

Submitted electronically via www.regulations.gov

December 8, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comments on the Draft Guidance for Industry - “Over-the-Counter Pediatric Liquid Drug Products Containing Acetaminophen”. 79 Fed. Reg. 60854-60855 (October 8, 2014). Docket No. FDA-2014-D-1473

The Consumer Healthcare Products Association (CHPA¹) appreciates the opportunity to provide comments to the FDA in response to the October 8, 2014 Federal Register notice announcing the availability of draft guidance for industry “Over-the-Counter Pediatric Liquid Drug Products Containing Acetaminophen”. CHPA and its member companies have an interest and expertise in acetaminophen-containing over-the-counter (OTC) products and support FDA’s efforts to improve the safe use of acetaminophen.

FDA has noted that this draft guidance is intended to help drug manufacturers minimize the risk to consumers of acetaminophen-related liver damage resulting from medication errors or accidental ingestion of OTC acetaminophen-containing pediatric liquid drug products. A number of recommendations are provided for acetaminophen concentration, container labels and carton labeling, packaging, and associated delivery devices.

CHPA members continue to support approaches to reduce adverse events associated with misuse/overdose and accidental unsupervised ingestion of acetaminophen-containing products sold OTC. To this end, CHPA members have undertaken a number of efforts aimed at enhancing the safe use of acetaminophen products including a voluntary action to phase out all existing concentrated drop formulations of OTC, single-ingredient, oral, liquid acetaminophen products and market only the 160 mg/5mL formulation.

The CHPA Educational Foundation is a member of the Acetaminophen Awareness Coalition which works to educate patients and consumers on the appropriate use of acetaminophen-containing medications. CHPA and a number of its members participate in an American Society for Testing and Materials (ASTM) work group developing standard practice test characteristics to measure the efficacy of flow restrictors/flow control devices in limiting accessibility of liquid medicine contents to young children. CHPA has also recently updated its voluntary guidelines²

¹ CHPA, founded in 1881, is a national trade association representing manufacturers and distributors of over-the-counter medicines and dietary supplements (www.chpa.org).

² In November 2009, CHPA released a voluntary guideline intended to improve the consistency and standard format of volumetric measures within the dosing directions and on the dosing device for OTC oral liquid drug products

for dosing of orally-ingested liquid pediatric products, implementing a number of measures aimed at reducing medication errors (*e.g.*, use of "mL" only in dosing directions and on devices).

CHPA's comments on the Draft Guidance are organized into General Comments and Detailed Comments by Section (Attachment 1).

1. General Comments

- a) While we applaud FDA efforts to enhance the safe use of all OTC products, including those containing acetaminophen, we strongly encourage the agency to adopt the suggested changes through the rulemaking process. CHPA has previously submitted detailed comments supporting FDA's efforts to modernize the monograph system³ and remains committed to working with the agency to ensure finalization of rulemaking proceedings on the remaining tentative final monographs. Further, FDA has previously noted that some of the recommendations addressed in the guidance could be addressed through the rulemaking process.⁴
- b) We recommend that FDA's definition of "pediatric liquid drug products", as provided in this Draft Guidance, include only those products indicated exclusively for use in children. For reasons outlined below (c) we recommend that products labeled for use in both older children and adults (*i.e.*, "family products") be considered outside the scope of this guidance.
- c) The Draft Guidance recommends adoption of container features contributing to more accurate dosing and reducing accidental ingestion (*e.g.*, flow restriction devices). While flow restrictor/syringe technology has been voluntarily implemented by manufacturers of single ingredient pediatric acetaminophen products, the general utility of current flow restrictor technology has not been demonstrated or implemented to date with products labeled for older children and adults. These products require administration of various larger volumes of liquid based on patient weight/age, and we are concerned that packaging technology options suitable for use in these products containing acetaminophen may not be currently available or fully validated to ensure the devices can be easily understood and accurately used by consumers. We recommend that qualification of devices that impart additional child-resistance packaging features remain under the jurisdiction of the Consumer Products Safety Commission.

with dosing directions for children (monograph as well as approved NDA/ANDA products). A revised version of this document (see Attachment 2) was approved by the CHPA Board of Directors on November 14, 2014.

