

# Requesting FDA Feedback on Combination Products

## Guidance for Industry and FDA Staff

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Office of Combination Products (OCP)  
Center for Biologics Evaluation and Research (CBER)  
Center for Drug Evaluation and Research (CDER)  
Center for Devices and Radiological Health (CDRH)**

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# Requesting FDA Feedback on Combination Products

## Guidance for Industry and FDA Staff

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

### I. Introduction

The purpose of this guidance is to discuss ways in which combination product sponsors<sup>1</sup> can obtain feedback from FDA on scientific and regulatory questions and to describe best practices for FDA and sponsors when interacting on these topics.<sup>2</sup> These interactions can occur through application-based mechanisms, such as the pre-submission process used in the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER)<sup>3</sup> and the formal meetings used in the Center for Drug Evaluation and Research (CDER) and CBER,<sup>4</sup> or through Combination Product Agreement Meetings (CPAMs),<sup>5</sup> as appropriate.

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<sup>1</sup> As defined in 21 CFR 3.2, a “sponsor” is any person who submits or plans to submit an application to FDA for premarket review (e.g., an entity that is developing a combination product for a future application and wishes to interact with FDA on scientific or regulatory questions specifically related to its combination product). The term “application,” for purposes of this guidance, includes an investigational new drug application (IND), new drug application (NDA), abbreviated new drug application (ANDA), investigational device exemption (IDE) application, premarket approval application (PMA), premarket notification (510(k)), humanitarian device exemption (HDE) application, product development plan (PDP), request for classification submitted under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (De Novo request), and biologics license application (BLA). Note that an HDE may not be the appropriate pathway to market for a combination product. For questions about the availability of the HDE pathway for combination products, please contact the Office of Combination Products by email at [combination@fda.gov](mailto:combination@fda.gov).

<sup>2</sup> For additional information on principles of premarket review for combination products, including how to determine which type of application is appropriate, see [Principles of Premarket Pathways for Combination Products, Draft Guidance for Industry and FDA Staff](#) which, when final, will represent FDA's current thinking on this topic.

<sup>3</sup> See [Requests for Feedback and Meetings for Medical Device Submissions: The O-Submission Program, Guidance for Industry and Food and Drug Administration Staff](#).

<sup>4</sup> See [Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, Draft Guidance for Industry](#), [Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products, Draft Guidance for Industry](#) and [Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA, Guidance for Industry](#). When final, these guidances will represent FDA's current thinking on these topics.

<sup>5</sup> The 21<sup>st</sup> Century Cures Act (Public Law No. 114-255) (Cures Act) amended section 503(g) of the FD&C Act (21 USC 353(g)) to include a new section 503(g)(2)(A) establishing an additional meeting type for combination product sponsors – CPAMs – to address the standards and requirements for marketing authorization (e.g., approval,

We are issuing this guidance consistent with the Agency’s ongoing commitment to enhancing clarity and transparency regarding regulatory considerations for combination products, and in accordance with the mandate under section 503(g)(8)(C)(vi) of the FD&C Act (21 USC 353(g)(8)(C)(vi)), which was added by section 3038 of the Cures Act. Section 503(g)(8)(C)(vi) requires FDA to issue a final guidance addressing: (1) the structured process for managing pre-submission interactions with sponsors developing combination products; (2) best practices to ensure FDA feedback in such pre-submission interactions represents the Agency’s best advice based on the information provided during these pre-submission interactions; and (3) how CPAMs relate to other FDA meeting types, what information should be submitted with a request for a CPAM, and the form and content of agreements reached through a CPAM.

## **II. Background**

This section discusses what combination products are, how they are assigned to a “lead center,” intercenter coordination for their premarket review, and whom to contact in FDA regarding combination product questions.

### **A. What are combination products and how does FDA regulate them?**

A combination product is a product comprised of any combination of a drug, device, and/or biological product (see 21 CFR 3.2(e)).<sup>6</sup> The drugs, devices, and biological products included in combination products are referred to as “constituent parts” of the combination product (see 21 CFR 3.2(k)).

A combination product is assigned to an Agency center that will have primary jurisdiction (i.e., the “lead center”) for that combination product’s premarket review and regulation. Under section 503(g)(1) of the FD&C Act (21 USC 353(g)(1)), assignment of a combination product to a lead center is based on a determination of which constituent part provides the primary mode of action (PMOA) of the combination product.<sup>7</sup> The lead center for premarket review of the combination product also has the lead for postmarket regulation. Regardless of the PMOA, Agency components coordinate as appropriate to ensure efficient, effective regulation of combination products.

### **B. Whom should I contact for preliminary or general questions?**

If you are uncertain whether your product is a combination product or a constituent part of a combination product, or which center has primary jurisdiction, you can contact the Office of

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clearance) 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 (CGMP).

<sup>6</sup> A combination solely of two or more of the *same* type of medical product is *not* a “combination product” for purposes of section 503(g) of the FD&C Act and as defined at 21 CFR 3.2(e). For example, two drugs combined into a single dosage form or multiple devices in a kit together would not be combination products.

<sup>7</sup> The “primary mode of action” of a combination product is “the single mode of action of a combination product expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.” Section 503(g)(1)(C) of the FD&C Act (21 USC 353(g)(1)(C)); see also 21 CFR 3.2(k) (defining “mode of action”), (m) (defining “primary mode of action”).

