Unit Containers and Unit-Dose Containers for Capsules and Tablets."

E. The firm monitors the long-term stability of each marketed lot of the unit-dose products throughout the expiration dating period for all appropriate specifications, including the strength of active ingredients, by testing each lot at least once every three months. The firm performs the initial (time-zero) testing on a sample that has been packaged in unit-dose packaging for the purpose of evaluating the effect of heat sealing on the product. Once data to support the expiration dating period of up to 18 months have been generated using appropriate stability testing on at least three lots, the firm may discontinue testing every marketed lot in unit-dose packaging. Expiration dating periods of longer than 18 months on unit-dose packaging may be used once appropriate stability data have been obtained that fully support the expiration dating period prior to marketing the lots.

F. If any of the testing, examinations, or investigations performed by the firm reveal that a product may not meet appropriate specifications prior to the expiration date assigned to the product, the firm will reevaluate the expiration dating period for the product. If, based on the reevaluation, the firm determines that a shortened expiration dating period is appropriate, it will use the shortened period for subsequent marketed lots of the same product.

G. The firm conducts a prompt recall of any lot that falls outside of appropriate specifications.

H. The firm is operating in compliance with the CGMP regulations, in 21 CFR parts 210 and 211, and with the iron regulations, in § 310.518, in all other respects.

The FDA expects that sufficient stability testing will be performed in a timely fashion; therefore, the agency does not expect to be guided by this statement of policy after *July 15, 1999.*