Recommended Warning for Over-the-Counter Acetaminophen-Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions

Guidance for Industry

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

January 2017
Compliance

Contains Nonbinding Recommendations

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Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA is informing manufacturers, members of the medical and scientific community, and other interested persons that at this time we do not intend to take action against the marketing of single- and combination-ingredient, acetaminophen-containing, nonprescription (commonly referred to as over-the-counter (OTC)) drug products bearing an allergy warning as described in this guidance (see section III, Discussion and Policy) alerting consumers that the use of acetaminophen may cause severe skin reactions.[2] This guidance is intended to apply to single- and combination-ingredient acetaminophen-containing products marketed under the Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) Drug Products for Over-the-Counter Human Use, published in the *Federal Register* (53 FR 46204, November 16, 1988).

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

Acetaminophen, included in many prescription and OTC products, is a common active ingredient indicated to treat pain and reduce fever. On August 1, 2013, FDA issued a Drug Safety Communication (DSC) informing the public that use of acetaminophen has been associated with

[1] This guidance has been prepared by the Office of Unapproved Labeling Compliance in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] Acetaminophen containing combination products include acetaminophen in combination with cough and cold products (see 21 CFR 341.40), acetaminophen in combination with antacids (see 21 CFR 331.15), and acetaminophen in combination with diuretics (53 FR 46194 at 46201, November 16, 1988) as described in the IAAA TFM (53 FR 46204 at 46255, November 16, 1988).

a risk of rare but serious skin reactions.[3] These skin reactions, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, can be fatal.

The DSC explained that reddening of the skin, rash, blisters, and detachment of the upper surface of the skin can occur with the use of drug products that contain acetaminophen. These skin reactions can occur with the first-time use of acetaminophen or even if acetaminophen has been used in the past without any problems. FDA advised health care professionals to be aware of this rare risk and consider acetaminophen, along with other drugs already known to have such an association, when assessing patients with potentially drug-induced skin reactions. FDA also advised that anyone who develops a skin rash or reaction while using acetaminophen or any other pain reliever/fever reducer should stop taking the drug and seek medical attention right away. Furthermore, the announcement advised that anyone who has experienced a serious skin reaction when taking acetaminophen in the past should not take the drug again and should contact their health care professional to discuss alternative pain relievers/fever reducers.

In the announcement, FDA stated that it planned to require manufacturers of acetaminophen-containing prescription drug products to include a warning statement on their product labels to address the risk of serious skin reactions and that it would request the same warning be added by manufacturers of OTC acetaminophen-containing drug products marketed under an approved application. In the fall of 2013, FDA sent letters to manufacturers holding new drug applications (NDA) and abbreviated new drug applications (ANDA) requiring in some cases and requesting in others that a warning statement be included on the labeling for all products (both prescription and OTC) containing acetaminophen marketed under NDAs and ANDAs. At this time, all of the required labeling changes and most of the requested labeling changes have been made by the relevant manufacturers.

FDA also indicated that it planned to encourage manufacturers of acetaminophen-containing drug products marketed under the TFM to similarly add a warning about serious skin reactions to their product labels.

III. DISCUSSION AND POLICY

FDA recommends that manufacturers of all acetaminophen-containing OTC drug products (both single- and combination-ingredient acetaminophen products) marketed pursuant to the TFM for IAAA Drug Products include language in labeling warning consumers that acetaminophen may cause severe skin reactions.

At this time, FDA does not intend to take action against the marketing of products containing the following allergy warning language, as long as those products are otherwise marketed in compliance with the TFM and applicable regulations:

[3] FDA Drug Safety Communication: FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen. http://www.fda.gov/Drugs/DrugSafety/ucm363041.htm.

> Allergy alert: Acetaminophen may cause severe skin reactions. Symptoms may include: [bullet] skin reddening [bullet] blisters [bullet] rash
> If a skin reaction occurs, stop use and seek medical help right away.

This guidance does not address alternative allergy warning language that may otherwise misbrand the product.

The recommended allergy warning should appear under the "Warnings" heading section of the Drug Facts label under the subheading "Allergy Alert," and, when included, must directly follow the liver warning (21 CFR 201.326) on acetaminophen-containing drug products. FDA recommends that this warning be included on all packaging configurations.

For products that contain both acetaminophen and aspirin, the Allergy alert warning, when included, must appear after the Reye's syndrome warning and before the Liver and Stomach bleeding warnings (21 CFR 201.326).

