Over-the-Counter Pediatric Oral Liquid Drug Products Containing Acetaminophen

Guidance for Industry

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

August 2015
Drug Safety

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Contains Nonbinding Recommendations

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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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to help drug manufacturers, packagers, and labelers minimize the risk to consumers of acetaminophen-related liver damage associated with the use of nonprescription also known as over-the-counter or OTCpediatric oral liquid acetaminophen drug products. Many of these products are marketed under the OTC conditions stated in FDA's Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for OTC Human Use (the IAAA TFM).[2] FDA plans to address portions of the tentative final monograph through the notice and comment rulemaking process. In the meantime, however, to encourage safer use of these products, we are providing recommendations regarding acetaminophen concentration, container labels, carton labeling, and packaging of such products as well as for any associated delivery devices. FDA's recommendations are designed to encourage safer use of these products by minimizing the potential for acetaminophen overdosing due to medication errors or accidental ingestion. Unless otherwise specified, these recommendations apply to both single-ingredient and combination-ingredient OTC oral liquid drug products (such as suspensions, solutions, elixirs, and syrups) that are labeled for use in children under 12 years of age and contain acetaminophen. This guidance does not address OTC acetaminophen oral liquid drug products for use in both children and adults or for adults only.

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.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at FDA.

[2] "Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph," 53 FR 46204 (November 16, 1988), available at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/UCM078460.pdf.

II. BACKGROUND

Acetaminophen is marketed in many OTC drug products as a pain reliever and fever reducer. Most OTC acetaminophen products are marketed under FDA's ongoing rulemaking to establish a final monograph for OTC IAAA drug products.[3] These products must conform to the conditions described in the IAAA TFM and FDA's general regulations for OTC drug marketing (21 CFR 330.1) and labeling (21 CFR 330.10 and part 201). They also must be labeled with acetaminophen-related warnings and other information as specified in 21 CFR 201.326.

OTC pediatric oral liquid drug products containing acetaminophen have been associated with overdoses due to medication errors that resulted in serious adverse events, including severe liver damage and death. In particular, there have been reports of overdose attributed to confusion between concentrated acetaminophen drops (80 milligrams (mg)/0.8 milliliters (mL) and 80 mg/mL) and acetaminophen oral liquid (160 mg/5 mL). In addition to overdoses due to dosing errors, there have been reports of overdose from accidental ingestion by children.

This guidance is part of FDA's ongoing initiative to reduce the risk of acetaminophen-related liver injury associated with all OTC and prescription acetaminophen-containing products. As part of that initiative, in June of 2009, three FDA committees, the Drug Safety and Risk Management Advisory Committee, the Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee, met jointly to consider a range of risk reduction measures. Among other measures, these Advisory Committees recommended moving to a single, standardized acetaminophen concentration for OTC pediatric oral liquid drug products because the availability of multiple concentrations causes confusion and errors among both consumers and health care professionals.[4]

In May of 2011, FDA convened a joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee to discuss the use of acetaminophen in children.[5] Shortly before the meeting, the Consumer Healthcare Products Association (CHPA) proposed to voluntarily phase out all of the existing single-ingredient concentrated drop formulations of OTC pediatric oral liquid drug products and market only the 160 mg/5 mL

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[3] For more information about the IAAA monograph, see FDA's Web site at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm070484.htm#Original, and "Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph," 53 FR 46204 (November 16, 1988) (IAAA TFM), available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/UCM078460.pdf.

[4] Summary Minutes of the Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee, held June 29-30, 2009, are available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM179888.pdf.

[5] Summary Minutes of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee, held May 17-18, 2011, are available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM264147.pdf.

formulation.[6] At the Advisory Committee meeting, FDA took note of CHPA's voluntary transition to a single concentration of pediatric oral liquid acetaminophen.
In response to CHPA's voluntary transition to a single concentration of OTC oral liquid acetaminophen products, FDA published a Drug Safety Communication on December 22, 2011, to inform the public of the 160 mg/5 mL concentration now marketed for children ages 2 to 3 years and to recommend that end users of the product read the Drug Facts label to identify the concentration of the oral liquid acetaminophen, dosage, and directions for use.[7]

FDA is issuing this guidance to address ongoing concerns about the potential for acetaminophen overdose associated with these products and to promote their safe use. Besides overdose due to confusion associated with the multiple pediatric formulations with varying concentrations, there have also been reports of overdose attributed to:

1. Concomitant administration of two products containing acetaminophen;[8]
2. Inadequate prominence of acetaminophen concentration information on container labels and carton labeling;
3. Inconsistent and/or confusing units of measurement (e.g., cc, mL, tsp, and tbsp) under "Directions" in the Drug Facts Panel and elsewhere in labeling;
4. Dosage delivery device not being packaged with the medication; and
5. Poorly designed delivery devices (e.g., devices with difficult-to-read markings or device designs that make it difficult to dispense a precise dose.