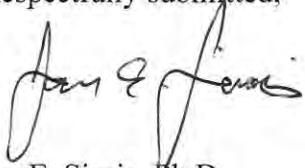
³ Comments of the Consumer Healthcare Products Association in Response to the Notice of Hearing on the Over-the-Counter Drug Monograph System (Docket No. FDA-2014-N-0202)

http://www.chpa.org/05_08_14_Monograph.aspx

⁴ At a May 17, 2011 [Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee](#) FDA (Dr. Carol Holquist) noted "One thing you could do under the monograph is to specify the dose in terms of a specific unit of measure" (p. 242). FDA also acknowledged that limiting to a single acetaminophen concentration (pp. 239-240) and providing a single standardized chart regarding dosing (p. 240) were changes that could be accomplished under the monograph.

CHPA and its members look forward to working with FDA to further develop this guidance.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Jay E. Sirois". The signature is fluid and cursive, with a large initial "J" and "S".

Jay E. Sirois, Ph.D.

Director, Regulatory & Scientific Affairs

Attachment 1

CHPA Detailed Comments on Draft Guidance for Industry on “Over-the-Counter Pediatric Liquid Drug Products Containing Acetaminophen”

I. INTRODUCTION

Line numbers	Section Title
I.	INTRODUCTION
29-31	We recommend that FDA limit this guidance to only those liquid OTC acetaminophen products indicated exclusively for use in children. As such, we request clarification from the agency that the proposed definition for pediatric liquid drug products excludes products labeled for use by both children and adults (<i>i.e.</i> , “family products”).
II.	BACKGROUND
52-55	We recommend that FDA delete use of the word “many” from the following statement “... <i>there have been many reports of overdose attributed to confusion between concentrated acetaminophen drops (80 mg/0.8 mL and 80 mg/mL) and acetaminophen oral liquid (160 mg/5 mL).</i> ” It is CHPA member experience that there have been very few reports of adverse events associated with confusion between these products.
73-76	CHPA disagrees with the statement that a May 2011 Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee “ <i>recommended the use of a flow restrictor or another feature designed to prevent excessive dosing...</i> ” Advisory Committee recommendations should be restricted to questions subjected to the voting process. As this question was not raised during this or any other Advisory Committee meeting, we believe that FDA should delete this sentence. ⁵
92	We recommend deleting this statement. CHPA members have always included a dosing device with pediatric single ingredient acetaminophen products.

⁵ There has also been no universal industry agreement on the implementation of flow restrictor devices. CHPA members are working as part of the ASTM workgroup on developing standard practices for testing the efficacy of flow restrictors. However, before these devices are widely used additional testing must be done.

III.	RECOMMENDATIONS
126-127	As use of OTC acetaminophen products is widely recognized as safe and effective when used as directed for children aged 6 months to 2 years ⁶ we recommend the age range of “6 months to 3 years” be used on the Principal Display Panel (PDP) for single ingredient liquid OTC infant acetaminophen products. This will enhance safe use of the product and reduce medication errors by ensuring that caregivers/parents of infants select the proper product and dosing device.
129-132	We recommend that FDA delete the statement regarding formatting and placement of a Quick Response (QR) code. This information would be more appropriate for inclusion in a general guidance on labeling.
134-137	We recommend that FDA support the inclusion of a picture of an infant on single ingredient acetaminophen products. Infant products with an age-appropriate dosing device (syringe) are used by children as young as age 6 months (and even younger at the discretion of a physician), and there is unanimous agreement that dosing information for children 6 months to 2 years should be included on the OTC Drug Facts for infant’s acetaminophen. ⁶ That way, the product, with the appropriate dosing device (syringe) would be identifiable and available to use in this population.
139-143	We recommend that FDA delete information regarding use of the word “new” as this is more appropriate for inclusion in a general guidance on labeling. While CHPA members do not include the term “new” on product packaging for longer than 6 months, product distribution is beyond their control and thus products with this labeling may remain on the shelf for periods longer than 6 months.
148-151	We recommend that FDA not restrict placement of an image of a dosing device to the PDP. We further recommend that the dosing device image on the outer carton (where the device is not visible) be allowed to portray liquid in order to convey important information regarding flavorings/colors (<i>e.g.</i> , grape, cherry, <i>etc.</i>). Further, when the product is provided to consumers in the primary package (<i>i.e.</i> , no outer carton) such that the dosing device is clearly visible at point-of-sale, no image need be included on labeling.
155	We recommend that FDA provide additional information on what would constitute an appropriate dosage delivery device.

