Combination Products Coalition

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February 24, 2020

VIA ELECTRONIC SUBMISSION

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

Re: Docket No. FDA-2019-D-4739: Requesting Food and Drug Administration Feedback on Combination Products; Draft Guidance for Industry and Food and Drug Administration Staff

To Whom It May Concern:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to provide comments on FDA's "Requesting Food and Drug Administration Feedback on Combination Products; Draft Guidance for Industry and Food and Drug Administration Staff" dated December 26, 2019 (the "Draft Guidance").

CPC appreciates FDA's efforts to enhance clarity and transparency of regulatory considerations for combination products through the publication of the Draft Guidance outlining the feedback mechanisms available to sponsors. CPC has carefully evaluated FDA's Draft Guidance and agrees with many of the suggestions. However, CPC has identified the following overall concerns and suggestions, as well as our specific comments, which are provided on subsequent pages.

1. Although the Draft Guidance is intended to introduce the CPAM pathway and explain how this new meeting type can be used, CPC does not believe that the Draft Guidance meets the statutory objective of describing how a CPAM should be used, relative to other meeting types. FDA should revise the Draft Guidance to describe the parameters for CPAM interactions, including when a CPAM would be appropriate over an application-based mechanism along with examples.

[1] 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 CPC to bring a special, broad, and unique perspective to these issues.

2. The Draft Guidance seems to generally discourage the use of a CPAM and frequently tells sponsors to not use a CPAM, as the Draft Guidance emphasizes FDA views that application-based mechanisms are "the most efficient and effective." We also note that the FR Notice mentions that FDA expects only one CPAM meeting per year to occur across CDER and CBER, further emphasizing FDA's position that CPAMs are generally discouraged. CPC encourages FDA to embrace this new meeting type and develop an approach for CPAM interactions to support reaching agreements on the standards and requirements for marketing authorization of a combination product and/or other issues relevant to a combination product, such as requirements related to postmarket modification of the product or current good manufacturing practices ("CGMPs"). CPC considers that cross-cutting topics, such as human factors and control strategies, are within the category of "requirements for marketing authorization" described in 503(g)(2)(A). Productive engagement with FDA is key for understanding the expectations for marketing authorization and Industry has experienced difficulties engaging with FDA on human factors topics, such as comparative or threshold analyses and study designs, as the typical response received is to file the human factors information and FDA will provide feedback in writing. This does not allow for engagement and dialogue, as is provided for other topics, particularly when human factors elements from multiple Centers (e.g. DMEPA within CDER, and the Human Factors team within CDRH) is desired. CPC recommends that FDA include opportunities for iteration of proposals, which are linked back to the earlier discussion to allow for sponsors to receive FDA feedback, revise proposals and discuss with FDA until 'agreement is reached,' which is common to other types of formal meetings.

3. CPC recommends that FDA provide more detailed timelines for the CPAM submissions and responses, similar to those outlined in the draft guidance, *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. CPC recommends that a table outlining the steps, timelines and format expectations, such as the following be included in the guidance. Although the Draft Guidance did not clarify steps relating to submission of the meeting package and FDA preliminary responses, these are included in the proposed table, as these are critical steps in the overall interaction process.

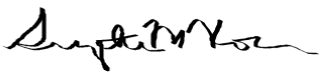
Process Step	**Format**	**Timeline**
Submission of meeting request	Per Table 1 in Draft Guidance	Start of process
Notification of meeting granted or denied	In writing. If granted, the letter will include the date, time and location and/or conferencing arrangements, as well as expected FDA participants	21 calendar days from receipt of meeting request
Scheduled meeting date	Included in meeting granted letter	75 calendar days from receipt of meeting request
Submission of meeting package	Per Table 1 in Draft Guidance	Received by FDA no later than xx calendar days before scheduled date of meeting
Send FDA preliminary responses to questions in the meeting package	In writing	No later than **xx** calendar days before the meeting date

Process Step	**Format**	**Timeline**
Notify FDA of any changes in planned attendees	In writing	No later than 5 calendar days prior to the meeting
Notify FDA whether meeting is still needed	In writing, including a revised meeting agenda indicating which questions will be discussed in the meeting	No later than **xx** calendar days following receipt of FDA's preliminary responses
Meeting minutes issued by FDA	In writing	Within 30 calendar days after the meeting

4. The guidance should focus on the new or distinct information related to combination product meetings through the application-based and CPAM mechanisms and remove the content that is duplicated from other guidance. References may be provided to other guidance as appropriate, given that it is generally informative to understand all engagement mechanisms available to combination product sponsors.

