Requesting FDA Feedback on Combination Products

Guidance for Industry and FDA Staff

DRAFT GUIDANCE

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Food and Drug Administration
Office of Combination Products (OCP)
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Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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[1] can obtain feedback from FDA on scientific and regulatory questions and to describe best practices for FDA and sponsors when interacting on these topics.[2] These interactions can occur through application-based mechanisms (generally the most efficient and effective approach), such as the pre-submission process used in CDRH and CBER[3] and the formal meetings used in CDER and CBER,[4] or through Combination Product Agreement Meetings (CPAMs),[5] as appropriate.

[1] 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 The term "application," for purposes of this draft guidance, includes an investigational new drug application (IND), new drug application (NDA), abbreviated new drug application (ANDA), investigational device exemption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 biologic 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.

[2] 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.

[3] See *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program, Guidance for Industry and Food and Drug Administration Staff.*

[4] 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, Draft Guidance for Industry*. When final, these guidances will represent FDA's current thinking on these topics.

[5] The 21st 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 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).

We are publishing 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 prior to a CPAM, and the form and content of agreements reached through a CPAM.

II. Background

This section discusses what combination products are, their assignment to a "lead Center," intercenter coordination for their premarket review, and whom to contact in FDA regarding combination product questions.

A. What is a combination product?

A combination product is a product comprised of any combination of a drug, a device, and/or a biological product.[6] The drugs, devices, and biological products included in combination products are referred to as "constituent parts" of the combination product.

Under 21 CFR 3.2(e), a combination product includes:

- A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity (a "single entity" combination product, such as a prefilled drug or biological product syringe or drug-eluting stent);

- Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (a "co-packaged" combination product, such as a surgical or first-aid kit containing devices and drugs);

- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose (a "cross-labeled" combination product,

[6] 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.

as might be the case for a light-emitting device that is intended for use with a specific light-activated drug); and

- Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect (another type of cross-labeled combination product).

B. How does FDA review and regulate combination products?

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.[7] For example, if the PMOA of a device-biological product combination product is attributable to the biological product, the center responsible for premarket review of such a biological product would have primary jurisdiction for the regulation of the combination product.

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.

C. 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 Combination Products (OCP). If you wish to obtain a binding determination from FDA regarding classification 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.[8]

If you know the lead Center for your combination product (e.g., there is a pending application), 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.[9]

If you have general questions regarding intercenter collaboration on combination products, combination product regulation, combination product guidance or policy, or need help in

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[7] 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").

[8] 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 and Additional Product Classification Issues, Guidance for Industry and FDA Staff*.

[9] The lead Center Product Jurisdiction Officer can be contacted at CBERProductJurisdiction@fda.hhs.gov, CDERProductJurisdiction@fda.hhs.gov or CDRHProductJurisdiction@fda.hhs.gov.

navigating the combination product review process at FDA, contact OCP (combination@fda.gov).[10]

III. Best Practices Regarding Interactions Between FDA and Sponsors for 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. To this end, the following are critical aspects to help ensure efficient and productive interactions between FDA and sponsors when sponsors request feedback on combination products:

- Appropriate Product Identification and Processing. Submissions made under an application-based mechanism and CPAM requests (hereafter referred to as "submissions/requests") should be submitted to the appropriate lead Center and appropriately routed by FDA to staff within the centers for review. As noted in Section IV.B below, a CPAM is only available for combination products. 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.[11]

- Timely Use of Appropriate Communication Procedures. Communications between the Agency and sponsor should be timely and the mechanisms for such communication (meetings, written responses, etc.) should be those that are specified in FDA guidance.

- Clear, Robust Information Sharing. Communications 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 under an application-based mechanism or CPAM request.

[10] OCP is required to coordinate premarket reviews for combination products; oversee their timeliness 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 (when finalized). See section 503(g)(8) of the FD&C Act (21 USC 353(g)(8)).

[11] 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.

A. Sponsor Best Practices

To ensure that interactions are efficient and productive, the sponsor should:

- Pose 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.

- Provide 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 III.C below and relevant guidance 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 the overall combination product.

- Communicate 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).

