How to Prepare a Pre-Request for Designation (Pre-RFD)

Guidance for Industry

Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Combination Products website at https://www.fda.gov/CombinationProducts/default.htm.

For questions on the content of this guidance, contact the Office of Combination Products at combination@fda.gov

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0845 (expires October 31, 2020).

See additional PRA statement in Section VI of the guidance.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products in the Office of the Commissioner

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I. PURPOSE

This guidance is intended to assist sponsors in obtaining a preliminary assessment from the U.S. Food and Drug Administration (FDA or Agency) through the Pre-Request for Designation (Pre-RFD) process. Specifically, this guidance explains the Pre-RFD process at the Office of Combination Products (OCP) and helps a sponsor understand the type of information to provide in a Pre-RFD.

The Pre-RFD process is available to provide informal, non-binding feedback regarding the regulatory identity or classification of a human medical product as a drug, device, biological product, or combination product. In addition, this informal process provides information about a non-combination or combination product's assignment to the appropriate Agency Center (Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), or Center for Biologics Evaluation and Research (CBER)) for premarket review and regulation.

Additional information on topics outside the scope of this guidance may be found on our website (at http://www.fda.gov/CombinationProducts/default.htm.) These topics include the definitions of a non-combination and combination product, as well as information about the formal Request for Designation (RFD) process.

II. BACKGROUND

Since its establishment on December 24, 2002, OCP has served as a resource for sponsors at various stages of development of their product. Sponsors often seek OCP feedback on whether their medical product will be regulated as a drug, a device, a biologic, or a combination product, and which FDA medical product Center (CDER, CBER, or CDRH) will regulate it, if it is a non-combination product, or will have the primary jurisdiction for the premarket review and regulation of the product, if it is a combination product.

There are two ways that a sponsor can receive such a feedback from OCP. One option is to submit an RFD to receive a formal, binding determination for the sponsor's product with respect to classification and/or center assignment that may be changed under conditions specified in section 563 of the Federal Food, Drug, and Cosmetic Act (FD&C) Act and 21 CFR 3.9 in the regulations. The RFD process is codified in 21 CFR Part 3, and OCP has issued a guidance

about this process (see "How to Write a Request for Designation" at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126053.htm). A second more flexible option is for a sponsor to submit an inquiry to OCP to receive a preliminary jurisdictional assessment, which is not binding.

Many sponsors seek to utilize more flexible approachable ways to interact with OCP and the medical product Centers to obtain feedback from the Agency before submitting a marketing application to the Agency. Over time, these informal methods of obtaining feedback have become increasingly customary with sponsors, and for some, even preferable to the formal RFD process. Accordingly, FDA is enhancing the transparency and consistency of the process, which will now be called the "Pre-Request for Designation (Pre-RFD) Program," available through OCP. This guidance describes this structured process with clear recommendations for sponsors wishing to submit Pre-RFDs. It also provides the process for review of Pre-RFDs by FDA staff, the general timeframes for sponsors to receive feedback from OCP, and the process for scheduling teleconferences and meetings in relation to a Pre-RFD.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidance documents means that something is suggested or recommended, but not required.

III. GENERAL INFORMATION REGARDING THE PRE-RFD PROCESS FOR NON-COMBINATION AND COMBINATION PRODUCTS[1]

A. What is a Pre-RFD?

A Pre-RFD is a clear and concise written submission that a sponsor may make to OCP to request FDA's preliminary, nonbinding assessment of (1) the regulatory identity or classification of a product as a drug, device, biological product, or combination product, and/or (2) whether CBER, CDER, or CDRH will regulate the product if it is a non-combination product, or which of those Agency Centers will have primary jurisdiction for the premarket review and regulation, if it is a combination product.

OCP will provide a written preliminary classification and/or jurisdictional assessment of the product based on the information provided in a specific Pre-RFD. Our goal is to provide you with our feedback within 60 calendar days of receipt of the basic information that you should provide, and we will communicate with you during our review as needed. You can also contact us at any time during the review to ask questions or get clarification. Moreover, if it appears that

[1] For the purposes of this guidance document, parties who submit a Pre-RFD to the Agency are referred to as "sponsors," "you" or "your"; the terms "we," "us," and "our" refer to FDA staff from the Office of Combination Products.

we will not be able to complete our review within 60 calendar days after receipt of the information, we will communicate the need for more review time to you in a timely manner.

Please note that if you change your product significantly after submitting the Pre-RFD to us, such as changing its indication or ingredients, OCP's feedback may no longer be applicable. Accordingly, we recommend that you contact OCP if you make such a change. Additionally, if you have classification or assignment questions regarding multiple related products or product families that have different configurations, ingredients, and/or proposed uses or indications, we recommend submitting a separate Pre-RFD for each product.