FDA issued a guidance for industry on dosage delivery devices in 2011 to help address points 4 and 5.[9]

III. RECOMMENDATIONS

To avoid confusion and the potential for dosing errors, FDA recommends that OTC oral liquids containing acetaminophen for pediatric use be formulated, packaged, labeled, and provided with an appropriate dosing device as described below. Unless noted otherwise, the following recommendations apply to both single-ingredient and combination-ingredient OTC oral liquid

[6] See May 4, 2011, CHPA press release entitled "OTC Industry Announces Voluntary Transition to One Concentration of Single-Ingredient Pediatric Liquid Acetaminophen Medicines," available at http://www.chpa.org/05_04_11_PedAcet.aspx.
[7] FDA Drug Safety Communication: *Addition of another concentration of liquid acetaminophen marketed for infants*, available at http://www.fda.gov/Drugs/DrugSafety/ucm284741.htm.
[8] Mitigating the risk of concomitant administration is addressed in the *Organ-Specific Warnings: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use — Small Entity Compliance Guide*, July 2010. See Table 2 of that guidance. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[9] FDA guidance for industry *Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

drug products that contain acetaminophen and are labeled only for use in children under 12 years of age.[10]

Product Concentration

- All single-ingredient acetaminophen oral liquids for pediatric use marketed under the conditions specified in the IAAA TFM should have a concentration of 160 mg acetaminophen per 5 mL.

Label and Labeling

- For single-ingredient acetaminophen oral liquids, the statements "160 mg/5 mL" or "160 mg per 5 mL" should be prominently presented on the principal display panel (PDP) of the container label and carton labeling immediately below or to the right of the active ingredient name (i.e., acetaminophen) and in the same font size as the active ingredient name.

- If age is presented on the PDP, the age should correspond to the age range and units of age (e.g., months or years) as stated in the Drug Facts Panel under the heading "Directions."

- If there is an image of a child on the PDP, the image should be representative of the age group identified under "Directions" in the Drug Facts label. For example, a product labeled for use in children 2 years of age or older should not show an infant on the PDP.

- Use of the word "new" should always include a statement that specifies what is new about the product (such as new directions or a new delivery device). This statement should be in conjunction with and have the same prominence as the word "new." Unless required by the Agency, any statement describing the product as "new" should not appear for a period longer than 6 months.

- The dosing directions in the Drugs Facts label should be provided only in milliliters (mL).

- If an included dosage delivery device is not clearly visible at point-of-sale, an image or picture of the dosage delivery device should appear on the PDP. It should be located on the lower half of the PDP and the dosage delivery device may appear empty or depict the lowest labeled dose.

[10] The Agency may consider issuing future guidance to industry that addresses additional topics such as patient populations;, age- or weight-based dosing;, formulation properties (e.g., solubility, viscosity);, and instructions for cleaning, reuse, and storage of delivery devices.

Drug Delivery[11]

- The product package should include an appropriate dosage delivery device, such as a calibrated and labeled oral syringe or dosing cup.[9]

- As the dosing directions should be in milliliters (mL), accordingly the dosage delivery devices should have calibrated units of liquid measurement expressed in milliliters (mL) only.

- If a firm wants to provide a dosage delivery device other than a graduated, clearly marked oral cup or syringe, it should conduct usability studies before the device is introduced into the market to ensure the device can be easily understood and accurately used by consumers. In such cases, we encourage the firm to discuss the proposed innovative dosage delivery device with FDA before introducing the device into the market.

- We recommend the adoption of container features designed to improve safety by potentially contributing to more accurate dosing and helping to reduce the incidence and magnitude of accidental acetaminophen ingestion by children, such as an appropriate flow restrictor contained in the opening of the immediate container. If a flow restrictor is included, it should be attached to the container in a way that prevents it from being pushed into the bottle or easily removed. Firms are encouraged to discuss innovative containers/packaging features with FDA before introduction into the market.[12]

[11] This guidance is not intended to address the adequacy of dosage delivery devices to deliver the labeled dosage.
[12] If applicable, these products must be compliant with the poison prevention packaging standards found in Title 16 of the Code of Federal Regulations (16 CFR 1700.15).