⁶ At the [May 18, 2011 Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee](#) the final vote for Question 2 – “Do the PK, safety, and efficacy data support the addition of new labeled dosing directions corresponding to a 10 to 15 milligram per kilogram dose for children 6 months to 2 years of age?” was 21 yes, zero no, and zero abstentions.

Attachment II

CHPA VOLUNTARY GUIDELINES

CHPA VOLUNTARY GUIDELINES

Standard terminology and format for labeling of volumetric measures on OTC pediatric orally ingested liquid drug products

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1. Summary

In 2008, the Centers for Disease Control and Prevention (CDC) convened a stakeholder meeting to share information and expertise on medication overdoses in children. One of the key initiatives defined by the PROTECT group was to refine dosing measures on product labeling to reduce the possibility of unintentional medication overdose. Use of nonstandard dosing devices (*e.g.*, kitchen spoons) or inconsistent dosing directions on product labeling can result in consumer confusion and administration of an inappropriate medication dose.

As a direct result of the PROTECT initiative, CHPA developed a voluntary guideline for industry suggesting ways to standardize volumetric measures in dosing directions and dosing devices for oral pediatric liquid drug products, including preferred use of “mL” as the unit of measure for dosing instructions. Other recommendations provided in the 2009 CHPA guideline were consistent with those in a concurrently released FDA guidance on OTC dosage delivery devices (finalized in 2011).

CHPA is updating voluntary labeling guidelines for liquid products intended to be given to children under 12 years (previously approved in November 2009). Key changes include deletion of spoon labeling (*i.e.*, teaspoon, tablespoon) in dosing directions and on dosing devices; specifying use of “mL” only in dosing directions and on devices; and deletion of the volumetric unit of measure definition (*i.e.*, mL = milliliter). These changes are based on recent activity from FDA (issued a Draft Guidance on pediatric liquid acetaminophen products specifying that dosing directions be provided in mL only), the National Council on Prescription Drug Programs (issued a White Paper recommending that mL be the standard unit of measure for liquid prescription products), and the CDC (which through the PROTECT initiative encourages the adoption of an mL only standard for dosing directions and devices).

2. Objective and Scope

To improve patient safety by decreasing the potential for overdoses, underdoses and other errors when patients or caregivers measure and administer orally ingested OTC liquid medications, these guidelines identify and support consistent terminology, format, and text for volumetric measures within the dosing directions on the outer packaging, the immediate container label, and the dosing device for OTC orally ingested liquid drug products intended for use in children, defined as <12 years of age. Products covered by this voluntary guidance include those marketed pursuant to an OTC Monograph as well as those approved via a New Drug Application (NDA) or Abbreviated NDA (ANDA). Implementation of these guidelines, once approved as part of a members’ label and packaging change process, may take up to several years.

Although similar principles may apply, this document does not address other OTC liquid products such as oral medications indicated for adults and children 12 years and over, prescription medicines or dietary supplements. In addition, the guidance does not address products with children’s dosing intended for topical or non-ingested use such as crèmes or pastes, gargles/mouth rinses or sprays.

3. Background

Communications exist for parents and caregivers about the best ways to give medicines to children, especially the proper use of oral liquid medicines (2-7). Key points provided to parents and caregivers are to always read the label carefully, use the dosing device that comes with the product and to understand the types of liquid measure units for dosing liquid medicines. The use of preferred volumetric measure terms, units and abbreviations, as well as potential areas to avoid has also been suggested (7-14).