We appreciate the opportunity to provide input on the Draft Guidance. We ask that the Agency consider this feedback as it finalizes the guidance and we 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 Revision
n/a		CPC recommends that the FDA consider options for access to quick and informal communications between the Agency and sponsors to address issues raised during the review or areas where clarification may be required as this could lead to faster and more consistent resolution of concerns. We believe this mechanism is already available (i.e., through the OCP email address) and it would be useful to highlight in this guidance.	Provide additional opportunities to engage with FDA, specifically related to quick/informal clarifications.
35	I	The parenthetical phrase in this line is additional commentary that is unnecessary.	"application-based mechanisms ~~**(generally the most efficient and effective approach)**~~…"
42 -47	I	Section 503(g)(8)(C)(vi) requires FDA to issue a final guidance addressing: how CPAMs relate to other FDA meeting types, what information should be submitted prior to a CPAM, and the form and content of agreements reached through a CPAM. However, the guidance does not explain how CPAMs relate to other FDA meeting types or when CPAM would be appropriate instead of another meeting type. It merely encourages sponsors to use traditional meeting mechanisms wherever possible. CPC believes that topics that present unique combination product concerns could utilize this meeting type, and CPC views that the CPAM could be appropriate for the following topics: - Human Factors - Control strategies - New technologies - Submission content expectations - Postmarketing changes	FDA should provide more examples of what meeting topics would be appropriate for application-based meeting mechanisms and which would be appropriate for CPAM. Provide clear parameters for what should go through the CPAM pathway.
46	I	Introduction doesn't clarify that the Draft Guidance is also introducing a brand new meeting type option.	"…and (3) **introduce a new interaction option available to sponsors, CPAMs, when they can be utilized,** how they relate to other FDA meeting types, what information should be

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			submitted prior to a CPAM, and the form and content of agreements reached through a CPAM."
48-104	II	This Background section is duplicative of the content which is included in other combination product guidance documents and is unnecessary to repeat in this guidance. For example, the content in Section II of the *Principles of Premarket Pathways* draft guidance is almost identical.	Delete this section.
105-204	III	The majority of the content in this section isn't distinct to combination products. It would be more helpful to Industry for this guidance to focus on the unique considerations for combination products and specifics for the CPAM meeting type.	Here and throughout, can't there be reference to the existing FDA meeting guidance as a baseline for interaction guidance and then this guidance be distinguishing what is unique to these types of meetings? Section A, B and C could be reduced to focus on unique combo product meetings specifically or by simply referencing prior guidance documents.
147-149	III.A	A sponsor may need the expertise of another Center or office/division. In our experience, even when the presence of certain staff is requested, not all the requested staff attend and sponsors are sometimes unaware until the meeting. Sponsors may want to reschedule a meeting if requested staff cannot attend, but cannot do so if they are unaware. Suggest outlining ways in which sponsors can engage informally with the primary POC in the lead Center prior to submitting a meeting request, and once submitted, to ensure the meeting can be productive for all parties.	"…communications should be directed to the identified POC within the lead Center who will engage appropriate expertise." Suggested to add "**Sponsors may request the expertise or attendance of specific Centers or staff. Sponsors are encouraged to reach out to the POC within the lead Center informally to ensure such staff can attend and address scheduling matters early in meeting planning.**"