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Combination Products (OCP) ([combination@fda.gov](mailto:combination@fda.gov)). If you wish to obtain a binding determination from FDA regarding classification<sup>8</sup> and/or center assignment, you may submit a request for designation (RFD) to OCP, or if you wish to obtain informal feedback, you may submit a pre-RFD to OCP.<sup>9</sup>

If you know the lead center for your combination product (e.g., there is a pending submission), contact the FDA Point of Contact (POC) (see Section III.B below) or, if you do not yet have an FDA POC, contact the lead center Product Jurisdiction Officer (PJO).<sup>10</sup> In some circumstances, combination products may not require premarket authorization (e.g., some kits), and in those cases you should contact the lead center PJO. If you are unsure of the lead center, if you have general questions regarding intercenter collaboration on combination products, combination product regulation, combination product guidance or policy, or if you need help in navigating the combination product review process at FDA, contact OCP ([combination@fda.gov](mailto:combination@fda.gov)).<sup>11</sup>

### **III. Best Practices Regarding Interactions Between FDA and Sponsors of Combination Products**

Combination product sponsors and the FDA share common goals of ensuring that combination products are safe and effective and that the regulatory requirements and processes associated with their premarket review and postmarket regulation are clear, efficient, effective, and appropriately implemented. When sponsors request feedback on combination products, timely communication and robust information sharing are critical aspects to help ensure efficient and productive interactions between FDA and sponsors. The sections below highlight specific considerations to help ensure productive combination product interactions:

- Appropriate Submission and Processing. Submissions made under an application-based mechanism and CPAM requests (hereafter referred to as “submissions/requests”) should

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<sup>8</sup> Please note that “classification” as used in this guidance refers to a product’s designation as a drug, device, biological product, or combination product. This is distinct from the use of the term “classification” in reference to the class (Class I, II, or III) of a device as described in section 513(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

<sup>9</sup> See [How to Write a Request for Designation \(RFD\), Guidance for Industry](#) and [How to Prepare a Pre-Request for Designation \(Pre-RFD\), Guidance for Industry](#); see also [Classification of Products as Drugs and Devices & Additional Product Classification Issues, Guidance for Industry and FDA Staff](#).

<sup>10</sup> The lead center PJO can be contacted at [CBERProductJurisdiction@fda.hhs.gov](mailto:CBERProductJurisdiction@fda.hhs.gov), [CDERProductJurisdiction@fda.hhs.gov](mailto:CDERProductJurisdiction@fda.hhs.gov) or [CDRHProductJurisdiction@fda.hhs.gov](mailto:CDRHProductJurisdiction@fda.hhs.gov).

<sup>11</sup> OCP is required to: coordinate premarket reviews for combination products; oversee the timeliness of premarket reviews and the alignment of feedback to the sponsor; ensure there is a primary POC(s) in the lead center; coordinate communications between the lead and consulting center(s) if requested; ensure meetings with the sponsor are attended by each center involved in the review, as appropriate; and ensure that the consulting center(s) advise as appropriate on relevant regulations, guidances, and policies, and follow this guidance. OCP is also required to ensure the consistency and appropriateness of postmarket regulation of combination products. See section 503(g)(8) of the FD&C Act (21 USC 353(g)(8)).

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be submitted to the appropriate lead center, identifying the product as a combination product<sup>12</sup> and appropriately routed by FDA to staff within the centers for review.

- Timely Use of Appropriate Communication Procedures. Communications between the Agency and sponsor should be timely and the mechanisms for such communication (face-to-face meetings, teleconferences, written responses, etc.) should be those that are specified in FDA guidance.
- Clear, Robust Information Sharing. Information sharing between sponsors and the Agency, including communications regarding information submitted by sponsors and questions and information requests from FDA, should be clear and sufficiently robust to minimize repeat interactions on the same question and enable FDA to provide clear feedback in a timely manner.

The following sections provide best practices for both sponsors and FDA to enable such interactions for combination products whether in the application-based mechanism or CPAM context.

### **A. Sponsor Best Practices**

Below are recommendations to sponsors that we believe will help to ensure that interactions are efficient and productive.

- Submissions for a Combination Product. Submissions/requests should be submitted to the appropriate lead center. As noted in Section IV.B below, a CPAM is only available for combination products for which the lead center is clear. It is important that combination product sponsors identify their product as a combination product in CPAM requests, as well as when utilizing application-based mechanisms.
- Clear and Appropriate Questions. The specific feedback being requested should be clear in the questions being posed. Also, the questions should be appropriate to the stage of combination product development. For example, it would not be productive to ask questions related to full-scale manufacturing process controls if, for instance, the composition/design of the combination product is still being developed.
- Comprehensive Rationale and Supporting Information. The submission/request should include sufficient information to allow FDA to consider the issue(s) and provide feedback without the need for significant additional information requests (see also Sections IV.A and IV.B below and relevant guidances referenced in Appendices 1 and 2). When requesting FDA feedback on a particular issue, sponsors should provide sufficient information, as applicable, about how the issue relates to the constituent part(s) as well as

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<sup>12</sup> The Cures Act amended section 503(g) of the FD&C Act to require sponsors seeking “agency action” on a combination product to identify the product as such. See section 503(g)(8)(C)(v)(I) of the FD&C Act (21 USC 503(g)(8)(C)(v)(I)). We believe CPAM requests fall within this provision. Therefore, in a CPAM request, sponsors must identify their product as a combination product. Additionally, even if not required for all submissions requesting feedback through an application-based mechanism, we recommend that sponsors identify their product as a combination product in such submissions to help facilitate combination product reviews.

