
Guidance for Industry

Organ-Specific Warnings: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use — Small Entity Compliance Guide

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

**July 2010
OTC**

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to help small businesses understand and comply with FDA's organ-specific labeling regulation for over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic (IAAA) drug products. The regulation requires IAAA manufacturers to label their products with specific warnings and related information to alert consumers about potential liver injury and stomach bleeding associated with IAAA drug products. Manufacturers must be in compliance with the final rule beginning on April 29, 2010. The Food and Drug Administration (FDA) has prepared this guidance in accordance with section 212 of the Small Business Regulatory Fairness Act (Public Law 104-121).

FDA's guidance documents, including this guidance, 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. SUMMARY OF THE REGULATION AND THIS GUIDANCE

In the *Federal Register* of December 26, 2006 (71 FR 77314), the FDA published a proposed rule on the requirements for compliance with FDA's organ-specific labeling regulation for OTC IAAA drug products. In the *Federal Register* of April 29, 2009 (74 FR 19385), the FDA

¹ This small business compliance guide was developed by the Office of Nonprescription Products in the Center for Drug Evaluation and Research, FDA.

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published the final rule (2009 final rule), codified at 21 CFR 201.326.² On November 25, 2009, FDA published technical amendments to clarify several points in response to industry feedback.

The 2009 final rule changed the labeling requirements for OTC IAAA drug products by adding new warnings about liver injury for those using acetaminophen, and stomach bleeding for those using nonsteroidal anti-inflammatory drugs (NSAIDs). The rule also makes related changes to the principal display panel (PDP), ingredient listings, and other labeling information to highlight the presence of acetaminophen or NSAIDs and draw attention to the organ-specific warnings. Table 1 summarizes the requirements in the final rule. The specific language to be used in required warnings is shown in Table 2. You also will need to refer directly to the final rule for additional formatting instructions, such as type sizes, that are not described in this guidance.

² The regulation published in the Code of Federal Regulations (CFR) will reflect both the final rule and the technical amendments. This regulation replaces the alcohol warning that was previously in 21 CFR 201.322; the alcohol warning is now in 21 CFR 203.326(a)(1)(iii)(A).

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Table 1: Summary of Labeling Requirements

<p>Acetaminophen Products (21 CFR 201.326(a)(1))</p>	<ul style="list-style-type: none"> • Requirements apply to any OTC IAAA product containing acetaminophen, either alone or in combination with other active ingredients. • “Acetaminophen” must be included in the statement of identity on the principal display panel (PDP). • A “see new warning information” flag must appear on the PDP of all products that were first marketed on or before April 29, 2010, and must continue to be used for 1 year after the flag is first added to the PDP. • The “Warnings” section of Drug Facts labeling must include a “liver warning,” and related warnings against using more than one acetaminophen product at the same time, and “ask a doctor” warnings for persons who have liver disease or are taking warfarin. • If a retail product has both an outer and inner package/container, the “liver warning” must appear on both. • Different warning language is used for products labeled only for adults, only for children under 12 years old, or for adults and children under 12 years old. • Specific language to be used in required warnings is shown in Table 2 of this guidance. • Required labeling also must follow the instructions on format and placement detailed in the regulations (e.g., bolding/highlighting, type size, order of warnings).
<p>NSAID products (21 CFR 201.326(a)(2))</p> <p>(NSAIDs include, but are not limited to, the following active ingredients: aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate.)</p>	<ul style="list-style-type: none"> • Applies to any OTC IAAA product containing any NSAID active ingredient, either alone or in combination with other active ingredients. • The word “NSAID” must be included in the statement of identity on the PDP, either as part of the ingredient name (e.g., “ibuprofen (NSAID)”, or after the intended action of the NSAID ingredient (e.g., “Pain Reliever (NSAID)”). • A “see new warning information” flag must appear on the PDP of all products that were first marketed on or before April 29, 2010, and must continue to be used for 1 year after the flag is first added to the PDP. • The “Ingredients” section of the label must contain the term “NSAID*” after the NSAID ingredient, with an

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	<p>asterisk statement at the end of the ingredient list that states “*nonsteroidal anti-inflammatory drug.”</p> <ul style="list-style-type: none">• The “Warnings” section of Drug Facts labeling must include a “stomach bleeding warning” and related “ask a doctor” warnings.• If a retail product has both an outer and inner package/container, the “stomach bleeding warning” must appear on both.• Different warning language is used for products labeled only for adults, only for children under 12 years old, or for adults and children under 12 years old.• For products labeled only for children under 12 years old, the “Directions” section of the label must state “this product does not contain directions or complete warnings for adult use.”• Specific language to be used in required warnings is shown in Table 2 of this guidance.• Required labeling also must follow the instructions on format and placement detailed in the regulations (e.g., bolding/highlighting, type size, order of warnings).
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III. QUESTIONS AND ANSWERS

Question: Is the product I manufacture subject to this rule?