B. FDA Best Practices

To ensure that FDA review of an application-based mechanism or a CPAM request is efficient and productive, FDA should:

- Notify Sponsor of its FDA POC.[12] Once a submission/request has been accepted, consistent with Center guidance and processes, the lead Center should ensure that the sponsor is notified of its FDA POC[13] who is within the center to which the application for the combination product would be assigned. The POC should coordinate communications between the sponsor and FDA staff and be kept informed of the outcomes of any communications between FDA staff and the sponsor.

- Engage 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

[12] 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.
[13] 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.

appropriate.[14] If a sponsor has made a request for participants with particular expertise (see also Sections III.C below), 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))).

- Consolidate and Align 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 and include relevant input from all Agency centers and groups involved in review of the submission/request.

- Provide Reliable Advice. FDA's feedback should be captured in writing and reflect the Agency's best advice at the time given based on the information available to the Agency, regardless of the mechanism used for interacting with the FDA. FDA should not generally alter its feedback once provided to the sponsor unless new information, for example, impacts the validity of the previously provided feedback, or regulatory changes alter requirements.

C. 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 provide. Highlighted below are examples of additional information for the sponsor to provide when the product is a combination product:

- 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 11); and

- Should include information on the combination product and the constituent parts, including:

    - For a drug or biological product-led combination product that includes a device constituent part, a device description, design diagram or other image, and identify components that are part of the device.

    - For a device-led combination product, provide the chemical name, established or proper name (if available), and structure, for the drug and/or biological product constituent part(s).

[14] 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*.

- For a device-led combination product, provide the route of administration and/or dosing information for the drug and/or biological product constituent part(s).

- For combination products that contain an active ingredient that is included in an approved drug product that the sponsor seeks to cross reference or rely upon in its submission, identify the application number of the approved product.

- For combination products that contain 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.

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

For CPAM requests, the sponsor should:

- Product Information.

  - 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.

  - Include, as relevant, the same information referenced in Section III.C above for the constituent parts of the combination product. As previously noted, it is important that combination product sponsors identify their product as a combination product in CPAM requests.

- Background. 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. Include the requested form of communication (i.e., face-to-face meeting, teleconference, or written response). Summarize why the specific communication format is appropriate. If proposing a face-to-face meeting or teleconference, provide three proposed meeting dates/times, dates and times when the sponsor is not available, and a proposed agenda.

- Agreement Proposals Generally. Identify the specific proposals for which the sponsor seeks FDA agreement. Proposals should be grouped by discipline (e.g., Pharmacology/Toxicology, Pharmaceutical Quality/Chemistry and Manufacturing Controls (CMC), Engineering, Human Factors) where possible. The proposals should be limited to those for which the sponsor is seeking agreement from FDA.

- Rationale and Data Supporting Proposals. Provide rationale(s) and data adequate to support FDA's review of the agreement proposals. Organize the rationale(s) and data by topic when appropriate.

- Attendees. 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. If the sponsor wishes to request that a specific FDA staff member or expertise be included in the meeting, that information should be included in the CPAM request. 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).

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. The Agency encourages the use of application-based mechanisms as generally offering the most efficient and effective means to obtain feedback upon which the combination product sponsor can rely.[15] Specific questions on topics for which the Agency has already published technical guidance, such as requests for clarification on how to conduct testing described in an FDA guidance or in accordance with a recognized standard, should be addressed through application-based mechanisms.

CPAMs may complement, but should not replace, application-based mechanisms and should not be used to resolve disputes regarding scientific or regulatory matters that would otherwise be reviewed under the lead Center's dispute resolution and/or appeals processes.[16] Because it may be challenging to reach agreement in circumstances of uncertainty or limited data, the Agency encourages sponsors to consider CPAMs only when they believe they have identified the indication for use and design of the combination product they will pursue and sufficient information can be provided to ensure an effective review by all relevant disciplines and centers. Accordingly, it may be helpful to interact through application-based mechanisms to provide FDA an opportunity to evaluate technical data or engage in scientific discussion before considering a CPAM.

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

[15] See Section II.C regarding whom to contact for preliminary and general questions.

[16] 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 at combination@fda.gov.

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.[17]

As discussed above, 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. 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.[18] Application-based mechanisms include specialized meeting types and opportunities designed to address specific requests (e.g., breakthrough status 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 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[19]).

