



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-D-4739]

Requesting Food and Drug Administration Feedback on Combination Products; Draft Guidance for Industry and Food and Drug Administration Staff; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "Requesting FDA Feedback on Combination Products." The purpose of this guidance is to discuss ways in which combination product sponsors can obtain feedback from FDA on scientific and regulatory questions and to describe best practices for FDA and sponsors when interacting on these topics. 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 and Research (CBER) and the formal meetings used in the Center for Drug Evaluation and Research (CDER) and CBER, or through Combination Product Agreement Meetings (CPAMs), as appropriate.

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2019-D-4739 for "Requesting FDA Feedback on Combination Products." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket

number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Office of Combination Products, Food and Drug Administration, Bldg. 32, Rm. 5129, 10903 New Hampshire Ave., Silver Spring, MD 20993. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Melissa Burns, Office of Combination Products, Food and Drug Administration, 301-796-5616, melissa.burns@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry and FDA staff entitled "Requesting FDA Feedback on Combination Products." The purpose of this guidance is to discuss ways in which combination product sponsors can obtain feedback from the Agency on scientific and regulatory questions. These interactions can occur through application-based mechanisms, such as the pre-submission process used in CDRH and CBER and the formal meetings used in CDER and CBER, or through CPAMs, as appropriate.

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 Federal Food, Drug, and Cosmetics Act (FD&C Act) (21 U.S.C. 353(g)(8)(C)(vi)), which was added by

section 3038 of the 21st Century Cures Act (Pub. L. No. 114-255) (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.

FDA is in the process of operationalizing the procedures related to submission and receipt of a CPAM request. Therefore, if a sponsor wishes to submit a CPAM request to FDA at this time, the sponsor should first contact the Product Jurisdiction Office for the lead Center (CBERProductJurisdiction@fda.hhs.gov, CDERProductJurisdiction@fda.hhs.gov, or CDRHProductJurisdiction@fda.hhs.gov) and the Office of Combination Products (combination@fda.hhs.gov) prior to submitting a CPAM request to help ensure that the CPAM request is efficiently received and processed by FDA.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Requesting FDA Feedback on Combination Products." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44

U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the *Federal Register* concerning each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Combination Product Agreement Meetings Under FD&C Act Section 503(g)(2)(A)(i); Requesting FDA Feedback on Combination Products.

Description of Respondents: Respondents to this collection of information are combination product sponsors that submit CPAM requests.

Burden Estimate: This draft guidance includes recommendations regarding information that sponsors should include in CPAM requests. Specifically, the draft guidance states that for CPAM requests, sponsors should:¹

¹ The draft guidance also notes that combination products must be identified as such in CPAM requests under section 503(g)(8)(C)(v)(I) of the FD&C Act.

- *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:
 - 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).
 - 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.

- *Background.* Describe the status of product development, summarize any previous interactions with FDA on the product, including applications, application-based mechanisms, other meetings, Request for Designations (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 has not received any CPAM requests since the enactment of the Cures Act in December 2016. FDA estimates that less than one CPAM request will be received per year by each medical product center (CBER, CDER, and CDRH). To provide a conservative estimate of burden, FDA estimates that approximately one CPAM request will be submitted per year to each medical product center. FDA estimates that it will take sponsors approximately 25 hours to compile and draft the information that this draft guidance recommends should be included in a CPAM request.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden¹

| FDA Center | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Hours per Response | Total Hours |
|------------|--------------------|---------------------------------|------------------------|--------------------|-------------|
| CDER | 1 | 1 | 1 | 25 | 25 |
| CDRH | 1 | 1 | 1 | 25 | 25 |
| CBER | 1 | 1 | 1 | 25 | 25 |
| Total | | | | | 75 |

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

This draft guidance also refers to previously approved collections of information found in FDA regulations. The collections of information pertaining to orphan drug provisions in 21 CFR part 316 are approved under OMB control number 0910-0167; the collections of information pertaining to investigational device exemption submission provisions in 21 CFR part 812 are approved under OMB control number 0910-0078; the collections of information pertaining to investigational new drug submission provisions in 21 CFR part 312 are approved under OMB control number 0910-0014; and the collections of information pertaining to biologics licensing submission provisions in 21 CFR part 601 are approved under OMB control number 0910-0338.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either <https://www.fda.gov/combination-products/guidance-regulatory-information/combination-products-guidance-documents> or <https://www.regulations.gov>.

Dated: December 18, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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