In response to reports of unintentional overdoses attributed at least in part to products with confusing or inconsistent labels and measuring devices, FDA released a draft voluntary guideline addressing dosage delivery devices for OTC liquid drug products in November 2009. The FDA voluntary guidance for industry (*Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products*) which was finalized in May 2011 provided specific recommendations for aligning dosing devices with the accompanying dosing directions for orally ingested OTC liquid medications (15). In October 2014, FDA also released a draft guidance addressing medication errors and unintentional ingestions of pediatric drug products containing acetaminophen (16). Other authoritative bodies have also released guidance on best practices for reducing medication errors, including those associated with orally ingested liquids (17-21).

In 2009, CHPA conducted an industry-wide survey of OTC oral liquid drug products with dosing directions for children in order to determine potential areas for improving the consistency and standard formatting of volumetric measures. A number of improvements were suggested including standardization of abbreviations, decimals and fractions; representation of volumetric measures in a dosing chart; use of a dosing device (provided with the product); and consistency in volumetric measures between the dosing device and the labeling dosing directions. These recommendations were provided in the CHPA voluntary guideline released in November 2009.

At the time the FDA guidelines were released, a published analysis of product labeling for marketed pediatric oral liquid OTC medications with dosing information for children younger than 12 years found numerous instances of variable dosing directions and inconsistency between dosing directions and measuring devices (22). A more recent study assessed adherence to recommendations provided in the FDA and CHPA guidelines aimed at reducing dosing errors among national brand name orally ingested OTC liquid pediatric medications (23). Recommendations included those which directly addressed potential dosing errors of ≥ 3 -fold (e.g., do not use atypical units, include a dosing device, do not use trailing zeroes, etc.).

Results from this study demonstrated a high level of adherence to the recommendations. Additional opportunities for standardization were noted by the authors including promotion of milliliter (mL) as the standard unit for dosing orally ingested liquid medications as well as the design and marking of dosing devices.

A recently released white paper from the National Council for Prescription Drug Programs (NCPDP - *Recommendations and Guidance for Standardizing the Dosing Designations on Prescription Container Labels of Oral Liquid Medications*, March 2014) provided recommendations and guidance for standardizing the dosing designation used on prescription

container labels of oral liquid medications (24). Recommendations included use of milliliter (mL) as the standard unit of measure, a practice shown to reduce dosing errors (25); use of leading zeros before the decimal point for dosage amounts less than one and avoidance of the use of trailing zeros after a decimal point; and use of dosing devices with numeric graduations and units that correspond to the container labeling.

4. Specific Recommendations

The following recommendations address the labeling dosing directions on the outer packaging, the immediate container labeling, and the dosing device, for OTC orally ingested liquid drug products with dosing directions for children.

4.1 OTC Drug Facts Dosing Directions: Outer Package and Immediate Container Labeling

A. *Dosing Directions:*

Provide a statement(s) that:

1. encourages a consumer to select the right dose
2. use the dosing device that accompanies the product
3. keep dosing device with product/do not discard dosing device

Example dosing directions (see also Appendix)

“Find right dose on chart. Use only enclosed [*insert specific name of product’s dosing device (e.g., “dosing cup”, “oral syringe”)*] specifically designed for use with this product. Do not use any other dosing device.”

B. *Dosing Directions:* Guidelines for Volumetric Measures

1. Use a tabular format to provide dosing directions (if space permits)
2. Use milliliter (mL) as the only unit of measure in the dosing directions (e.g., 5 milliliter or 5 mL)
3. Avoid use within labeling dosing directions of the following: teaspoon, tablespoon, cubic centimeters, cc, dram, fluid ounce, Fl. Oz., and dropper(ful) or any other less common or nonstandard volumetric measures.
4. For fractional volumes, use a decimal; if <1 mL volume, use decimal with a leading zero (e.g., 0.5 mL) to help avoid 10-fold dosing errors. Avoid use of trailing zeros after a decimal (i.e., use 1 mL not 1.0 mL) to help avoid 10-fold dosing errors.

