Combination Products Coalition

1227 25th St. NW #700
Washington, DC 20037
combinationproducts.com
202.861.4199

FDA-2019-D-0078

VIA ELECTRONIC SUBMISSION

May 6, 2019

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

Re: Docket No. FDA-2019-D-0078: Principles of Premarket Pathways for Combination Products: Draft Guidance for Industry and FDA Staff

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to offer comments on FDA's "Principles of Premarket Pathways for Combination Products: Draft Guidance for Industry and FDA Staff" (hereinafter the "Draft Guidance").

Overall, the CPC believes the Draft Guidance represents a positive step forward in clarifying FDA's expectations for premarket pathways for combination products, which are not currently prescribed in other guidance. In addition, we believe that the Draft Guidance has the potential to drive increased efficiency and consistency in the premarket review of combination products, leading to benefits realized both by sponsors and FDA.

However, while the CPC agrees with many of the recommendations in the Draft Guidance, we ask that FDA revise the document as follows:

1. The text provided in Footnote 11 states that the Draft Guidance is focused on products submitted within a single application, particularly single-entity and co-packaged combination products. If this will be the primary scope of the final guidance, it should be clarified much earlier in the document. We note that cross-labeled combination products are largely excluded from the Draft Guidance, except within the definitions section. We ask that FDA provide additional guidance on cross-labeling concerns,

[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.

including considerations that would require either one or multiple marketing applications. Considerations for cross-labeled products and detail regarding sponsors' ability to submit multiple applications for cross-labeled combination products should be included.

2. Provide additional guidance on when the data and information needed to obtain marketing authorization for a non-lead constituent part either differs or does not differ from that needed as a stand-alone product.

3. Provide further guidance on how to effectively utilize prior FDA findings of safety or effectiveness or substantial equivalence of an approved or cleared constituent part.

In addition to this high-level feedback, we have included certain additional comments and proposed changes to the Draft Guidance in Appendix A.

Finally, the Federal Register Notice (announcing the availability of the Draft Guidance) posed a question regarding whether there are any steps FDA should take to avoid duplication of effort or duplicate data submissions, and minimize unnecessary burden where review of a combination product consists of two applications. The CPC recommends that FDA work toward a streamlined regulatory project management process to avoid multiple requests being sent to manufacturers, which can result in the provision of duplicative information. This could potentially be accomplished through the use of a single portal to store and share information (e.g., submission package, interactive responses, additional information, etc.) or by designating a single point of contact (e.g., OCP) to help manage and coordinate the process.

*** * * ***

We appreciate the opportunity to provide input on the Draft Guidance and are happy to meet with the Agency to clarify or discuss any of our suggestions.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

Appendix A: Requested Revisions

LINE #	COMMENT w/ RATIONALE	PROPOSED CHANGE
General Comments		
• The Draft Guidance runs contrary to new language added to the Federal Food, Drug, and Cosmetic Act ("FDCA") by the 21st Century Cures Act ("Cures Act"). Specifically, as amended by the Cures Act, the FDCA provides: "Nothing in this subsection [(related to the regulation of combination products)] shall be construed as prohibiting a sponsor from submitting separate applications for the constituent parts of a combination product, unless the Secretary determines that a single application is necessary." We interpret this to mean that two applications will be presumed acceptable, unless FDA can show that the submission of two applications is not appropriate. In the Draft Guidance, however, FDA seems to reverse this position, suggesting that a single application is "generally appropriate for a combination product," unless a sponsor can show why two applications would be necessary (see lines 133-134). As detailed below, we ask that FDA clarify its position on this point, and include in the Annex to the Draft Guidance an additional example (where the use of two applications is more appropriate than one). • The first several pages of the Draft Guidance define combination products as including single entity combination products, co-packaged combination products, and cross labeled combination products. Throughout the document, though, FDA simply refers to combination products and its proposed one submission presumption. Within Footnote 11, FDA clarifies that cross-labeled combination products are mostly excluded from the Draft Guidance; if this scope will carry over to the final guidance, it should be clarified earlier in the document (e.g., in the introduction section). • The Draft Guidance does not support digital health development. There are no digital health considerations presented or examples mentioned. • The Draft Guidance's position that a device that is not a device constituent part of any combination product (i.e., a device that is not combined with a drug or biologic constituent) cannot be used as a predicate for a device-led combination product is inconsistent with current FDA policy. FDA should accept such devices as predicates, e.g., wound dressings that are coated. • The Draft Guidance lacks references to (both drug and device) Master Files commonly used between drug and device companies. We recommend adding this in the paragraph on lines 190-195.		
Specific Comments		
Line 93: Basics of interacting with FDA		
Line 106	Capture OCP in the sentence regarding Center coordination as this is a focus of OCP's role.	"…Centers, as well as OCP, are expected to coordinate as appropriate prior to issuance of such communications."
Line 117	Please clarify how sponsors are supposed to identify their products as combination products. For example, for drug submissions, is this expectation limited to product identification in FDA 356h and 1571 forms, or is there a location in a submission where this should be stated?	"Please note that, under section 503(g)(8)(C)(v), sponsors are required to identify their products as combination products, per FDA Form 356h and 1571, in seeking Agency action with respect to the product."