B. Combination Product Agreement Meetings (CPAMs)

CPAMs are intended as a means for sponsors (in addition to the application-based mechanisms noted above) to obtain clarity and certainty and are available for combination products for which the lead Center assignment is clear.[20]

In response to a written CPAM request, FDA must:

- Meet with the sponsor within 75 calendar days 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)).

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[17] While application-based mechanisms are available, and generally should be utilized, for all combination products, cross-labeled combination products for which a sponsor may anticipate submitting or has submitted separate marketing application for each constituent part (e.g., an NDA for the drug and a 510(k) for the device), can raise distinct considerations. Prior to the submission of separate marketing applications for cross-labeled combination product constituent parts, all interactions with FDA should be through the lead Center for the combination product, 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 the marketing applications (e.g., due to the relative timing of the submissions for the constituent parts).

[18] See *Requests for Feedback and Meetings on Medical Device Submissions: The Q-Submission Program, Guidance for Industry and Food and Drug Administration Staff.*

[19] https://www.fda.gov/industry/policiesguidance/links-center-specific-submission-preparation-guidelines.

[20] 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.

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

- 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,[21] or (2) it is otherwise justifiable to deviate from the agreement based on scientific evidence or 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.

1. 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; and
- Provide complete information, including the content described in Section III.D above.

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.

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

[21] 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.

Table 1. Submission Process for CPAM Requests[22]

Lead Center	Combination Product Application Type	CPAM Request Process
CBER	IND, NDA, BLA, ANDA	Submit the CPAM request: • Electronically or to the CBER Document Control Center;[23] • Address CPAM request to the appropriate review division; and • Specify the application number, if applicable, in the cover letter.[24] NOTE: The CPAM package (including all information necessary for review) should be provided *with* the initial request.
	IDE, PMA, 510(k), De Novo, HDE, PDP	Submit a valid eCopy[25] to the CBER Document Control Center. Specify the application number, if applicable, in the cover letter.
CDER	IND, NDA, BLA	Submit the CPAM request: • Electronically or to the CDER Document Control Center;[23] • Address CPAM request to the appropriate review division; and • Specify the application number, if applicable, in the cover letter.[24] NOTE: The CPAM package (including all information necessary for review) should be provided *with* the initial request.
	ANDA	Submit the CPAM request: • Electronically to CDER NextGen Collaboration Portal. • Specify the application (or pre-assignment) number.[24]
CDRH	IDE, PMA, 510(k), De Novo, HDE, PDP	Submit a valid eCopy[25] to the CDRH Document Control Center. Specify the application number, if applicable, in the cover letter.

[22] 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.
[23] See *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, Guidance for Industry*.
[24] 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.
[25] See *eCopy Program for Medical Device Submissions, Guidance for Industry and Food and Drug Administration Staff.*

2. 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 scientific or regulatory disputes that would otherwise be reviewed under the lead Center's dispute resolution and/or appeals processes.[26] 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. 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 request confirming receipt and providing a meeting time (if requested) or providing a substantive basis for not granting the CPAM.

- CPAM Interaction. If the sponsor submits a written 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 prior to, or in follow-up to a meeting to request clarification. Also, sponsors may choose to submit a request for written feedback only, or FDA may contact the sponsor if we believe written feedback only would be appropriate.

- Written Feedback on a CPAM and CPAM Agreements. FDA intends to provide written feedback to the sponsor within 30 calendar days following the meeting or within 75 calendar days of receipt of the request if no meeting is held. FDA's written feedback should indicate, for each area for which the sponsor sought FDA agreement that:

    - FDA agrees with the sponsor's proposal and the specifics of the agreement;

    - FDA does not agree with the sponsor's proposal and why FDA does not consider the sponsor's proposal acceptable; or

    - FDA cannot agree to the proposal at this time 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. If a sponsor wants to submit information to respond to

[26] 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.

identified inadequacies/insufficiencies, the sponsor can do so by using an application-based mechanism or submitting a new CPAM request.

3. 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. 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, 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.

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).