4.2 Dosing Device: Dosing Device Accompanying the Product

A. *Dosing Device*: Guidelines for Volumetric Measures

1. Provide a calibrated dosing device with all orally-ingested liquid products.
2. Dosage delivery devices should not be significantly larger than the largest dose described in the labeled dosage directions and should permit clear measurement and delivery of the smallest labeled dosage.
3. Provide graduated markings on the dosing device that include dosage(s) specified in the dosing directions.
4. Use contrasting graduated markings (*e.g.*, etched or printed) so as to aid the readability of the measured liquid.
5. Use the milliliter (mL) volumetric unit(s) of measure only.
6. For fractional volumes, use the same decimal format and style provided in the dosing directions.

5. Appendix: Examples

5.1 Examples: Dosing Directions Statement(s)

Example A:

“Measure the dose correctly using the enclosed [insert specific name of product’s dosing device, *e.g.*, dosing cup, oral syringe]”

Example B:

“For accurate dosing, use the enclosed [insert specific name of product’s dosing device, *e.g.* dosing cup, oral syringe] to measure a dose”

Example C: Label statement using only mL (infant acetaminophen products)

“Find right dose on chart below”

“Use only enclosed [insert specific name of product’s dosing device, *e.g.*, dosing cup, oral syringe] designed for use with this product. Do not use any other dosing device.”

5.2 Examples: OTC Drug Facts Directions

Example A

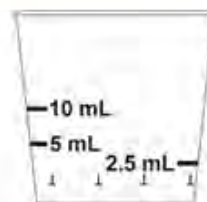
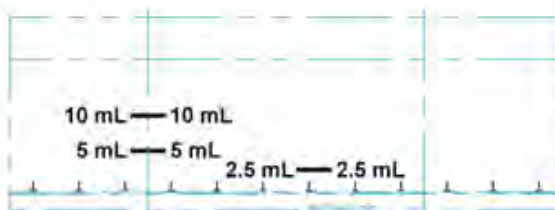
Drug Facts

Directions

- for accurate dosing, use the enclosed [insert specific name of product's dosing device, *e.g.* dosing cup, oral syringe] to measure a dose

adults and children 6 years and over	10 mL once daily; do not take more than 10 mL in 24 hours.
adults 65 years and over	5 mL once daily; do not take more than 5 mL in 24 hours.
children 2 to under 6 years of age	2.5 mL once daily; do not give more than 2.5 mL in 24 hours.
children under 2 years of age	do not use

Directions	
<ul style="list-style-type: none"> ■ use only with enclosed dosing cup ■ find right dose on chart below 	
adults and children 6 years and over	5 mL or 10 mL once daily depending upon severity of symptoms; do not take more than 10 mL in 24 hours.
adults 65 years and over	5 mL once daily; do not take more than 5 mL in 24 hours.
children 2 to under 6 years of age	2.5 mL once daily. If needed, dose can be increased to a maximum of 5 mL once daily or 2.5 mL every 12 hours. Do not give more than 5 mL in 24 hours.
children under 2 years of age	ask a doctor
consumers with liver or kidney disease	ask a doctor



Example B

Drug Facts***Directions***

- shake well before using
- use only enclosed dosing device

adults and children 6 years and over	30 mL once daily; do not take more than 30 mL in 24 hours.
adults 65 years and over	15 mL once daily; do not take more than 15 mL in 24 hours.
children 2 to under 6 years of age	7.5 mL once daily. do not give more than 7.5 mL in 24 hours.
children under 2 years of age	do not use

Example C

Drug Facts***Directions***

- shake well before using
- use only with enclosed dosing device
- find right dose on chart below. If possible, use weight to dose; otherwise use age.
- fill to dose level
- dispense liquid slowly into child's mouth, toward inner cheek
- if needed, repeat dose every 4 hours
- do not use more than 5 times in 24 hours

Weight (lb)	Age (yr)	Dose (mL)
Under 24	Under 2	Call a doctor
24-35	2-3	5 mL

Attention: specifically designed for use with enclosed dosing device. Do not use any other dosing device with this product.

6. References

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Adopted: November 17, 2009

Revised: November 14, 2014