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the overall combination product.

- Communications Through the Identified FDA POC. The sponsor should communicate with FDA through the designated POC. Even in situations where the focus of the request is an issue for which expertise primarily resides outside the lead center, communications should be directed to the identified POC within the lead center who will engage appropriate expertise (see Section III.B below). Sponsors can contact the POC within the lead center to request engagement of appropriate staff to help to ensure availability of necessary expertise and address scheduling matters early in meeting planning.

### **B. FDA Best Practices**

Below are FDA best practices we believe will help to ensure that review of submissions/requests is efficient and productive.

- Notifying Sponsor of the FDA POC.<sup>13</sup> Once a submission/request has been accepted, consistent with center guidance and processes, the lead center should ensure that the sponsor is notified of the FDA POC.<sup>14</sup> The POC should coordinate communications between the sponsor and FDA staff, including ensuring efficient communications involving the non-lead center, and be kept informed of the outcomes of any communications between FDA staff and the sponsor.
- Engaging Relevant Expertise. The lead center should engage appropriate expertise from other medical product centers and the OCP, as needed, to support comprehensive review and feedback for the submission/request. Such staff should be engaged early in the review process and invited to related meetings or other interactions with the sponsor, as appropriate.<sup>15</sup> If a sponsor has made a request for participants with particular expertise to engage on matters concerning the product, FDA generally intends to include such staff in meetings and other interactions when appropriate (e.g., they have expertise relevant to the issues being discussed). Sponsors may also request that OCP participate in meetings or otherwise engage on regulatory matters concerning combination products (see section 503(g)(8)(C)(v)(II) of the FD&C Act (21 USC 353(g)(8)(C)(v)(II))). In situations where a feedback request relates solely to issues reviewed by the non-lead center, the lead center will work to ensure that information is transmitted promptly to the other center.
- Consolidated, Aligned, and Reliable Feedback. FDA should provide comprehensive responses, to the extent possible based on the information provided, to the issues posed in the submission/request. The feedback provided to the sponsor should represent the current thinking of the FDA based on the information provided and include relevant input

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<sup>13</sup> Under section 503(g)(8)(C)(iii) of the FD&C Act (21 USC 353(g)(8)(C)(iii)), OCP must ensure that a designated person or persons in the primary Agency center is the primary POC(s) for the sponsor of the combination product.

<sup>14</sup> In CBER and CDER, the FDA POC is typically a Regulatory Project Manager (RPM), and in CDRH, the FDA POC is typically a Lead Reviewer.

<sup>15</sup> See [Staff Manual Guide \(SMG\) 4101, Inter-Center Consult Request Process](#) regarding, among other things, expectations and processes for intercenter consultation on combination products; see also [SMG 4103, Expectations and Procedures for Engagement Among Medical Product Centers and Office of Combination Products on Regulations and Guidance Pertaining to Combination Products](#).

from all Agency centers and groups involved in review of the submission/request. FDA should not generally alter its feedback once provided to the sponsor unless new information or updated scientific thinking, for example, including as reflected in subsequently issued guidance, regulations or laws, impacts the validity of the previously provided feedback.

## **IV. Feedback Mechanisms Available for Combination Products**

The sections below discuss the various ways sponsors can interact with FDA via application-based mechanisms or CPAMs to discuss combination product issues.<sup>16</sup>

### **A. Application-based Mechanisms**

The application-based mechanisms for interacting with FDA that are available to drugs, devices, and biological products are also available for combination products. These mechanisms are typically the most efficient and effective for communication with FDA and are based on the application type that would be submitted for the combination product.<sup>17</sup> This section provides considerations for application-based mechanisms when used to address combination product issues. Sponsors should also review associated guidance relevant to the specific application-based mechanism (see Appendices 1 and 2).

All interactions with FDA should be coordinated through the lead center for the combination product (see Section III.A above) and using the application-based mechanisms of that center, regardless of the feedback being requested. For example, if a sponsor has general questions on the drug constituent part of a device-led combination product, that interaction would occur through CDRH and the appropriate application-based mechanism would be the pre-submission meetings process.<sup>18</sup> Coordinating interactions through the lead center helps to ensure appropriate engagement from all members of the review team (including, as appropriate, review team members in other centers(s)) and that interactions, including those that occur by e-mail and telephone, are appropriately captured in the administrative record. Application-based mechanisms include specialized meeting types and opportunities designed to address specific

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<sup>16</sup> Although the Agency can discuss product-specific issues only with the product sponsor and those whom the sponsor designates, other entities involved in combination product development (e.g., constituent part developers, master file holders) and manufacturing may request feedback from FDA relating to their regulated activities. Although such entities cannot use application-based mechanisms or CPAMs, such entities may contact the lead center for the combination product using the existing process for general inquiries ([CBER Manufacturers Assistance](#), [CDER Drug Information](#), [CDRH Division of Industry and Consumer Education](#)). If the lead center is not known, these entities can contact OCP for assistance ([combination@fda.gov](mailto:combination@fda.gov)). The center or OCP will coordinate, as necessary, to provide feedback or direct the entity to an appropriate mechanism for additional feedback.