LINE #	COMMENT w/ RATIONALE	PROPOSED CHANGE
Line 121: Basics of premarket regulation of combination products		
Line 133-134	Statement suggesting a presumption that a single application is appropriate should either be tied to a specific type of combination product (i.e., drug-led combination product in a prefilled syringe or autoinjector). Alternatively, it should be clarified that a single application may not be appropriate for specific types of combination products (i.e., cross-labeled combination products). The content in the Footnote 11 is buried and needs to be highlighted more prominently.	Add clarifying language to the end of sentence: "With regard to premarket authorization pathways, FDA's current thinking is that a single application is generally appropriate for a combination product, particularly for a drug-led single entity or co-packaged combination products." Additionally, we ask that FDA provide additional guidance on premarket authorization pathways for products under separate marketing authorizations. What constitutes a cross-labeled combination product (marketed under separate authorizations) and the regulatory requirements for such products (as they relate to each other) are not well-established and are points of continuous regulatory uncertainty for sponsors. We see a variety of products affected by these questions, including specialized drug-delivery devices, digital health products used in conjunction with drugs or biologics, specialized reconstitution or preparation devices (such as closed system transfer devices), and certain types of diagnostic devices.
Line 149-150	"The Agency anticipates that a single application may not be appropriate in limited cases." We ask that FDA provide further insight into considerations for when multiple applications may be more appropriate (the referenced ICCR Staff Manual Guide doesn't provide further insight into this), or at least provide some applicable examples. This can assist sponsors in determining the appropriate regulatory strategy for such products, including when developing a proposal to discuss with FDA.	As indicated in the comment for lines 133-134, above, substantial ambiguity remains in what constitutes a cross-labeled combination product. We recommend that FDA provide further guidance on what products constitute cross-labeled combination products. Further, we highly recommend that FDA provide further insight into the relevant considerations in determining when a single application is not appropriate, as well as applicable examples. Overall, we believe there should be flexibility on the chosen regulatory pathway, consistent with Section 3038 of the Cures Act, to be discussed with FDA at a pre-filing meeting as indicated on lines 148-149. There are various business reasons for companies to choose a multiple-application approach, and as long as the approval standards remain in

LINE #	COMMENT w/ RATIONALE	PROPOSED CHANGE
		place for the submitted products, as indicated throughout this Draft Guidance, these pathways should remain available to applicants.
Footnote 11	"[T]he focus of this guidance is review of combination products for which marketing authorization is sought under a single application." This statement should be highlighted in the introduction of the Draft Guidance and a separate section/document should be created for cross-labeled combination products. This is extremely pertinent to the overall scope of this document since combination products under a single marketing authorization constitute only a subset of all combination products.	Move sentence from footnote to introduction, scope, and/or title of document. Consider how to provide information on cross-labeled combination products as additional sections within this Draft Guidance in order to appropriately cover all types of combination products, as listed in Section II.A. Also, see comment on lines 133-134, above, requesting additional guidance on cross-labeled combination products.
Line 170-173	Document states that data needed to support the safety and effectiveness of "the non-lead constituent part of a combination product may differ from the data and information needed to obtain marketing authorization for that article as a stand-alone product." We ask that FDA explain the considerations for determining whether the product does versus does not differ as the use of the term *may* implies that there are situations in which data would not differ, in which case any previous findings of safety and effectiveness and/or substantial equivalence may be able to stand on their own. The ability of sponsors to utilize data and information from a previous finding of safety and effectiveness and/or substantial equivalence in cases where there are no new concerns raised is important from a least burdensome perspective, particularly when concerning a device constituent.	Please add further guidance on (including examples) of cases when the data and information needed to obtain marketing authorization for a non-lead constituent part both differs and does not differ from that needed as a stand-alone product. <u>Potential example of a case where additional data and information are necessary:</u> • Device constituents co-packaged or integrated (to create a single-entity combination product) with a drug constituent (drug PMOA) where the device constituents are not used within their cleared/approved indication for use. <u>Potential example of a case where additional data and information are not necessary:</u> • Device constituents co-packaged with a drug constituent (drug PMOA) where the device constituents are used to deliver the drug within their cleared/approved indication for use, including route of administration, volume, administration method, and user interface.

