Restricted Delivery Systems: Flow Restrictors for Oral Liquid Drug Products

Guidance for Industry

DRAFT GUIDANCE

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March 2020
Drug Safety

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Guidance for Industry

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Restricted Delivery Systems: Flow Restrictors for Oral Liquid Drug Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 provides recommendations regarding the use of restricted delivery systems[2,3] to limit unintentional ingestion[4] of oral liquid drug products (e.g., oral solution, oral suspension) by children.[5] The recommendations in this guidance apply broadly to oral liquid drug and biological products.[6,7] Accordingly, this guidance is intended for manufacturers of oral liquid drug and biological products. In this guidance, the term *manufacturer* is used broadly to include firms that market drug products under the Over-the-counter (OTC) Drug Review; holders of new

[1] This guidance has been prepared by the Office of Surveillance and Epidemiology, the Division of Nonprescription Drug Products, and the Division of Pediatric and Maternal Health in the Center for Drug Evaluation and Research (CDER), in collaboration with the Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER), and the Office of Combination Products at the Food and Drug Administration.

[2] For the purpose of this guidance, a restricted delivery system is defined as "a Packaging system designed or constructed to restrict (control) the amount of the drug product that may be delivered in order to limit unintended access by children and other similarly vulnerable populations. [. . .] One component of the Restricted delivery system is the flow restrictor, which is a Packaging component that restricts the flow of liquid. The flow restrictor may be used as part of a Restricted delivery system or as an adaptor to facilitate use of a measuring device for oral medicinal liquids. A flow restrictor should not compromise CPSC standards for special packaging [Child-resistant and Senior-friendly packaging (16 CFR §1700.15 et seq.)]." General Chapter <659> Packaging and Storage Requirements, United States Pharmacopeia (USP) 40-NF 35. As used in this guidance, the term *restricted delivery system* is distinct from the term *restricted device* as defined in 21 CFR 807.3(i).

[3] This guidance provides specific recommendations for flow restrictors and general recommendations that may be applicable to a range of restricted delivery systems, including flow restrictors. FDA acknowledges the potential for development of new restricted delivery systems and is including general recommendations for consideration.

[4] Accessing medication without caregiver permission or oversight is also referred to in this guidance as *accidental exposure*, *unsupervised ingestion*, *unsupervised exposure*, and *accidental ingestion*.

[5] The principles in this guidance also apply to other similarly vulnerable populations.

[6] References to *drugs* and *biological products* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262) that are drugs. For the purposes of this guidance, *drug product* or *drug* will be used to refer to human prescription drugs and biological products that are regulated as drugs.

[7] Manufacturers should determine whether a restricted delivery system is appropriate for use with their product. Restricted delivery systems may not be appropriate for some products (e.g., activated charcoal solutions, oral glucose solutions, or bulk stock bottles).

drug applications (NDAs), biologics license applications (BLAs), and abbreviated new drug applications (ANDAs); and firms that manufacture components packaged or labeled for commercial distribution with oral liquid drug products, including firms that buy product in bulk to sell under their own label and add a flow restrictor to the product when they fill the bulk product into direct-to-consumer packaging.

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 1970, the Poison Prevention Packaging Act (PPPA) was enacted to protect children (under 5 years of age) from unintentional exposure to certain household substances, including foods, drugs, and cosmetics.[8] Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), a drug that has packaging or labeling that is in violation of an applicable regulation issued pursuant to section 3 or 4 of the PPPA is deemed to be misbranded.[9] FDA was responsible for enforcing the PPPA until 1973, when jurisdiction was transferred to the U.S. Consumer Product Safety Commission (CPSC).[10]

CPSC's regulations list "standards for special packaging"[11,12] (also referred to in this guidance as *child-resistant packaging* (CRP)) for a wide range of household products, including most oral prescription drugs and many nonprescription drug products.[13] There are different ways to make packaging child-resistant, with the most common forms being a child-resistant closure (e.g., a *safety cap*) and certain unit-of-use blister packaging (e.g., puncture-resistant and peel-push blisters). However, not all container closures (i.e., packaging components that contain and protect drug products), including unit-of-use packaging, are child-resistant. Furthermore, *child-resistant* should not be equated to *child-proof*, because CRP is not designed to completely eliminate the possibility of an accidental pediatric ingestion. It can only impede access to harmful products.