<sup>17</sup> While application-based mechanisms are available, and generally should be utilized, for all combination products, cross-labeled combination products for which separate marketing authorizations are being sought for the constituent parts (e.g., a new drug application (NDA) for the drug and a premarket notification (510(k)) for the device) can raise distinct considerations. Prior to filing of separate marketing authorization submissions, all interactions with FDA should be coordinated through the lead center for these combination products, regardless of the feedback being requested. The sponsor(s) may wish to discuss with the centers (and OCP as needed) how best to ensure efficient, coordinated engagement during review of marketing authorization submissions (e.g., in light of the differing user fee performance goals associated with the submission types for each constituent part).

<sup>18</sup> See [Requests for Feedback and Meetings on Medical Device Submissions: The Q-Submission Program. Guidance for Industry and Food and Drug Administration Staff.](#)

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requests (e.g., breakthrough designation for a device) and product types (e.g., complex generics). Appendices 1 and 2 list examples of common issues and the application-based mechanisms for combination product sponsors to use to obtain FDA feedback on them.

For application-based mechanisms, FDA processing and FDA feedback to the combination product sponsor should be provided consistent with the existing process outlined for the type of interaction (see relevant guidances referenced in Appendices 1 and 2; see also information on [electronic submissions](#)).

### ***1. Information to Include When Requesting Feedback on a Combination Product Through an Application-Based Mechanism***

For application-based mechanisms, sponsors should refer to applicable guidance (see guidances referenced in Appendices 1 and 2) as the primary reference regarding what information to submit to FDA. The submission should identify the product for which feedback is being requested as a combination product (see section 503(g)(8)(C)(v)(I) of the FD&C Act (21 USC 353(g)(8)(C)(v)(I)) and footnote 12). In addition to information generally provided under an application-based mechanism, the following information should also be included for the non-lead constituent part to allow FDA to efficiently review the submission for the combination product under the application-based mechanism:

- For a drug or biological product-led combination product that includes a device constituent part:
  - A device description, design diagram or other image,
  - Identification of components that are part of the device, and
  - If the combination product contains a device constituent part that is a cleared or approved device that the sponsor seeks to cross reference, identify the application or submission number for the previously cleared or approved device.
- For a device-led combination product:
  - Information identifying and describing the drug and/or biological product constituent part(s), including, as applicable, chemical name, established or proper name, and structure,
  - The route of administration and/or dosing information for the drug and/or biological product constituent part(s), and
  - If the combination product, contains an active ingredient that is included in an approved drug product that the sponsor seeks to cross reference or rely upon in its submission, the application number of the approved product.

## **B. Combination Product Agreement Meetings (CPAMs)**

CPAMs are intended as a means (in addition to the application-based mechanisms) for sponsors to obtain clarity and certainty and are available for combination products for which the lead center assignment is clear.<sup>19</sup> The purpose of a CPAM is to address the standards and requirements for marketing authorization of a combination product and other issues relevant to a combination product, such as requirements related to postmarket modification of the product or CGMPs.

In response to a written CPAM request, FDA must:

- Meet with the sponsor within 75 calendar days<sup>20</sup> of receiving the request; and
- Document any agreements made with the sponsor in writing and make them part of the administrative record.

See section 503(g)(2)(A)(i) and (iii) of the FD&C Act (21 USC 353(g)(2)(A)(i) and (iii)).

Any agreement under section 503(g)(2)(A) shall remain in effect unless deviation from it is:

- agreed upon in writing by the FDA and sponsor; or
- pursuant to a decision by certain individuals specified in the statute (as appropriate) that (1) an issue has been identified since the agreement was reached that is essential to determining whether the standard for marketing has been met,<sup>21</sup> or (2) it is otherwise justifiable to deviate from the agreement based on scientific evidence, for public health reasons.

See section 503(g)(2)(A)(iv) of the FD&C Act (21 USC 353(g)(2)(A)(iv)).

As noted in Section IV.A above, the Agency encourages the use of application-based mechanisms as they generally offer the most efficient and effective means to obtain feedback.

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<sup>19</sup> If FDA concludes that a determination of the PMOA is needed, the sponsor cannot make a CPAM request until after the Agency determines the PMOA. See section 503(g)(2)(A)(i) of the FD&C Act (21 USC 353(g)(2)(A)(i)); see also Section II.C regarding how to obtain a classification or PMOA determination.

<sup>20</sup> Section 503(g)(2)(A)(i) of the FD&C Act (21 USC 353(g)(2)(A)(i) indicates that “[i]f the sponsor submits a written meeting request, the Secretary shall, not later than 75 calendar days after receiving such request, meet with the sponsor of such combination product.”

<sup>21</sup> Section 503(g)(2)(A)(iv) reads: “Any such agreement shall remain in effect, except—  
(I) upon the written agreement of the Secretary and the sponsor or applicant; or  
(II) pursuant to a decision by the director of the reviewing division of the primary agency center, or a person more senior than such director, in consultation with consulting centers and the Office, as appropriate, that an issue essential to determining whether the standard for market clearance or other applicable standard under this Act or the Public Health Service Act applicable to the combination product has been identified since the agreement was reached, or that deviating from the agreement is otherwise justifiable based on scientific evidence, for public health reasons.”