Answer: This rule applies to all OTC IAAA drug products that contain acetaminophen or any NSAID, either as a single active ingredient or in combination with any other active ingredients. This rule applies to OTC IAAA drug products marketed under an OTC monograph or an approved new drug application (NDA) or abbreviated new drug application (ANDA). This rule does not apply to topical drug products that contain acetaminophen or NSAIDs.

Question: How do I know if an active ingredient in my product is an NSAID?

Answer: NSAIDs are analgesic/antipyretic ingredients used to relieve pain, fever, and/or inflammation. They include, but are not limited to, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate. If you are uncertain whether an ingredient is an NSAID, ask the FDA Contact shown below.

Question: I manufacture an OTC IAAA product with annual sales of less than \$25,000. Is my drug product subject to this rule?

Answer: Yes. Small businesses are not exempt from this rule.

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Question: **When must I be in compliance with this rule? Can I still distribute inventory that was labeled, but not shipped, before the new requirements became effective?**

Answer: This rule (including the November 25, 2009, technical amendments) became effective on April 29, 2010. After that time, all products that you introduce or deliver for introduction into interstate commerce must be labeled in compliance with this rule.

Question: **What will happen if I fail to comply with this rule by April 29, 2010?**

Answer: Beginning April 29, 2010, your drug product will be misbranded under section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(f)(2)), and subject to regulatory action.

Question: Does the regulation specify the exact language I must use for warnings and other required label statements?

Answer: Table 2 shows the exact language that must be used for the required warning statements. The rule also specifies exact language for some other required statements (e.g., statement of identity, ingredient lists, directions); these are indicated by quotation marks in Table 1.

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Table 2: Required Wording for Warnings

	Acetaminophen	NSAIDs
Products Labeled for Adults Only	<p>“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.”</p> <p>“Do not use with any other drug containing acetaminophen (prescription or non-prescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.”</p> <p>“Ask a doctor before use if you have liver disease.”</p> <p>“Ask a doctor or pharmacist before use if you are taking the blood thinning drug warfarin.”</p> <p>[Note: this statement does not apply to combination products that contain acetaminophen and NSAIDs, which are already required to include a warning about blood thinning drugs under the stomach bleeding warning for NSAIDs.]</p>	<p>“Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you • are age 60 or older • have had stomach ulcers or bleeding problems • take a blood thinning (anticoagulant) or steroid drug • take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) • have 3 or more alcoholic drinks every day while using this product • take more or for a longer time than directed.”</p> <p>“Ask a doctor before use if • stomach bleeding warning applies to you • you have a history of stomach problems, such as heartburn • you have high blood pressure, heart disease, liver cirrhosis, or kidney disease • you are taking a diuretic.”</p> <p>“Stop use and ask a doctor if you experience any of the following signs of stomach bleeding: • feel faint • vomit blood • have bloody or black stools • have stomach pain that does not get better.”</p>

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	Acetaminophen	NSAIDs
Products labeled only for children under 12 years of age	<p>“Liver warning: This product contains acetaminophen. Severe liver damage may occur if your child takes</p> <ul style="list-style-type: none"> • more than 5 doses in 24 hours, which is the maximum daily amount • with other drugs containing acetaminophen.” <p>“Do not use with any other drug containing acetaminophen (prescription or non-prescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.”</p> <p>“Ask a doctor before use if your child has liver disease.”</p> <p>“Ask a doctor or pharmacist before use if your child is taking the blood thinning drug warfarin.” [Note: this statement does not apply to combination products that contain acetaminophen and NSAIDs, which are already required to include a warning about blood thinning drugs under the stomach bleeding warning for NSAIDs.]</p>	<p>“Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if your child</p> <ul style="list-style-type: none"> • has had stomach ulcers or bleeding problems • takes a blood thinning (anticoagulant) or steroid drug • takes other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others) • takes more or for a longer time than directed.” <p>“Ask a doctor before use if</p> <ul style="list-style-type: none"> • stomach bleeding warning applies to your child • child has a history of stomach problems, such as heartburn • child has not been drinking fluids • child has lost a lot of fluid due to vomiting or diarrhea • child has high blood pressure, heart disease, liver cirrhosis, or kidney disease • child is taking a diuretic.” <p>“Stop use and ask a doctor if child experiences any of the following signs of stomach bleeding:</p> <ul style="list-style-type: none"> • feels faint • vomits blood • has bloody or black stools • has stomach pain that does not get better.”
Products Labeled for Adults and Children Under 12 Years of Age	<p>“Liver warning: This product contains acetaminophen. Severe liver damage may occur if</p> <ul style="list-style-type: none"> • adult takes more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount • child takes more than 5 doses in 24 hours 	<p>“Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if the user</p> <ul style="list-style-type: none"> • has had stomach ulcers or bleeding problems • takes a blood thinning (anticoagulant) or steroid drug • takes other drugs containing prescription