CRP is regarded as an important public health safety tool for reducing the incidence of harmful health outcomes related to unintentional ingestions.[14] Many oral liquid drug products are

[8] Poison Prevention Packaging Act of 1970 (PPPA) (Pub. L. 91-601, 84 Stat. 1670), enacted December 30, 1970.
[9] See section 502(p) of the FD&C Act (21 U.S.C. 352(p)).
[10] Consumer Product Safety Act (Pub. L. 92-573, 86 Stat. 1207), October 27, 1972, Sec. 30.
[11] See 16 CFR part 1700. See also definitions in section 2 (4) of the PPPA.
[12] *Special packaging* and *child-resistant packaging* are used interchangeably in this guidance.
[13] See 16 CFR part 1700 for substances requiring special packaging and the relevant packaging standards and testing procedures.
[14] Early studies in the 1960s demonstrated a nearly a 10-fold reduction in unsupervised pediatric ingestions with medicines with special packaging distributed from the Fort Lewis-McChord Air Force Base in Washington. During the years CRP has been used to package drugs, cosmetics, and household chemicals, the number of children who

marketed with CRP features. However, even with the availability of this safety tool, adverse events related to unintentional ingestion of drug products, including oral liquid drug products, continue to be reported. One analysis of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES)[15] data estimated that children younger than 6 years old account for more than 9,500 annual Emergency Department (ED) visits attributed to the unintentional ingestion of oral liquid drug products.[16]

Additional measures should also be considered to help reduce unintentional ingestion of oral liquid drug products, including safe and secure product storage.[17] Exposure-limiting packaging, such as a restricted delivery system, is one such measure that complements CRP. Specifically, restricted delivery systems are intended to restrict the flow of liquid from the opening of a container. Restricted delivery systems are not a replacement for CRP and use of restricted delivery systems should not compromise CRP. Rather, manufacturers should consider using a combination of CRP and restricted delivery systems to further reduce unintentional ingestion of oral liquid drug products.

III. DISCUSSION OF FLOW RESTRICTORS

An example of a restricted delivery system is a flow restrictor, which can be added to the neck of a bottle to restrict or control the flow of liquid. Flow restrictors can be added to a container at the site of manufacture, or they can be co-packaged with the drug product and added to the container at the time of use. Alternatively, the design of the container can be such that the flow restrictor is molded and integrated into the bottle neck and cannot be separated from the bottle. Bottles containing a flow restrictor may need a dosing device, such as an oral syringe, to extract the drug product. Depending on the design and technology, flow restrictors can be of the open or closed type.

1. ***Closed Flow Restrictors***. In general, a closed flow restrictor limits access to a single-unit volume at one time. A closed flow restrictor can be designed with a self-closing valve

have died from ingesting toxic household substances has declined significantly. See https://www.cpsc.gov/Regulations-Laws--Standards/Statutes/Poison-Prevention-Packaging-Act/.

[15] NEISS-CADES is an expansion of the CPSC National Electronic Injury Surveillance System (NEISS), used to monitor consumer-product-related injuries. NEISS-CADES collects data on all adverse drug events treated in U.S. hospital emergency departments, whether or not associated with consumer products. NEISS data are collected from a nationally representative sample of U.S. hospital emergency departments; NEISS-CADES uses a subsample of those emergency departments for its data collection. See https://www.cpsc.gov/Research--Statistics/NEISS-Injury-Data.

[16] Lovegrove MC, Weidle NJ, Budnitz DS. Trends in emergency department visits for unsupervised pediatric medication exposures, 2004-2013. Pediatrics 2015 Oct;136(4): e821-829 (annual national estimate in ED visits for unsupervised exposures involving oral liquid medication by children younger than 6 years old between 2010 and 2013).

[17] Safe and secure product storage is a complementary safety measure that is important to keep in mind. When medications are stored in reach and sight of children, children are able to gain access to and defeat CRP or restricted delivery systems in some instances, thereby reducing the effectiveness of these packaging measures. Therefore, FDA recommends that all drugs, irrespective of the type of packaging, be stored safely out of the reach and sight of children to further the overall public health efforts to address unintentional ingestion of drug products.

that opens when the dosing device is inserted and reseals after removal of the dosing device. Closed flow restrictors are designed such that the valve orifice matches a corresponding dosing device, and in some cases, the design may be so specific that it includes a lock-and-key mechanism needing a designated dosing device.

2. ***Open Flow Restrictors.*** An open flow restrictor allows for a continuous, controlled volume. When an oral syringe is used, an open flow restrictor does not reseal after removal of the oral syringe and when the bottle is inverted it permits a slow flow of liquid from the container.