We note that although the provision does not expressly refer to whether marketing clearance or other applicable standard “has been met,” that appears to be the meaning of the statutory provision.

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**1. Information to Include When Requesting Feedback on a Combination Product Through a CPAM**

Below are recommendations on what should be included in CPAM requests *at the time the request is submitted* (see also Section IV.B.2 below).

- **Product Information**. Sponsors:
  - Should include the product name, description of the overall combination product and constituent parts, indications for use statement, and, as applicable, route of administration and dosing information.
  - Should include, as relevant, the same information referenced in Section IV.A.1 above for the constituent parts of the combination product.
  - Must identify their product as a combination product (see footnote 12).
- **Background**. Sponsors should describe the status of product development, summarize any previous interactions with FDA on the product, including applications, application-based mechanisms, other meetings, RFDs or pre-RFDs, and identify the proposed regulatory pathway if not already established.
- **Meeting Request**. Sponsors should include the requested form of communication (i.e., face-to-face meeting, teleconference, or written response). If proposing a face-to-face meeting or teleconference, provide three proposed meeting dates and times within the 75-day timeframe and a proposed agenda that includes the allotted time to discuss each proposal.
- **Agreement Proposals**. Sponsors should identify the specific proposals and/or items of the proposal(s) for which the sponsor seeks FDA agreement. These should be grouped by discipline (e.g., Pharmacology/Toxicology, Pharmaceutical Quality/Chemistry and Manufacturing Controls (CMC), Engineering, Human Factors) where possible. The issues should be limited to those for which the sponsor is seeking agreement from FDA.
- **Rationale and Data Supporting Proposals**. Sponsors should provide rationale(s) and data adequate to support FDA's review of the agreement proposals, and organize the rationale(s) and data by topic when appropriate.
- **Attendees**. Sponsors should include a list of planned participants from the sponsor's organization, including names and titles. A list of names, titles and affiliations of consultants and interpreters should also be included. If this information changes, it should be updated no later than 5 business days prior to the meeting. All non-U.S. citizens attending a meeting in an FDA facility are subject to additional security screening. You should inform the FDA POC of non-U.S. citizens attending no less than two weeks prior to the meeting to ensure the appropriate information is available and provided. If the sponsor wishes to request that a specific FDA staff member or expertise be included in

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the meeting, that information should be included in the CPAM request (see also Section III above).

### **2. *Submitting a CPAM Request***

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;
- Identify the type of engagement being requested (face-to-face meeting, teleconference, or written response); and
- Provide the complete information described in Section IV.B.1 above, so that FDA can assess whether a CPAM is the most efficient mechanism for interaction, coordinate between centers, and ensure that FDA has sufficient information to evaluate the agreement proposal(s) or specific items thereof.

FDA encourages sponsors, where possible, to consolidate related issues for the combination product that are ready for consideration into a single CPAM request, as opposed to submitting multiple CPAM requests. FDA discourages submitting multiple CPAM requests for related issues because the Agency would likely not be able to reach agreement on the sponsor’s proposals independently. FDA also discourages submission of CPAM requests if there is an application for the combination product under active FDA review; application-based mechanisms should be used, as appropriate, at that stage.

Sponsors should follow the submission process described in Table 1 to ensure appropriate receipt and routing of the CPAM request.

**Table 1. Submission Process for CPAM Requests<sup>22</sup>**

<b>Lead Center</b>	<b>Combination Product Application Type</b>	<b>CPAM Request Process</b>
CBER	IND, NDA, BLA, ANDA	<p>Submit the CPAM request:</p> <ul style="list-style-type: none"> <li>• Electronically or to the CBER Document Control Center;<sup>23</sup></li> <li>• Address CPAM request to the appropriate review division; and</li> <li>• Specify the application number, if applicable, in the cover letter.<sup>24</sup></li> </ul> <p>NOTE: The CPAM package (including all information necessary for review) should be provided <i>with</i> the initial request.</p>
	IDE, PMA, 510(k), De Novo, HDE, PDP	<p>Submit a valid eCopy<sup>25</sup> to the CBER Document Control Center. Specify the application number, if applicable, in the cover letter.</p>
CDER	IND, NDA, BLA	<p>Submit the CPAM request:</p> <ul style="list-style-type: none"> <li>• Electronically or to the CDER Document Control Center;<sup>23</sup></li> <li>• Address CPAM request to the appropriate review division; and</li> <li>• Specify the application number, if applicable, in the cover letter.<sup>24</sup></li> </ul> <p>NOTE: The CPAM package (including all information necessary for review) should be provided <i>with</i> the initial request.</p>
	ANDA	<p>If the ANDA has not yet been submitted to FDA, submit the CPAM request:</p> <ul style="list-style-type: none"> <li>• Electronically to <a href="#">CDER NextGen Collaboration Portal</a>.</li> <li>• Specify the application number.<sup>24</sup></li> </ul> <p>If the ANDA is being submitted at the same time as the CPAM request, or the ANDA has already been submitted to FDA, submit the CPAM request:</p> <ul style="list-style-type: none"> <li>• Through the FDA Electronic Submission Gateway (ESG).</li> <li>• Specify the application number.<sup>24</sup></li> </ul>

<sup>22</sup> Submitting a CPAM request to the lead center would be appropriate for any combination product including cross-labeled combination products for which a sponsor may anticipate submitting or has submitted separate applications for each constituent part.

