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

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

**November 2015
OTC**

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Organ-Specific Warnings: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use — Labeling for Products That Contain Acetaminophen Guidance for Industry¹

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I. INTRODUCTION

This guidance is intended to inform manufacturers of certain nonprescription (also referred to as over-the-counter or (OTC)) internal analgesic, antipyretic, and antirheumatic (IAAA) drug products that contain acetaminophen of the circumstances in which FDA does not intend to object to the inclusion of a liver warning that differs from that required under § 201.326(a)(1)(iii)(A) and § 201.326(a)(1)(v)(A) (21 CFR 201.326(a)(1)(iii)(A) and 21 CFR 201.326(a)(1)(v)(A)), provided the warning appears as described below.

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

In the *Federal Register* of December 26, 2006 (71 FR 77314), FDA published a proposed rule on organ-specific warnings and related labeling for OTC IAAA drug products. In the *Federal Register* of April 29, 2009 (74 FR 19385), FDA published the final rule (2009 final rule). On November 25, 2009, FDA published a technical amendment (74 FR 61512) to clarify several provisions in response to industry feedback. The 2009 final rule, as amended, changed some of the labeling requirements for OTC IAAA drug products to inform consumers about the risk of liver injury when using acetaminophen, and the risk of stomach bleeding when using nonsteroidal anti-inflammatory drugs. It went into effect on April 29, 2010, and is codified at 21 CFR 201.326.

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

Contains Nonbinding Recommendations

Section 201.326(a)(1)(iii)(A) requires that the labeling for OTC IAAA products that contain acetaminophen that are labeled for adults only include the liver warning described below. Section 201.326(a)(1)(v)(A) requires that the labeling for OTC IAAA products that contain acetaminophen and are labeled for adults and children under 12 years of age must include in their labeling a similar but not identical liver warning as described below:

Adults Only (§ 201.326(a)(1)(iii)(A)):

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.

Adults and children under 12 years of age (§ 201.326(a)(1)(v)(A)):

Liver warning: This product contains acetaminophen. Severe liver damage may occur if • adult takes more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount [optional: “for this product”] • child takes more than 5 doses in 24 hours • taken with other drugs containing acetaminophen • adult has 3 or more alcoholic drinks every day while using this product.

Although the currently proposed maximum daily dose of acetaminophen for adults is 4,000 milligrams (mg),² some OTC IAAA products that contain acetaminophen have directions for use that provide a maximum daily dose of acetaminophen for that product that is less than 4,000 mg. 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 a 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) and § 201.326(a)(1)(v)(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) and § 201.326(a)(1)(v)(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 the intent of the regulation.

² The Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic 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)).

Contains Nonbinding Recommendations

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 does not intend to object to the inclusion of liver warnings as described in section III.A below in the labeling of such products.

III. DISCUSSION AND POLICY

A. Products labeled for adults only and products labeled for adults and children under 12 years of age

When an OTC IAAA product containing acetaminophen is labeled for adults only or labeled for adults and children under 12 years of age and its directions for use result in a maximum daily dose of acetaminophen for the product that is less than 4,000 mg for adults, FDA does not intend to object if a manufacturer chooses to use the following language on the drug's labeling, in place of the first bullet of the liver warnings required by § 201.326(a)(1)(iii)(A) and § 201.326(a)(1)(v)(A), respectively:

Adults Only:

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.

Adults and children under 12 years of age:

Liver warning: This product contains acetaminophen. Severe liver damage may occur if • adult takes more than 4,000 mg of acetaminophen in 24 hours • child takes more than 5 doses in 24 hours • taken with other drugs containing acetaminophen • adult has 3 or more alcoholic drinks every day while using this product.

FDA believes that this alternative language in the first bullet 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 for adults may result in severe liver damage.

B. Products labeled only for children under 12 years of age

OTC IAAA products containing acetaminophen that are labeled only for children under 12 years of age must continue to include in their labeling the liver warning required under § 201.326(a)(1)(iv) and described below :

Children under 12 years of age:

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Liver warning: This product contains acetaminophen. Severe liver damage may occur if your child takes: • more than 5 doses in 24 hours, which is the maximum daily amount [optional: “for this product”] • with other drugs containing acetaminophen.