The efficacy of flow restrictors has been demonstrated in the pediatric population.[18,19] Children age 3 to 4 years are typically able to empty the entire contents of bottles without flow restrictors within 2 minutes; however, when a bottle was fitted with a flow restrictor, children of the same age were prevented from completely emptying the bottle contents within a 6-minute period.[20] In cases of unintentional liquid acetaminophen ingestions, the average individual dose was lower in cases that involved bottles with flow restrictors.[21] In general, the incorporation of a flow restrictor reduces the total volume of liquid children are able to extract from liquid medicine bottles, which may reduce the risk of harm resulting from unintentional ingestions.

[18] Lovegrove MC, Hon S, Geller RJ, Rose KO, Hampton LM, Bradley J, Budnitz DS. Efficacy of flow restrictors in limiting access of liquid medications by young children. Journal of Pediatrics 2013 Oct; 163(4): 1134-1139.

[19] Geller RJ, Hon SL, Reynolds KM, Burnham RI, Badillo R, Ketcham S, Muresan N, Peters ME, Stokkeland KL, Green JL. Do New Child Resistant Closures Reduce Injury Following Accidental Ingestion? 2015 Annual Meeting of the North American Congress of Clinical Toxicology (NACCT). Clinical Toxicology 2015: 53:639-777.

[20] Lovegrove et al. assessed the efficacy of flow restrictors in 110 children age 36 to 59 months in a block randomized trial with a convenience sample from five preschools. The authors noted that flow restrictors on uncapped (open) bottles decreased the ability of young children to remove liquid medicine from bottles when compared to uncapped or partially opened bottles without flow restrictors. In this randomized study, 3- and 4-year-old children were able to remove the entire contents of nearly all bottles without flow restrictors that were either open (96%; 25 out of 26 children) or incompletely closed (82%; 68 out of 83 children) within 2 minutes. However, none of the children emptied a bottle with a flow restrictor in less than 6 minutes, and only 6% (7 out of 110 children) emptied a bottle with a flow restrictor within the full 10-minute testing period. Furthermore, the maximum amount of liquid the youngest children studied (age 36 to 41 months) were able to remove was less than 5 milliliters. Overall, the study findings showed that children removed less total liquid from bottles with flow restrictors when compared to open or incompletely closed control bottles.

[21] Geller et al. conducted a 6-month poison center phone survey of 1,952 parents of children who had unintentional ingestions of liquid drug products that demonstrated the potential efficacy of flow restrictors in children younger than 12 years old. The survey identified 289 cases of single-ingredient unintentional acetaminophen ingestions among children of the 528 parents who completed the survey. The majority (88.1%) of these children were younger than 3 years old. The authors noted that the unintentional ingestions involving liquid acetaminophen with flow restrictors resulted in a lower estimated average dose, whereas the unintentional ingestions involving packaging without flow restrictors resulted in a 2.5 times larger risk of an estimated exposure greater than 150 milligrams (mg)/kilogram (kg), which is the threshold dose used by some poison centers for referral to a health care facility. The American Academy of Clinical Toxicology (ACCT) guidelines and POISINDEX recommend 200 mg/kg as the threshold dose for which referral to ED is suggested in cases of acetaminophen toxicity.

IV. GENERAL RECOMMENDATIONS

Manufacturers should consider the use of a restricted delivery system, such as a flow restrictor, as an additional measure to further reduce the risk of unintended ingestions of oral liquid drug products.

As manufacturers seek to develop restricted delivery systems, they are strongly encouraged to discuss with FDA any proposed restricted delivery system early in the development process.[22]

Standardized test methodologies[23,24] for assessing restricted delivery systems for liquid consumer products are currently being developed. We recommend that manufacturers consider general testing methods and parameters that assess product functionality for labeled use and assess performance necessary to prevent unintentional ingestions. Manufacturers should also consider elements such as those discussed below when developing a restricted delivery system for their oral liquid drug product.

A. Restriction Effects[25]

FDA recommends targeted restriction effects to limit the amount of an oral liquid drug product that may be delivered over a period of time. The majority of unintended ingestion cases occur within 5 minutes of access to drug products,[26] and an analysis of NEISS-CADES data reports that 60% of unintentional OTC liquid medication ingestions involve children 2 years old and younger.[27] Accordingly, the recommended targeted restriction effects of the restricted delivery system should reduce the amount of liquid that flows from a bottle in a 5-minute period based on the toxic dose of the drug product to a 2-year-old child.[28,29]

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[22] For products marketed under the OTC Drug Review, contact the Division of Nonprescription Drug Products in CDER's Office of New Drugs. For products requiring premarket review (i.e. "new drugs" under section 201(p) of the FD&C Act (21 U.S.C. 321(p)), contact the appropriate review division within FDA.