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162-166	III.B	FDA "generally intends" to include requested participants is not a sufficient commitment and can lead to unproductive meetings that are not a good use of time for FDA or the sponsor. If a sponsor has made a request for participants with particular expertise to attend, and such staff cannot attend, there are practical implications for the sponsor. The meeting may not be productive or useful for the sponsor, because the sponsor may not be able to obtain the feedback needed on certain key questions that are part of a larger meeting request. Often the sponsor is not aware these staff cannot attend until the day of the meeting, when the sponsor has sometimes travelled for the meeting. The sponsor may be willing to reschedule to ensure appropriate staff can attend, or conduct a teleconference instead, to avoid this situation, if the sponsor could be made aware earlier.	Revise this section to note that the lead Center POC will notify sponsors at a certain time point which staff will be attending. If requested staff with the relevant expertise are not attending, FDA should notify the sponsor and describe why the requested participants are not available for the meeting. If requested staff cannot attend, FDA should allow the sponsor to work with the POC to reschedule the meeting, schedule a separate meeting with the non-lead Center, or other mutually agreeable options.
197-198	III.C	It is not clear why the route of administration and/or dosing information would be included only for device-led combination products.	"For ~~a device-led~~ combination products **which are intended to administer a dose of a drug and/or biological product**, provide the route of administration and/or dosing information for the drug and/or biological product constituent part(s)."
236	III.D	This section refers to business days, but the remainder of the guidance includes timeframes measured in calendar days.	Revise to calendar days for consistency: "If this information changes, it should be updated no later than 5 ~~business~~ **calendar** days prior to the meeting."
239-240	III.D	See comment to line 162-166 regarding ensuring that requested expertise and participants are able to attend, or communicating early with the sponsor if this isn't possible, so a workable solution can be reached.	"FDA should ~~**generally**~~ accommodate such requests when appropriate (i.e., the expertise is necessary to address the proposed agreement) and possible (i.e., schedules permitting). **If a request cannot be accommodated, FDA should communicate with the sponsor at the earliest possible time point and provide the reason that the request cannot be accommodated. This will allow the POC and the sponsor to find a mutually agreeable solution, such as rescheduling the meeting or meeting directly with the non-lead Center.**"

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253-259	IV	The existing application-based mechanisms require a significant amount of time and effort by sponsors and FDA. Oftentimes, meetings are not granted at early stages of development, or feedback is provided as written response only. Expecting that application-based mechanisms are used first and then submit a CPAM to gain the 'agreements' is not an efficient approach. This approach is duplicative and reduces the value of the CPAM meeting type.	Maintain recommendations to consider a CPAM when the indication for use and design of the combination product is available and sufficient information can be provided to ensure an effective review, but FDA should provide clear recommendations on the types of interactions which would be suited for the CPAM approach
265 – 267	IV.A	Meetings with some Centers (e.g. CDER, for drug-led combination products) can be difficult to obtain and have long timelines. If the feedback being requested is from CDRH, and all the questions relate to a device constituent part, it seems sponsors of drug-led combination products should be able to utilize the pre-sub process for efficiency, while keeping the lead Center POC informed. This would reduce the burden on CDER and result in more timely feedback on these device-specific issues.	"As discussed above, **wherever possible,** all interactions with FDA should be through the lead Center for the combination product and using the application-based mechanisms of that Center~~, regardless of the feedback being requested~~**. However, when feedback requested relates solely to the constituent part regulated by the non-lead Center, sponsors may engage the non-lead Center using its meeting mechanisms, so long as sponsors copy the POC from the lead Center and keep the lead Center informed so the administrative record can be maintained.**"
280	IV.B	The definition of CPAMs is buried in footnote 5 and needs to be reiterated throughout the guidance, as well as define when CPAMs should be used over application based mechanisms.	"CPAMs are intended as a means for sponsors to obtain clarity and certainty and are available for combination products for which the lead Center assignment is clear. **The purpose of a CPAM is to address the standards and requirements for marketing authorization of a combination product and/or other issues relevant to a combination product, such as requirements related to postmarket modification of the product or current good manufacturing practices (CGMPs). They should be utilized when there is conflicting or unclear advice between Centers or across applications on similar issues or products.**"
After 287 (Footnote 17)	IV.B	Footnote 17 does not seem to contemplate the difficulty this would present for cross-labeled combination products where the constituent parts are made by separate manufacturers who each hold separate	"…Prior to the submission of separate marketing applications for cross-labeled combination product constituent parts, ~~all~~ interactions with FDA **regarding the combination product** should be through the lead Center for the combination product,

