Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

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

Re: Docket No. FDA-2020-D-0567: Restricted Delivery Systems: Flow Restrictors for Oral Liquid Drug Products Guidance for Industry

To Whom It May Concern:

The Combination Products Coalition ("CPC") welcomes the opportunity to provide comments on FDA's "Restricted Delivery Systems: Flow Restrictors for Oral Liquid Drug Products Guidance for Industry" dated March 2020 (the "Draft Guidance").[1]

The CPC has carefully evaluated FDA's Draft Guidance and has identified the following overall concerns and suggestions, as well as our specific comments, which are provided on subsequent pages.

1. We ask that FDA further clarify the designation of restricted delivery systems, including whether they are considered as medical devices, as part of the drug container closure system/package or combination products. In particular, the following questions should be addressed:

    a. Would a bottle fitted with a restricted delivery system supplied without any additional dosing devices be considered a drug-device combination product subject to 21 CFR Part 4?

    b. If the restricted delivery system has a measuring (or counting) function or if the labeling instructs a certain amount of drug to be given (e.g., invert vial to add 5

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad, and unique perspective to these issues.

drops of liquid into milk, turn bottle to dispense 5 micro tablets), does that make a difference in the designation of the restricted delivery system?

c. Is a press-in bottle adapter (PIBA) which is used to reduce the size of the orifice, such that a user can use an oral dispenser to withdraw the dose, considered a flow restrictor and a restricted delivery system?

2. The Draft Guidance should lay out considerations and recommendations for use of restricted delivery systems, but should not outline requirements for their use, as a guidance document does not establish legally enforceable responsibilities. As such, we ask that the Draft Guidance be updated to provide considerations for manufacturers to address during their risk-based development activities and revise the sections which appear to be defining requirements, including those sections that:

   a. Characterize a restricted delivery system as "warranted" for drug products with a narrow therapeutic index (lines 142-143).

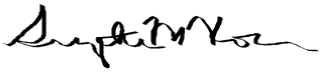
   b. Recommend including a compatible dosing device in the packaging (lines 167-168).

   c. Recommend use of the "optimal" flow restrictor, when the requirement should be for a safe and effective flow restrictor (lines 172-173).

   d. State that it is "vital" that the restricted delivery system not be easily removed or pushed through the neck of the bottle (lines 189-191).

We appreciate the opportunity to provide input on the Draft Guidance. We ask that the Agency consider this feedback as FDA finalizes the Draft Guidance and look forward to further dialogue with the Agency to clarify or discuss any of our suggestions.

Very truly yours,



Suzette Roan
CPC Submissions Working Group Chair
On behalf of the Combination Products Coalition

Line	Section	Comment	Proposed Revisions (additional text in **blue bold**)
141 – 146	IV.A	Sponsor should determine whether a restricted delivery system is warranted based on the therapeutic window of the drug.	"The ~~use of~~ **need for** a restricted delivery system that limits access to a single-unit volume at one time, such as a closed flow restrictor, **should be assessed by the manufacturer as part of the risk management activities. We highly recommend that manufacturers consider including restricted delivery systems** ~~is warranted~~ for drug products with a narrow therapeutic index. ~~because there is a small difference between therapeutic and toxic doses~~. **The risk management activities should inform if there is a need for restricted delivery systems (i.e. flow restrictor), based on considerations such as the drug product toxicity and dose.** 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."
167 – 168	IV.B	Many products on the market, particularly prescription drugs, may not include a dosing device (e.g. oral syringe) because a syringe is readily obtainable from the pharmacy when a patient receives the prescribed medication. Therefore, manufacturers should have the option to provide clear instruction to identify the right type of dosing device in the labeling, as opposed to mandating co-packaging.	"If a dosing device should be used for the restricted delivery system, a compatible dosing device should be included in the product packaging **or specifications and/or device information to allow the user to identify devices appropriate for use with the restricted delivery system should be included in the product labeling**."
172 – 173	IV.B	The Draft Guidance recommends that the optimal flow restrictor should be used, but there may be other factors which would result in a safe and effective flow resistor being chosen, even if it is not the 'optimal'. Selection of the flow restrictor to use should follow the least burdensome approach. For example, new technology may be considered, but not selected as the manufacturing capacity is not available.	"Different types of flow restrictors (e.g., open or closed) should be considered and ~~the optimal~~ **a** flow restrictor **demonstrated to be safe and effective** should be used, **based on risk, balancing the objective of safe and effective performance with considerations on feasibility. and evaluation of all applicable information in making that selection**."

Line	Section	Comment	Proposed Revisions (additional text in **blue bold**)
177 – 184	IV.B	Compatibility of the dosing device is a general description. Recommend clarifying.	Add clarifications to address these considerations: Compatibility of the dosing device (e.g., calibrated and labeled oral syringe) with the restricted delivery system, such as design of connecting interfaces, should be carefully considered and evaluated during the design process.
177 – 178	IV.B	If a restricted delivery system will be considered a Combination Product (see general comments), then it should be clear that performance testing is "verification" and not release testing."	"Performance **(verification)** testing should include testing for the maximum number of doses available in the liquid drug container multiplied by a factor of 1.5."
186 – 191	IV.B	The recommendations are too specific, as they are assuming current designs. Recommend rewording to make the recommendations generally applicable to designs which have not been invented yet.	"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 **(e.g., not be easily removed presenting a choking hazard to children, not be easily pushed into the container contaminating the drug product).**" ~~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.~~
204 – 207	IV. C	It seems more appropriate for a pharmacist to provide replacement syringes, as the manufacturer does not have access to the prescription or dose for the patient. The pharmacist seems in the best position to ensure the patient has the appropriate replacement syringe or dosing cup, in a timely manner. Moreover, it seems overly burdensome to require a patient to contact the drug manufacturer via a toll-free number just to obtain replacement syringes. If this is intended only for OTC drugs, that should be made clear in the Draft Guidance. If not intended to apply only to OTC products, the agency should consider the burden on the patient and the manufacturer in proposing this method for obtaining replacement syringes.	"…the Agency recommends that the labeling of **over the counter** 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 **and cannot be obtained through other appropriate means (i.e. pharmacist or pharmacy).**"

Line	Section	Comment	Proposed Revisions (additional text in **blue bold**)
233	Appendix A	Based on the description provided in the Draft Guidance, it is not clear what would be considered as "Single Ingredient Product" vs "Fixed-Combination Drugs".	"Single-**drug** ~~ingredient~~ product" "**Drug-drug** ~~Fixed~~ combination**s**"