Guidance for Industry

Organ-Specific Warnings: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use — Labeling for Products That Contain Acetaminophen

DRAFT GUIDANCE

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

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I. INTRODUCTION

This draft guidance informs manufacturers of over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic (IAAA) drug products that contain acetaminophen of the circumstances in which FDA intends to exercise enforcement discretion with regard to the liver warning required under § 201.326(a)(1)(iii)(A) (21 CFR 201.326(a)(1)(iii)(A)).

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents 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


This draft guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
Contains Nonbinding Recommendations

Draft—Not for Implementation

Section 201.326(a)(1)(iii)(A) requires that the labeling for OTC IAAA products that contain acetaminophen and are labeled for adults only include the following liver warning:

**Liver warning:** This product contains acetaminophen. Severe liver damage may occur if you take ● More than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount [optional: “for this product”] ● With other drugs containing acetaminophen ● 3 or more alcoholic drinks every day while using this product.

Although the currently proposed maximum daily dose of acetaminophen is 4,000 milligrams (mg), some OTC products that contain acetaminophen have directions for use that provide a maximum daily dose of acetaminophen that is less than 4,000 mg for that product. Directions for use can result in a maximum daily dose of acetaminophen that is less than 4,000 mg for a variety of reasons, including additional active ingredient(s) in the drug product, and administration and dosage limitations based upon specific product indications and intended uses. In other instances, the limit on the daily dose of acetaminophen can be the result of a voluntary limitation by the manufacturer. For example, the maximum number of daily dosage units for an OTC acetaminophen-diphenhydramine combination drug intended as nighttime sleep aid and internal analgesic product is limited by the product’s indication, and the total daily dose of acetaminophen for the product is significantly less than 4,000 mg. The optional statement, “for this product,” in the first bullet of § 201.326(a)(1)(iii)(A) is intended to provide language to help consumers understand that the maximum number of daily dosage units for a product might not reflect the maximum daily dose of acetaminophen. However, the Agency understands that in certain circumstances, despite this optional statement, the wording of the first bulleted warning required under § 201.326(a)(1)(iii)(A) might be interpreted as indicating that severe liver damage is associated with a total daily dose of acetaminophen that is less than 4,000 mg. This suggestion is not intended by the regulation.

To address this potential confusion for OTC acetaminophen-containing products with directions for use that result in a maximum daily dose of less than 4,000 mg of acetaminophen, the Agency intends to exercise enforcement discretion in the circumstances described in section III.A below.

III. DISCUSSION AND POLICY

A. Products Labeled for Adults Only

When an OTC IAAA product containing acetaminophen is labeled for adults only and its directions for use result in a maximum daily dose of acetaminophen for the product that is less than 4,000 mg, FDA intends to exercise enforcement discretion if a manufacturer chooses to use

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2 The Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antiarthrotic Drug Products for OTC Human Use currently proposes that an OTC IAAA product with a daily dose of acetaminophen that does not exceed 4,000 milligrams (mg) in 24 hours, among other things, be considered generally recognized as safe and effective and not misbranded (see 53 FR 46204 at 46257 (November 16, 1988)).
the following language on the drug’s labeling, in place of the liver warning required by § 201.326(a)(1)(iii)(A):

Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take: ● More than 4,000 mg of acetaminophen in 24 hours ● With other drugs containing acetaminophen ● 3 or more alcoholic drinks every day while using this product.

FDA believes that this alternative language should eliminate the potential confusion described above and help ensure appropriate dosing of OTC acetaminophen-containing products, while also informing consumers that using more than the currently proposed maximum daily dose of 4,000 mg of acetaminophen may result in severe liver damage.

B. Products That Are Not Labeled for Adults Only

OTC IAAA products containing acetaminophen that are labeled only for children under 12 years of age, or for both adults and children under 12 years of age, must include in their labeling the liver warnings required under § 201.326(a)(1)(iv) and (v), respectively. For acetaminophen products labeled only for use by children under 12 years of age, the required liver warning explicitly states that severe liver damage may occur if a child takes more than 5 doses in 24 hours, rather than more than the maximum number of daily dosage units for the particular product. For acetaminophen products labeled for use by both adults and children under 12 years of age, the required liver warning allows for different maximum daily doses based on age. For these products, FDA believes that the language described in section III.A. above would likely add to consumer confusion about appropriate dosing. Therefore, FDA is not describing any general circumstances in which it intends to exercise enforcement discretion with respect to the liver warnings required for OTC IAAA acetaminophen products that are not labeled for adults only.