[23] See ASTM Standard F3375-19 Test Method for Assessing Non-Metered Restricted Delivery Systems for Liquid Consumer Products at: https://www.astm.org/Standards/F3375.htm

[24] ASTM News Release, New Standard Aims to Limit Children's Access to Liquid Medicines, Other Products. See link: https://www.astm.org/cms/drupal-7.51/newsroom/new-standard-aims-limit-children%E2%80%99s-access-liquid-medicines-other-products

[25] In this guidance, restriction effects are the changes to the amount of liquid drug product that may be delivered over a period of time in order to limit access by children and other similarly vulnerable populations.

[26] Ozanne-Smith J, Day L, Parsons B, Tibballs J, and Dobbin M. Childhood poisoning: Access and prevention. Journal of Pediatric Child Health. 2001; 37: 262–265.

[27] Lovegrove MC, Weidle NJ, Budnitz DS. Trends in emergency department visits for unsupervised pediatric medication exposures, 2004-2013. Pediatrics 2015; 136.

[28] FDA recommends using the 50th percentile weight for age estimates in toxic dose calculations; see CDC growth charts at https://www.cdc.gov/growthcharts/.

[29] Lovegrove, Weidle, Budnitz (Pediatrics 2015; 136) also note that children younger than 1 year of age accounted for 5% of ED visits for unsupervised ingestions. The visits for those age 1 and 2 years accounted for the majority of visits (this includes visits for unintended ingestion of both oral solid and liquid dosage forms). However, visits for oral OTC liquid medication exposures involved a proportionally greater number of children over the age of 2 years, which is one of the reasons why FDA chose 2-year-olds for the recommended targeted restriction effects.

Recommended restriction effects are described in Appendix A for some of the commonly identified oral liquid drug products that result in ED visits from unintentional ingestion. The restriction effects in Appendix A incorporate the recommendation above (regarding a 5-minute period and a 2-year-old child) and are based on general parameters used by poison center professionals (e.g., POISINDEX) in determining threshold doses that call for emergency evaluation, as well as on practice guidelines developed by the American Academy of Clinical Toxicology (AACT).[30,31]

The use of a restricted delivery system that limits access to a single-unit volume at one time, such as a closed flow restrictor, is warranted for drug products with a narrow therapeutic index[32] because there is a small difference between therapeutic and toxic doses. This type of restricted delivery system should also be considered for oral liquid drug products with significant toxicities at doses that are close to the therapeutic dose. For drug-drug combinations, manufacturers should consider the most toxic agent in the combination as well as the combined toxicity of all product ingredients in determining the desired restriction effect.

Viscosity of the liquid is another important consideration because it will determine the rate at which a liquid flows and influence the performance of restricted delivery systems. Restricted delivery systems should be suitable for use with a liquid with the viscosity of the particular formulation so that typical volumes can be reasonably dispensed by the target consumer/patient/caregiver populations. Products with high viscosity may be difficult for a parent or caregiver to extract from some restricted delivery system designs. Conversely, products with low viscosity, which flow freely, may benefit from a more restrictive packaging design.

B. Human Factors and Design Considerations

In addition to the preceding information, the following design considerations should be taken into account in selecting the most appropriate restricted delivery system for an oral liquid drug product:

- Restricted delivery systems should be constructed of materials that are safe for oral, skin, and mucosal contact, as well as compatible with the drug formulation.[33]

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[30] Chyka PA, Erdman AR, Manoguerra AS, Christianson G, Booze LL, Nelson LS, Woolf AD, Cobaugh DJ, Caravati EM, Scharman EJ, Troutman WD. Dextromethorphan poisoning: An evidence-based consensus guideline for out-of-hospital management. Clinical Toxicology 2008; 45(6): 662-677, DOI: 10.1080/15563650701606443.

[31] Scharman EJ, Erdman AR, Wax PM, Chyka PA, Caravati EM, Nelson LS, Manoguerra AS, Christianson G, Olson KR, Woolf AD, Keyes DC, Booze LL, Troutman WG. Diphenhydramine and dimenhydrinate poisoning: An evidence-based consensus guideline for out-of-hospital management. Clinical Toxicology 2008; 44(3): 205-223, DOI: 10.1080/15563650600585920.