IV. EXAMPLE OTC DRUG FACTS LABELS WITH RECOMMENDED WARNING

Products Containing Acetaminophen Only

Drug Facts
Active Ingredient (in each [insert dosage form]) **Purpose** **Acetaminophen XXX mg……..……...Pain reliever/fever reducer**
Uses *(Insert as described in an applicable OTC drug monograph or approved drug application.)*
Warnings **Liver warning:** This product contains acetaminophen. Severe liver damage may occur if you take: ▪ more than [insert quantity and dosage form] in 24 hours, which is the maximum daily amount ▪ with other drugs containing acetaminophen ▪ 3 or more alcoholic drinks every day while using this product **Allergy alert:** Acetaminophen may cause severe skin reactions. Symptoms may include: ▪ skin reddening ▪ blisters ▪ rash If a skin reaction occurs, stop use and seek medical help right away.
Do not use ▪ with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist. ▪ for more than 10 days for pain unless directed by a doctor ▪ for more than 3 days for fever unless directed by a doctor
Ask a doctor before use if you have ▪ liver disease
Ask a doctor or pharmacist before use if ▪ you are taking the blood thinning drug warfarin
Stop using and ask a doctor if ▪ symptoms do not improve ▪ new symptoms occur ▪ pain or fever persists or gets worse

If pregnant or breast-feeding, ask a health professional before use**.**

Keep out of reach of children. In case of accidental overdose, get medical help or contact a Poison Control Center right away. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

Directions
(Insert as described in an applicable OTC drug monograph or approved drug application.)

Other Information
(Insert any additional information that is not included under the other subheadings but which is required or is made optional under an OTC drug monograph(s), other OTC drug regulation(s), approved drug application, statute, or OTC drug guidance.)

Inactive Ingredients
(Insert a list of each inactive ingredient, using its established name.)

Questions or Comments
(Insert optional heading used to provide a telephone number of a source to answer questions about the drug product or to receive reports of adverse events associated with the use of the drug product.)

Products Containing Acetaminophen and Aspirin

Drug Facts

Active Ingredient (in each [insert dosage form]) Purpose
Acetaminophen XXX mg……..……...Pain reliever/fever reducer
Aspirin XXX mg (NSAID)*.……...Pain reliever/fever reducer
***nonsteroidal anti-inflammatory drug**

Uses
(Insert as described in an applicable OTC drug monograph or approved drug application.)

Warnings
Reye's syndrome: Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness.

Allergy alert: Aspirin may cause a severe allergic reaction which may include:
- hives.
- facial swelling.
- asthma (wheezing).
- shock.

Allergy alert: Acetaminophen may cause severe skin reactions. Symptoms may include:
- skin reddening
- blisters
- rash

If a skin reaction occurs, stop use and seek medical help right away.

Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take:
- more than [insert quantity and dosage form] in 24 hours, which is the maximum daily amount
- with other drugs containing acetaminophen
- 3 or more alcoholic drinks every day while using this product

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
Do not use ▪ with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist. ▪ for more than 10 days for pain unless directed by a doctor ▪ for more than 3 days for fever unless directed by a doctor
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

Stop using and ask a doctor if
▪ symptoms do not improve
▪ new symptoms occur
▪ pain or fever persists or gets worse
▪ 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
▪ if ringing in the ears or a loss of hearing occurs, consult a doctor before taking any more of this product.

If pregnant or breast-feeding, ask a health professional before use**.** It is especially important not to use aspirin during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery. **Keep out of reach of children.** In case of accidental overdose, get medical help or contact a Poison Control Center right away. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.
Directions *(Insert as described in an applicable OTC drug monograph or approved drug application.)*
Other Information *(Insert any additional information that is not included under the other subheadings but which is required or is made optional under an OTC drug monograph(s), other OTC drug regulation(s), approved drug application, statute, or OTC drug guidance.)*
Inactive Ingredients *(Insert a list of each inactive ingredient, using its established name.)*
Questions or Comments *(Insert optional heading used to provide a telephone number of a source to answer questions about the drug product or to receive reports of adverse events associated with the use of the drug product.)*

For additional questions regarding this guidance, contact Emily Baker, Office of Unapproved Drugs and Labeling Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-7524, Emily.Baker@fda.hhs.gov.