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	Acetaminophen	NSAIDs
	<ul style="list-style-type: none"> • taken with other drugs containing acetaminophen • adult has 3 or more alcoholic drinks everyday while using this product.” <p>“Do not use with any other drug containing acetaminophen (prescription or non-prescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.”</p> <p>“Ask a doctor before use if the user has liver disease.”</p> <p>“Ask a doctor or pharmacist before use if the user is taking the blood thinning drug warfarin.” [Note: this statement does not apply to combination products that contain acetaminophen and NSAIDs, which are already required to include a warning about blood thinning drugs under the stomach bleeding warning for NSAIDs.]</p>	<p>or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)</p> <ul style="list-style-type: none"> • takes more or for a longer time than directed • is age 60 or older • has 3 or more alcoholic drinks everyday while using this product.” <p>“Ask a doctor before use if</p> <ul style="list-style-type: none"> • stomach bleeding warning applies to user • user has history of stomach problems, such as heartburn • user has high blood pressure, heart disease, liver cirrhosis, or kidney disease • user takes a diuretic • user has not been drinking fluids • user has lost a lot of fluid due to vomiting or diarrhea.” <p>“Stop use and ask a doctor if user experiences any of the following signs of stomach bleeding:</p> <ul style="list-style-type: none"> • feels faint • vomits blood • has bloody or black stools • has stomach pain that does not get better.”

Question: Are the required warnings different for children and adults?

Answer: Yes. Different language is used for products labeled for adults only, products labeled only for children under 12 years of age, and products labeled for both adults and children under 12 years old. Please refer to Table 2 above for details.

Question: Does the regulation also contain instructions about the format and/or appearance of warnings and other required labeling?

Answer: Yes. You must refer to the regulation for specific instructions about the appearance, format, and placement of the required labeling (e.g., bolding/highlighting, type size and prominence, order of acetaminophen and/or NSAID warnings, and other applicable warnings). Your labeling also must

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comply with other applicable labeling requirements under the OTC monograph for IAAA drugs as well as the general labeling regulations for all OTC drugs in 21 CFR part 201, subpart C, including the “Drug Facts” labeling requirements in 21 CFR 201.66.

Question: **The retail package of my product has both an outer carton and an immediate container. Are the liver injury and stomach bleeding warnings required on the outer carton and the immediate container?**

Answer: Yes, these warnings must appear on both the outer container (e.g., carton) and the immediate (inner) container of a retail package. If the immediate container is a blister card, the warnings must appear on the blister card and remain intact and readable when the drug product is removed from the blister card. The warnings do not need to be included on each blister unit.

Question: **The retail package of my product consists of multi-dose blister cards inside a carton. What must I do to comply with the requirements to put the liver or stomach bleeding warning on the “immediate container”?**

Answer: Each blister card is considered a separate immediate container. In this case, the appropriate warning must appear on each blister card and remain intact and readable when individual doses of the product are removed from the blister card. This point was clarified in the technical amendments published on November 25, 2009.

Question: **Apart from blister cards, are there any exceptions or special provisions for other kinds of immediate containers that have limited space for labeling, such as stick packs and sachets?**

Answer: No. FDA believes that these types of immediate containers can accommodate the required warnings. We also are concerned that consumers may routinely remove these packages from the outer carton and fail to see the liver injury and stomach bleeding warnings if they are only printed on the carton.

Question: **What products are required to have the “see new warning information” flag on the PDP? How long must the flag remain on the PDP?**

Answer: The “see new warning information” must appear on the PDP of all OTC acetaminophen- or NSAID-containing IAAA products first marketed on or before April 29, 2010, and remain on the product for at least 1 year after the product is initially introduced into interstate commerce. Products newly introduced after that date do not require the flag, but must have all other organ-specific labeling required by this rule.

Question: **Do I need preapproval from FDA for labeling changes required by this rule?**

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Answer: For products marketed under the IAAA monograph, you do not need preapproval of labeling changes. For products marketed under NDAs and ANDAs, you will need to submit a CBE 0 (change to be effective immediately) labeling supplement.

Question: Do I need to list my revised labeling with FDA?

Answer: Yes. This change in labeling should be submitted to FDA through the drug listing process. Any updates must be submitted every June and December (section 510(j)(2) of the Federal Food, Drug, and Cosmetic Act; 21 CFR 207.21(b)). However, registrants (and, if applicable, private label distributors) are encouraged to submit updates through the registration and listing system more frequently as changes occur. Information on this process can be found at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm078801.htm>.

Question: **Does this rule apply to topical IAAA products?**

Answer: No, only internal (oral) OTC IAAA products are affected by this rule.

Question: **If I have questions about whether the drug product I manufacture is subject to this rule, how to comply with the rule, or any related issues, whom should I contact at FDA?**

Answer: You should contact Arlene Solbeck, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, MS 5411, Silver Spring, MD 20993, 301-796-2090.