LINE #	COMMENT w/ RATIONALE	PROPOSED CHANGE
		We do not believe these examples are comprehensive and would appreciate additional guidance from FDA on considerations for when the data and information requirements indeed differ. We also note that, for device constituents of combination products, the least burdensome provisions apply[2] and further guidance in this area would allow sponsors to understand the least burdensome means of establishing substantial equivalence or reasonable assurance of safety and effectiveness.
Line 184-194	This section provides a discussion on utilizing prior FDA findings of safety or effectiveness or substantial equivalence with respect to an approved or cleared constituent part. We appreciate the inclusion of this option, but believe significantly more detail is needed in order for sponsors to be able to utilize this streamlined option. We believe there are many circumstances when this concept has not been applied, and detailed guidance on this topic would allow sponsors the ability to implement this approach in a consistent manner.	We would like further guidance on, operationally, how to make reference to prior FDA findings of safety or effectiveness or substantial equivalence during the premarket submission process. In other words, how may a sponsor reference prior clearances or approvals within a marketing application, what data or information requirements may that reference replace, and how may public and non-public information be utilized? Regarding Line 187 that requires "a right of reference for another sponsor's data," please clarify when a right of reference is required versus not, since some regulatory pathways (such as device 510(k) and drug 505(b)(2)) do not require a right of reference for some aspects of obtaining authorization (intellectual property rights notwithstanding). We believe there are analogous cases where another product's authorization may be referenced without a right of reference, such as a device constituent's 510(k) clearance, as long as publicly available information proves useful to addressing the regulatory topic of concern. Additionally, when a right of reference is indeed required, we would appreciate further guidance on how to apply that depending on the regulatory pathway (such as a Letter of Authorization within a drug NDA or biologic BLA).

[2] *See* FDA, *The Least Burdensome Provisions: Concept and Principles: Guidance for Industry and FDA Staff* (2019), https://www.fda.gov/media/73188/download.

LINE #	COMMENT w/ RATIONALE	PROPOSED CHANGE
Line 261: Premarket Notification (510(k)) Submissions		
Line 303	It may be scientifically justified that a medical device that is not a device constituent part of any combination product is an appropriate predicate for a combination product device constituent part because it has the same technologic characteristics and intended use. For example, a drug-coated suture or orthopedic implant could have the same physical properties and performance (e.g., strength) with or without the presence of the drug.	We ask that FDA add context to the sentence, explaining that there could be cases where there is scientific justification for allowing a device that is not combined with a drug or biologic constituent to be used as a predicate for a 510(k) for a device-led combination product.
Line 363: Abbreviated New Drug Application (ANDA)		
Line 378	ANDAs for a drug-led combination product should also include sufficient information to demonstrate that the non-lead constituent part is compatible for use with the final formulation of the drug constituent part.	Would an ANDA in this case be used, if an existing drug is combined with a completely new delivery device?
Line 421: BLAs for Biosimilar and Interchangeable Biological Products Submitted under Section 351(k)		
Line 430	To meet the interchangeability standard, an applicant must show that its product "is biosimilar to the reference product," and must further show that the product "can be expected to produce the same clinical result as the reference product in any given patient" and that, for a product that is administered more than once to an individual, "the risk in terms of safety or diminished efficacy of alternating or switching between use of the [two products] is not greater than the risk of using the reference product without such alternation or switch."	Would this also apply to a biologic combined with a brand-new device constituent part using the same administrative route and dosing form? Or if the combination would include an additional device (e.g., a companion software)?
Line 464: ANNEX		
Line 482-483	These examples apply primarily to submissions made to CDRH. Additional examples for CDER and/or CBER-led submissions should be prepared and presented. Certain CDER/CBER examples do not easily follow the example format starting with a predicate device.	Potential example: Drug/Biologic PMOA Product(s): An investigational biologic or drug agent (refrigerated) intended for targeted organ delivery using a modified catheter/needle system with several ancillary devices [IV sets, syringes, trocar systems,

LINE #	COMMENT w/ RATIONALE	PROPOSED CHANGE
		retractors, device holders (i.e., third arms)] needed to provide surgical access. A single investigation (marketing) application could be submitted to facilitate the investigation. However, as a final product for approval and marketing, it would be more appropriate to file the Drug/Biologic separately from the device. The device could have general purpose 510(k) claims or specific intended uses that would be concurrently approved. Also, if the device company already has a 510(k) (e.g., for the catheter), that company would likely prefer dual marketing applications. If a single marketing application was required, any simple device change would require a CDER/CBER supplement, which would be burdensome for the potential risk of slight changes. Some minor device changes may not rise to the level of reporting under the special 510(k) paradigm, but may be required under CDER/CBER rules.