<sup>23</sup> See [Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, Guidance for Industry](#).

<sup>24</sup> If an application number has not been assigned, see information regarding requesting a pre-assigned application number available on FDA’s website at <https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number>.

<sup>25</sup> See [eCopy Program for Medical Device Submissions, Guidance for Industry and Food and Drug Administration Staff](#).

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Lead Center	Combination Product Application Type	CPAM Request Process
CDRH	IDE, PMA, 510(k), De Novo, HDE, PDP	Submit a valid eCopy <sup>25</sup> to the CDRH Document Control Center. Specify the application number, if applicable, in the cover letter.

### 3. FDA Response to a CPAM

The following outlines steps for the CPAM process:

- Acceptance of CPAM Request. Requests for CPAMs will generally be granted unless the request is not for a combination product or the PMOA for the combination product has not been determined (see section 503(g)(2)(A)(i) of the FD&C Act (21 USC 353(g)(2)(A)(i))). We note that it is not appropriate, however, to use CPAMs to resolve disputes that would otherwise be reviewed under the lead center’s dispute resolution and/or appeals processes (see also Section IV.C below).<sup>26</sup> We also note that if a sponsor does not include sufficient information in its request to allow for meaningful discussion or feedback, the Agency would likely not be able to reach agreement on the sponsor’s proposal.

FDA intends to contact the sponsor within 21 calendar days of receiving a CPAM request confirming receipt and providing a meeting time (if requested) or providing a substantive basis for not granting the CPAM. If FDA believes that an application-based mechanism may be more efficient and/or provide additional clarity, FDA may contact the sponsor and offer to convert to that application-based mechanism. If the sponsor agrees to the application-based mechanism, FDA will work with the sponsor so that the sponsor can efficiently pursue that mechanism.

- CPAM Interaction. Sponsors may choose to submit a request for a face-to-face meeting, a teleconference, or written feedback. If the sponsor submits a request for a face-to-face meeting or teleconference, and FDA accepts the request, FDA will schedule the meeting to occur within 75 calendar days of receiving the CPAM request. Meetings are typically one hour in duration. FDA may contact the sponsor if we believe written feedback only would be appropriate. FDA intends to provide a preliminary response to the sponsor prior to a face-to-face meeting or teleconference (see below). After receiving such a response, the sponsor should notify the FDA no later than 3 calendar days following receipt that a

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<sup>26</sup> See [Requests for Reconsideration at the Division Level Under GDUFA, Draft Guidance for Industry](#) (for CDER’s Office of Generic Drugs which, when final, will represent FDA’s current thinking on this topic), [Formal Dispute Resolution: Sponsor Appeals Above the Division Level, Guidance for Industry and Review Staff](#) (for CBER and CDER) and [Center for Devices and Radiological Health Appeals Processes, Guidance for Industry and Food and Drug Administration Staff](#). Combination product sponsors may obtain information on informal dispute resolution options from the lead center Ombudsman staff (see <https://www.fda.gov/about-fda/office-chief-scientist/contact-ombudsman-fda>). OCP is also available to assist FDA-regulated entities in resolving issues that may arise between them and centers or other FDA components, relating to premarket review or other regulatory issues for combination products. Requests for assistance may be submitted to OCP’s mailbox at [combination@fda.gov](mailto:combination@fda.gov).

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face-to-face meeting or teleconference is not needed or identifying the issues which the sponsor wants to further discuss at the meeting/teleconference.

- Preliminary Responses, Written Feedback, and CPAM Agreements. If the sponsor requests written feedback only, FDA intends to provide final written feedback to the sponsor within 75 calendar days of receipt of the request. If the sponsor requests a face-to-face meeting or teleconference, FDA intends to provide the sponsor preliminary responses to the CPAM request no later than 5 calendar days before the meeting/teleconference. If the sponsor then determines that a meeting/teleconference is not needed or is needed to discuss only certain issues (see above), FDA's preliminary response will represent the Agency's final written feedback (on all or the resolved issues) on a CPAM. If the meeting/teleconference is held, FDA intends to provide final written feedback to the sponsor within 30 calendar days following the meeting.

FDA's final written feedback should include the agreed upon proposals and indicate, for each proposal, or item thereof, for which the sponsor sought FDA agreement that:

- FDA agrees with the proposal or item thereof;
- FDA does not agree with the sponsor's proposal or item thereof and why FDA does not consider the sponsor's proposal or item thereof acceptable; or
- FDA cannot agree to the proposal or item(s) thereof at the time of the response due to inadequate or insufficient information. Such a response should include a summary of the additional scientific data or other information needed to support further review of the sponsor's proposal or item(s) thereof. If a sponsor wants to submit information to respond to identified inadequacies/insufficiencies, the sponsor can do so by using an application-based mechanism or submitting a new CPAM request.

If sponsors would like clarification regarding FDA's response to a CPAM request, including whether a CPAM or another mechanism would be appropriate for future interactions, they should promptly contact the FDA POC.