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		marketing authorizations for the product when not used in combination. This could render the manufacturer of one constituent part unable to avail themselves of the standard application meetings of the Center that regulates their specific product.	**however, each constituent part applicant maintains the ability to schedule application-based interactions for their marketing application type. ~~regardless of the feedback being requested.~~**"
Line 304	IV.B.1	The guidance requires sponsors to provide complete information when submitting a CPAM request, despite the fact that not all CPAM requests will be granted. This seems unduly burdensome, as compiling this documentation requires significant time and resources on the part of the sponsor. Suggest FDA follow the approach utilized for PDUFA meetings, where sponsors submit a meeting request with sufficient detail to outline the purpose of the meeting and reason for the request, followed by a detailed briefing document once the meeting has been granted.	"CPAM requests should: • Be submitted to the lead Center for the combination product using the processes described in Table 1 below; • Identify the submission as a "Combination Product Agreement Meeting Request" in the cover letter; and • Provide **adequate information for the FDA to assess the potential utility of the meeting and to identify FDA staff necessary to discuss proposed agenda items** ~~complete information, including the content described in Section III.D above.~~"
317-319	IV.B.2	This section notes that CPAMs are not a replacement for FDA's existing dispute resolution processes. While this is understandable, without guidance as to what is appropriate for a CPAM meeting, and what is meant by scientific and regulatory disputes, this section seems overly broad. It seems to remove all scientific discussions from use of a CPAM, which is not the intent of the statute.	"We note that it is not appropriate, however, to use CPAMs to resolve scientific or regulatory disputes that would otherwise be reviewed under the lead Center's dispute resolution and/or appeals processes. **However, when a sponsor believes there is confusion about, conflicting advice regarding, or a misunderstanding of the scientific evidence, such that additional clarity could be obtained via a CPAM meeting, such a meeting could be appropriate. If, after a CPAM, there is still disagreement between the sponsor and the agency, such a dispute should proceed through the appropriate dispute resolution or appeals processes.**"
326	IV.B.2	As mentioned earlier, it is a significant burden on the sponsor to compile the briefing book when the meeting may not be granted. If FDA opts not to grant the CPAM, is the idea that FDA will automatically convert	"If FDA believes another meeting type may be more efficient and provide greater clarity, FDA may contact the sponsor and offer to convert to that meeting type. FDA intends to contact the sponsor within 21 calendar days of receiving a CPAM

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		it to a different meeting type? Or is this section implying that it is possible FDA could just refuse to grant the CPAM and not convert to another meeting? It is not completely clear in this section, and given the burden on the sponsor, we suggest FDA clarify what will happen if a CPAM is not granted and sponsor recourse (e.g. dispute resolution mechanisms). We also suggest that a briefing book should not be required until the 21 day feedback is received and the meeting is granted.	request confirming receipt and providing a meeting time (if requested) or providing a substantive basis for not granting the CPAM. **Once the meeting is granted, the sponsor should provide a detailed briefing book within XX days. If the sponsor disagrees with the agency's decision to deny a CPAM meeting, standard dispute resolution and/or appeals mechanisms are available to the sponsor.**"
333	IV.B.2	Pre-meeting feedback is not mentioned for a CPAM. As noted in the Formal Meetings Guidance for PDUFA products, "Communications before the meeting between requesters and the FDA, including preliminary responses, can serve as a foundation for discussion or as the final meeting responses."	Suggest FDA note that pre-meeting feedback will be provided at least 5 days prior to the meeting, per existing guidance for PDUFA and MDUFA products.
356		An appendix should be added with examples of appropriate topics for a CPAM, which can be gathered via input from sponsors during this commenting period.	Examples of topics that would be appropriate for a CPAM: • Gaining agreement on expected postmarket modifications and the type of supplements or reporting that would be required for such modifications (e.g. iterative modifications to software, digital health products), particularly those affecting the "secondary" constituent part. • Pre-filing meeting for combination products to gain agreement on the device constituent part data package to be included in the marketing application or supplement for a drug/biologic-led combination product. This would be unique from other application-based mechanisms in that it would be a standalone meeting to discuss solely the data needed to support the device constituent part (e.g. HFE studies, clinical home use studies, design verification), rather than being part

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			of a larger meeting to discuss CMC and other drug filing issues. • Meeting to gain agreement on the HFE study plans, comparative or threshold analyses, and related topics for a combination product. This meeting would entail obtaining feedback not just on the summative validation study (for which there is an existing mechanism for protocol review), but on the overall HFE testing plan, including formative studies. When the only method for obtaining feedback on HFE plans is at the summative protocol stage, or in a pre-filing meeting after the study has been executed, all the data has been generated and it can cause significant delay to repeat all the formative and summative studies. Thus, an earlier meeting to align on the HFE study plan would be expedient for sponsors and the FDA. Additionally, this topic would be useful for a CPAM meeting when feedback from multiple Centers' HF teams (DMEPA from CDER, or the HF team from CDRH) is desired, particularly for co-packaged or cross-labeled combination products where varied approaches to the HFE plan may be taken.