[32] *Narrow therapeutic index drugs* are defined as those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity. See: Yu LX, Jiang W, Zhang X, Lionberger R, Makhlouf F, Schuirmann DJ, Muldowney L, Chen ML, Davit B, Conner D, Woodcock J. Novel bioequivalence approach for narrow therapeutic index drugs. Clinical Pharmacology and Therapies 2015; 97(3): 286-291.

[33] Guidance for Industry, *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

- If a dosing device should be used for the restricted delivery system, a compatible dosing device should be included in the product packaging.

The following considerations apply specifically to flow restrictors:

- Different types of flow restrictors (e.g., open or closed) should be considered and the optimal flow restrictor should be used.

- The flow restrictor should not leak when used.

- Performance testing should include testing for the maximum number of doses available in the liquid drug container multiplied by a factor of 1.5. For example, a 100 milliliter (mL) bottle that is intended to deliver 5 mL doses (contains 20 total 5 mL doses), should be tested 30 times (20 doses available x 1.5 safety margin = 30 performance tests). These performance tests should be conducted at all specified orientations or when not specified, all possible container orientations as defined by the product label.[34] Compatibility of the dosing device (e.g., a calibrated and labeled oral syringe) with the restricted delivery system should be carefully considered and evaluated during the design process.

When designing or selecting an appropriate restricted delivery system, manufacturers should balance the degree of restrictiveness with the need to ensure ease of use. For example, the restricted delivery system should not be overly burdensome in ways that discourage product use or that encourage improper use. In addition, it is vital that the restricted delivery system not be easily removed or pushed through the neck of the bottle, to avoid contaminating the drug product or presenting a choking hazard to children.

We encourage working with the appropriate review division at FDA to determine the submission information and types of studies that may be necessary for products that require premarket review. We recommend manufacturers consider human factors principles and usability studies as part of their development program.[35]

C. Directions for Use

Drug products must have labeling that bears adequate directions for use,[36] with limited exceptions;[37] when manufacturers choose to use a restricted delivery system for a drug product, this requirement includes providing adequate directions for using the drug product with the

[34] Specified by a compendial test or standardized test by a testing body, such as American Society for Testing and Materials (ASTM) or International Organization for Standardization (ISO).

[35] See Guidance for Industry and FDA Staff, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* (February 2016), and Guidance for Industry, *Safety Considerations for Product Design to Minimize Medication Errors* (April 2016). See also draft Guidances for Industry and FDA Staff, *Applying Human Factors and Usability Engineering to Medical Devices* (June 2011) and *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016).

[36] Section 502(f)(1) of the FD&C Act.

[37] See, e.g., 21 CFR 201.100 (prescription drugs for human use).

restricted delivery system.[38] In addition to meeting the general requirement for the labeling of a drug product to bear adequate directions for use, the Agency recommends that the labeling of drug products with a restricted delivery system include a toll-free telephone number or email address for consumers, patients, or caregivers to obtain replacement parts, when such parts (such as syringes) are needed to ensure optimal performance of the restricted delivery system.

To include a restricted delivery system in the packaging of drug products undergoing premarket review, we recommend contacting the appropriate review division staff to discuss the information to be submitted to the Agency to ensure that the drug product's labeling bears adequate directions for using the drug product with the restricted delivery system.

For oral liquid drug products marketed under the OTC Drug Review, at this time and based on our current understanding of the risks of these products, FDA does not intend to object to the use of an appropriate restricted delivery system, provided the labeling includes non-graphical instructions in the Drug Facts labeling that explain how to appropriately use the restricted delivery system, as well as applicable OTC drug monograph directions, and provided that the labeling satisfies all other applicable labeling requirements.[39] The additional non-graphical instructions should be limited to describing how to use the restricted delivery system to deliver the appropriate dose. If graphical images are necessary to ensure effective use of the restricted delivery system, a labeling insert may be included in the packaging to provide the necessary information to the consumer, patient or caregiver. If additional language is added to the Drug Facts labeling or a separate labeling insert is included in the packaging of products marketed under the OTC Drug Review, we recommend that the manufacturer establish that the target consumer/patient/caregiver population comprehends the additional language.[40]