#### ***4. Validity of Agreements Made Through CPAM***

Any agreement made through the CPAM process shall remain in effect except in the limited circumstances set forth in section 503(g)(2)(A)(iv) of the FD&C Act (21 USC 353(g)(2)(A)(iv)) as discussed in Section IV.B above. New information or updated scientific thinking, for example, including as reflected in subsequently issued guidance, may result in FDA identifying an issue that is essential to determining whether the standard for marketing authorization has been met. In addition, the formal agreement is product specific and is predicated on the sponsor not changing the basis of the agreement, such as failing to follow an agreed upon pre-clinical or clinical protocol, making substantive changes to an endpoint, altering the proposed intended use or indications or product design/contents, changing the manufacturing process or controls, or changing the investigational plan. CPAM agreements that are not subsequently followed by the sponsor are no longer valid, though FDA may consider data or information generated as it deems

appropriate for premarket review or postmarket regulation, as applicable. When FDA determines, for example, during review of a subsequent related submission, that a CPAM agreement is no longer in effect – entirely or in part – under section 503(g)(2)(A)(iv), FDA intends to notify the sponsor in writing of which portions of the agreement are no longer in effect and the basis for the decision.

### **C. Use of Application-based Mechanisms, CPAMs, and Dispute Resolution**

Consistent with our past practices, FDA intends to continue to provide as reliable and definitive feedback as possible based on the information provided. The Agency encourages combination product sponsors to interact through application-based mechanisms to provide FDA an opportunity to evaluate technical data or engage in scientific discussion *before* considering a CPAM.

Issues Appropriate for Application-Based Mechanisms. Application-based mechanisms are generally appropriate for requesting feedback on scientific issues, study design, testing approaches, or application preparation considerations for combination products or clarifying topics for which FDA has already published technical guidance (see Appendices 1 and 2 for examples of the types of issues appropriate for application-based mechanisms). If sponsors have questions on which application-based mechanism is appropriate, they should contact the lead center POC (if known) or the lead center PJO<sup>10</sup> if the sponsor has not previously interacted with FDA on the combination product.

Issues Appropriate for CPAMs. CPAMs may be appropriate for seeking agreement from FDA on an approach if previous feedback under an application-based mechanism has not provided sufficient certainty. CPAM should not be used to resolve disputes that would otherwise be addressed under the lead center’s dispute resolution or appeals process (see below).

Because the goal of CPAMs is *agreement* on a sponsor’s proposal(s) or items thereof, more information and data may be needed in a CPAM request, as compared to an application-based mechanism submission, to increase the likelihood of reaching an agreement. Relatedly, sponsors should submit a CPAM request only when they believe they have identified the indication for use and design of the combination product and the sponsor should be able to provide sufficiently robust information on the merits of the proposal(s) being made to ensure an effective review by all relevant disciplines and centers (see also Section IV.B.1 above). For issues where scientific evidence is limited and/or scientific thinking is evolving, a CPAM is unlikely to be productive (see also Section IV.B.4 above).

Issues Appropriate for Dispute Resolution/Appeal Through the Lead Center’s Dispute Resolution or Appeals Process. Dispute resolution/appeals using the lead center’s process are appropriate to address disagreement or disputes over constituent part or combination product issues identified as part of an FDA action (e.g., determinations that a product cannot be marketed, complete response actions, clinical holds, refuse to receive, etc.).<sup>26</sup> For example, if a combination product sponsor received a complete response (CR) letter related to a constituent part issue that it believes had been adequately addressed in the application, the sponsor could appeal the CR action following the appropriate process for doing so.

## Appendix 1. Examples of Application-based Mechanisms Available for Device-led Combination Products

The table below provides examples of the application-based mechanisms available for device-led combination products. All interactions with FDA should be through the lead center for the combination product regardless of the feedback being requested (e.g., the application-based mechanisms below should be used for device-led combination product interactions regardless of whether the issues involve the device, drug and/or biological product constituent part, or the combination product as a whole).

<b>Application Type(s)</b>	<b>Examples of Types of Issues</b>	<b>Application-based Mechanism<sup>17</sup></b>
Premarket Approval Application (PMA)	General questions and requests for feedback on product development, application preparation, or postmarket issues	Pre-submission - Meeting & Written Feedback or Written Feedback Only <sup>27</sup>
Premarket Notification (510(k)) De Novo Request Humanitarian Device Exemption (HDE)	Discuss proposed approach to address specific deficiencies identified during review of certain types of device applications where the application is either currently on hold (e.g., a 510(k) request for additional information), or where there are questions related to a clinical study design	Submission Issue Request - Meeting or Written Feedback <sup>27</sup>
Investigational Device Exemption (IDE)	Requests for designation of device-led combination products as Breakthrough Devices based on the eligibility criteria in section 515B of the FD&C Act	Designation Request for Breakthrough Device Q-Submission <sup>28</sup>

<sup>27</sup> See [Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program. Guidance for Industry and Food and Drug Administration Staff.](#)

<sup>28</sup> See [Breakthrough Devices Program. Guidance for Industry and Food and Drug Administration Staff.](#)

## Appendix 2. Examples of Application-based Mechanisms Available for Drug or Biological Product-led Combination Products

The table below provides examples of the application-based mechanisms available for drug and biological product-led combination products. All interactions with FDA should be through the application-based mechanism of the lead center for the combination product, regardless of the feedback being requested (e.g., the application-based mechanisms below should be used for drug and biological product-led combination product interactions regardless of whether the issues involve the device, drug and/or biological-product constituent part or the combination product as a whole).