Application Type(s)	**Examples of Types of Issues**	**Application-based Mechanism[17]**
Premarket Approval Application (PMA) Premarket Notification (510(k)) De Novo Request Humanitarian Device Exemption (HDE)	General questions and requests for feedback on product development, application preparation, or postmarket issues	Pre-submission - Meeting & Written Feedback or Written Feedback Only[27]
	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[27]
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[28]
Prior to a pre-submission for an IDE	*[Applications with CBER]* Preliminary consultation on innovative investigational products at early stages of development	INTERACT meeting[29]

[27] See *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program, Guidance for Industry and Food and Drug Administration Staff.*
[28] See *Breakthrough Devices Program, Guidance for Industry and Food and Drug Administration Staff.*
[29] 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.

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

The table below provides examples of the application-based mechanisms available for drug and biologic-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 biologic-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[17]**
Investigational New Drug Application (IND) for PDUFA Products New Drug Application (NDA) 351(a) Biologic License Application (BLA)[30]	Meetings necessary for an otherwise stalled product development program to proceed or to address an important safety issue	Type A Meeting[31]
	Pre-IND, Pre-BLA, Pre-NDA Meetings to discuss content and format of a proposed marketing or investigational application	Type B Meeting[31]
	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[31]
	Design and size of certain clinical trials, clinical studies, or animal studies	Special Protocol Assessment[32]
	Fast Track Designation, Breakthrough Therapy Designation, or Priority Review Designation	Designation Submission[33]
	[Applications with CBER] Designation as a Regenerative Medicine Advanced Therapy (RMAT)	RMAT Designation[34]
INDs for BsUFA Products 351(k) BLA[35]	Initial assessment limited to general discussion regarding feasibility of licensure under 351(k) of the PHS Act	Biosimilar Initial Advisory[36]
	Meetings necessary for an otherwise stalled development program to proceed or to address an important safety issue.	BPD Type 1 Meeting[36]

[30] 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."
[31] 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.
[32] See *Special Protocol Assessment, Guidance for Industry*.
[33] See *Expedited Programs for Serious Conditions – Drugs and Biologics, Guidance for Industry*.
[34] See *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, Guidance for Industry*.
[35] For additional information on biosimilars, see https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products.
[36] See *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products, Guidance for Industry*.

Application Type(s)	**Examples of Types of Issues**	**Application-based Mechanism[17]**
	Discuss specific issues related to, e.g., chemistry, manufacturing, CMC, study design, etc.	BPD Type 2 Meeting[36]
	In-depth data review and advice regarding an ongoing biosimilar development program.	BPD Type 3 Meeting[36]
	Format and content of a complete application or supplement.	BPD Type 4 Meeting[36]
	Design and size of certain clinical trials, clinical studies, or animal studies	Special Protocol Assessment[32]
Abbreviated New Drug Application (ANDA)	Information on a specific element of generic drug product development and certain postapproval submission requirements	Standard Controlled Correspondence[37]
	Specific scientific issues or questions prior to submitting an ANDA	Product Development Meeting[38] (intended for complex products under the Generic Drug User Fee Amendments of 2017 (GDUFA II)[39])
	Format and content of the ANDA to be submitted	Pre-Submission Meeting[38] (intended for complex products under GDUFA II[39])
	Specific issues/deficiencies identified during review of an application	Mid-Review Cycle Meetings[38] (intended for complex products under GDUFA II[39])
Prior to a pre-IND (for INTERACT) or planned but not yet submitted NDA,	*[Applications with CBER]* Preliminary consultation on innovative investigational products at early stages of development (prior to a pre-IND)	INTERACT meeting[40]

[37] See *Controlled Correspondence Related to Generic Drug Development, Draft Guidance for Industry which, when final, will represent FDA's current thinking on this topic*.
[38] See *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA, Draft Guidance for Industry,* which, when final, will represent FDA's current thinking on this topic.
[39] 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.
[40] 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.

Application Type(s)	**Examples of Types of Issues**	**Application-based Mechanism[17]**
BLA, ANDA, or IND (for Emerging Technologies Program)	*[Applications with CDER]* Potential concerns regarding the development and implementation of a novel product or manufacturing technology prior to filing a regulatory submission	Emerging Technology Program meetings[41]

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[41] See Emerging Technology Program for CDER products at https://www.fda.gov/about-fda/center-drug-evaluation-and-research/emerging-technology-program.