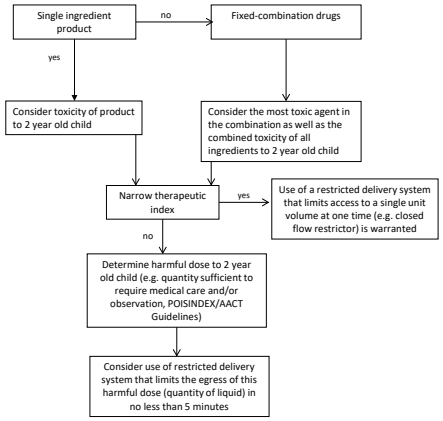
[38] Section 502(f)(1) of the FD&C Act. In addition, as a general matter, an ANDA is required to contain information to show that the labeling proposed for the generic drug is the same as the labeling for the reference listed drug (RLD), except for changes required because of differences approved under a suitability petition (see section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93), or because the generic drug and the RLD are produced or distributed by different manufacturers (see section 505(j)(2)(A)(v) of the FD&C Act). See also FDA's Draft Guidance entitled *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.*

[39] See, e.g., 21 CFR part 201 and 21 CFR 330.1.

[40] See Guidance for Industry, *Label Comprehension Studies for Nonprescription Drug Products* (August 2010).

APPENDIX A: PRODUCT-SPECIFIC RECOMMENDED RESTRICTION EFFECTS

Consider the following flow diagram when considering the use of a restricted delivery system.



The following drug product examples[1] are provided to illustrate the goal of restricting a toxic or harmful volume of liquid (based on the 50th percentile weight estimate for a 2-year-old)[2] accessible to a child within 5 minutes.

Acetaminophen[3]: Restricted delivery systems for acetaminophen-containing products should restrict the flow of liquid to a deliverable quantity not to exceed 2,400 milligrams (mg) of acetaminophen in a 5-minute interval. Due to the risk of liver failure, consider the use of a restricted delivery system that limits access to a single-unit volume at one time, such as a closed flow restrictor.

[1] These examples were chosen because 91% of ED visits for OTC liquid medication exposures involved acetaminophen, cough and cold remedies, ibuprofen, or diphenhydramine. See Lovegrove MC, Weidle NJ, Budnitz DS. Trends in emergency department visits for unsupervised pediatric medication exposures, 2004-2013. Pediatrics 2015;136.

[2] See footnote 27.

[3] Assumes a 200 mg/kg threshold and a12 kg child. For a 160 mg/5 mL concentration, this results in not to exceed (NTE) 75 mL in 5 minutes (min). Source: 200 mg/kg American Academy of Clinical Toxicology Guidelines (2,400 mg); 200 mg/kg POISINDEX (2,400 mg).

Dextromethorphan[4]: Restricted delivery systems for dextromethorphan-containing products should restrict the flow of liquid to a deliverable quantity not to exceed 90 mg of dextromethorphan in a 5-minute interval.

Diphenhydramine[5]: Restricted delivery systems for diphenhydramine-containing products should restrict the flow of liquid to a deliverable quantity not to exceed 90 mg of diphenhydramine in a 5-minute interval.

Ibuprofen[6]: Restricted delivery systems for ibuprofen-containing products should restrict the flow of liquid to a deliverable quantity not to exceed 2,400 mg of ibuprofen in a 5-minute interval.

Pseudoephedrine[7]: Restricted delivery systems for pseudoephedrine-containing products should restrict the flow of liquid to a deliverable quantity not to exceed 144 mg of pseudoephedrine in a 5-minute interval.

[4] Assumes a 7.5 mg/kg threshold and a12 kg child. For a 30 mg/5 mL concentration, this results in NTE 15 mL in 5 min. For a 15 mg/5 mL concentration, this results in NTE 30 mL in 5 min. Source: 7.5 mg/kg AACT Guidelines (90 mg); 10 mg/kg POISINDEX (120 mg).

[5] Assumes a 7.5 mg/kg threshold and a12 kg child. For a 12.5 mg/5 mL concentration, this results in NTE 36 mL in 5 min. Source: 7.5 mg/kg AACT (90 mg); 7.5 mg/kg POISINDEX (90 mg).

[6] Assumes a 200 mg/kg threshold and a12 kg child. For a 100 mg/5 mL concentration, this results in NTE 120 mL in 5 min. Source: 200 mg/kg POISINDEX (2400 mg).

[7] Assumes a 12 mg/kg threshold and a12 kg child. For a 30 mg/5 mL concentration, this results in NTE 24 mL in 5 min. Source: 12 mg/kg POISINDEX.