Application Type(s)	Examples of Types of Issues	Application-based Mechanism <sup>17</sup>
Investigational New Drug Application (IND) for PDUFA <sup>29</sup> Products  New Drug Application (NDA)  351(a) Biologic License Application (BLA) <sup>30</sup>	Meetings necessary for an otherwise stalled product development program to proceed or to address an important safety issue	Type A Meeting <sup>31</sup>
	Pre-IND, Pre-BLA, Pre-NDA Meetings to discuss content and format of a proposed marketing or investigational application	Type B Meeting <sup>31</sup>
	General questions and requests for feedback on product development or postmarket issues, or use of a biomarker as a new surrogate endpoint	Type C Meeting <sup>31</sup>
	Design and size of certain clinical trials, clinical studies, or animal studies	Special Protocol Assessment <sup>32</sup>
	Fast Track Designation, Breakthrough Therapy Designation, or Priority Review Designation	Designation Submission <sup>33</sup>
	[Applications with CBER] Designation as a Regenerative Medicine Advanced Therapy (RMAT)	RMAT Designation <sup>34</sup>
INDs for BsUFA <sup>35</sup> Products	Initial assessment limited to general discussion regarding feasibility of licensure under 351(k) of the PHS Act	Biosimilar Initial Advisory <sup>37</sup>

<sup>29</sup> Prescription Drug User Fee Act (PDUFA)

<sup>30</sup> A “351(a) BLA” is an application for licensure of a proposed biological product, submitted under section 351(a) of the Public Health Service (PHS) Act, also referred to as a “stand-alone BLA.”

<sup>31</sup> See [Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, Draft Guidance for Industry](#) which, when final, will represent FDA’s current thinking on this topic.

<sup>32</sup> See [Special Protocol Assessment, Guidance for Industry](#).

<sup>33</sup> See [Expedited Programs for Serious Conditions—Drugs and Biologics, Guidance for Industry](#).

<sup>34</sup> See [Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, Guidance for Industry](#).

<sup>35</sup> Biosimilar User Fee Act (BsUFA)

<sup>37</sup> See [Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products, Draft Guidance for Industry](#) which, when final, will represent FDA’s current thinking on this topic.

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<b>Application Type(s)</b>	<b>Examples of Types of Issues</b>	<b>Application-based Mechanism<sup>17</sup></b>
351(k) BLA <sup>36</sup>	Meetings necessary for an otherwise stalled development program to proceed or to address an important safety issue.	Biological Product Development (BPD) Type 1 Meeting <sup>37</sup>
	Discuss specific issues related to, e.g., chemistry, manufacturing, CMC, study design, etc.	BPD Type 2 Meeting <sup>37</sup>
	In-depth data review and advice regarding an ongoing biosimilar development program.	BPD Type 3 Meeting <sup>37</sup>
	Format and content of a complete application or supplement.	BPD Type 4 Meeting <sup>37</sup>
	Design and size of certain clinical trials, clinical studies, or animal studies	Special Protocol Assessment <sup>32</sup>
Abbreviated New Drug Application (ANDA)	Information on a specific element of generic drug product development and certain postapproval submission requirements	Controlled Correspondence <sup>38</sup>
	Specific scientific issues or questions prior to submitting an ANDA	Product Development Meeting <sup>39</sup> (intended for complex products under the Generic Drug User Fee Amendments of 2017 (GDUFA II) <sup>40</sup> )
	Format and content of the ANDA to be submitted	Pre-Submission Meeting <sup>39</sup> (intended for complex products under GDUFA II <sup>40</sup> )
	Specific issues/deficiencies identified during review of an application	Mid-Review Cycle Meetings <sup>39</sup> (intended for complex products under GDUFA II <sup>40</sup> )

<sup>36</sup> For additional information on submissions under section 351(k) of the PHS Act, including applications for biosimilar and interchangeable products, see <https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products>.

<sup>38</sup> See [Controlled Correspondence Related to Generic Drug Development, Draft Guidance for Industry](#) which, when final, will represent FDA’s current thinking on this topic.

<sup>39</sup> See [Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA, Guidance for Industry](#).

<sup>40</sup> The [GDUFA II Commitment Letter](#) defines “complex products,” which include complex drug-device combination products (e.g., prefilled auto-injectors, metered dose inhalers, extended-release injectables). Not all combination products are considered complex.

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<b>Application Type(s)</b>	<b>Examples of Types of Issues</b>	<b>Application-based Mechanism<sup>17</sup></b>
Prior to a pre-IND (for INTERACT) or planned but not yet submitted NDA, BLA, ANDA, or IND (for Emerging Technologies Program)	<i>[Applications with CBER]</i> Preliminary consultation on innovative investigational products at early stages of development (prior to a pre-IND)	INTERACT meeting <sup>41</sup>
	<i>[Applications with CDER]</i> Potential concerns regarding the development and implementation of a novel product or manufacturing technology prior to filing a regulatory submission	Emerging Technology Program meetings <sup>42</sup>

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<sup>41</sup> See Initial Targeted Engagement for Regulatory Advice on CBER products (INTERACT) program at <https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings-initial-targeted-engagement-regulatory-advice-cber-products>.

<sup>42</sup> See Emerging Technology Program for CDER products at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/emerging-technology-program>.