Though our Pre-RFD feedback is not binding on the Agency or sponsor, it is OCP's intent to provide the best advice possible based on the information provided in the Pre-RFD. OCP's review and written feedback will be made after an in-depth review, and it will contain a thorough and detailed rationale for our assessment. Moreover, our review will include involvement from the relevant Agency Centers, as well as the Office of Chief Counsel when necessary.

The following table highlights some of the key similarities and differences between the RFD and Pre-RFD processes.[2] Regarding similarities, in both processes certain basic information is needed for FDA to provide an assessment of the classification and assignment of a product. The basic information includes, for example, a description of the product, proposed use or indications, and a description of how the product achieves its intended therapeutic/diagnostic effects. In addition, a sponsor has the option to include additional information in a Pre-RFD that would be required for an RFD.

Differences between the RFD and Pre-RFD process include length of submission and depth of regulatory analysis that a sponsor must provide. For example, RFDs cannot exceed 15 pages, but no such length requirement exists for Pre-RFD submissions.[3] Moreover, for an RFD, a sponsor must provide an analysis of a product's classification, a primary mode of action (PMOA) analysis (if the RFD concerns combination product assignment), and a recommendation regarding Agency Center assignment. Such information is optional in the Pre-RFD process (additional details are provided in Section IV.A. and in Appendix A). We note that FDA would conduct the same type of PMOA analysis in a Pre-RFD as in a RFD regardless of whether a sponsor chooses to make a recommendation regarding the PMOA of its combination product in a Pre-RFD.

[2] Please note that the information listed in this Pre-RFD Guidance does not include all the necessary information required for an RFD. If you wish to submit an RFD, you should consult 21 CFR 3.7 as well as the guidance about what to include in an RFD (see "How to Write a Request for Designation" at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126053.htm).

[3] Although there is no page limit for Pre-RFDs, we encourage you to limit your Pre-RFD to a succinct summary of information relevant for OCP to make its preliminary assessment (see Sections III.E and IV.F).

Submission Type	RFD (Information Required)	Pre-RFD (Information Recommended)
Description of Product	Yes	Yes
Proposed Use or Indications for Use	Yes	Yes
Description of the manufacturing processes, including the sources of all components	Yes	Optional (if available; recommended if it is a human cell, tissue, or cellular- or tissue-based product (HCT/P) or a biological product)
Supportive Data/Studies	Yes	Optional (if available)
Description of how a product achieves its intended therapeutic/diagnostic effects	Yes	Yes
Analysis of Classification, Primary Mode of Action (PMOA), if it is a combination product, and Jurisdictional Assignment	Yes	Optional (if available)
Description of Related Products	Yes	Optional (if available)
Sponsor Recommendation	Yes	Optional (if available)
Page limit	Yes	No[4]

B. When should I submit a Pre-RFD?

A Pre-RFD may be submitted at any point during medical product development.

A Pre-RFD is especially beneficial when the classification of a product or the Agency Center to which it should be assigned is unclear or in dispute and your product is very early in its development, or if you are contemplating whether to pursue a specific configuration or a specific indication. Understanding how FDA regulates your product and the appropriate regulatory pathway to market for your product will help lead to better decision-making for your company.

We note that a Pre-RFD is not necessary for every product. For example, some products have clearly established classification and jurisdictional assignments. OCP has published a list of various examples of these types of products on its website at combination@fda.gov.

C. May I request a meeting with OCP to explain my product?

We encourage you to contact OCP before submitting your Pre-RFD if you have any questions, including if you are uncertain about the type of information to include.

[4] See footnote 3.

In most cases, the Agency will be able to make its preliminary assessment based on a well-written Pre-RFD. However, if you believe a meeting with OCP would be helpful in providing the Agency with a better understanding of how the product works, you can request a meeting either prior to or after submission of a Pre-RFD. If you request a meeting after submission of a Pre-RFD but prior to our feedback, please keep in mind that such a meeting will potentially extend the timeframe of review of your product, so that we can adequately consider issues raised during the meeting.

If you request a meeting, you should include an explanation of the issues you would like to address and any supportive information. Please note that the timing to schedule meetings may vary based on factors including the number of subject matter experts to be included from interested Agency Centers, the availability of conference rooms, and the complexity of the issues the product raises. When possible and appropriate, OCP encourages you to consider a teleconference instead of an in-person meeting.

Generally speaking, FDA will need about four weeks to review information submitted as part of the meeting request prior to the meeting. This timeframe will give OCP and the necessary subject matter experts from the Agency Centers adequate time to review, comment, and possibly follow-up on any issues prior to your meeting. Therefore, it is very important that you provide complete background information at the time of your initial meeting request. If you wish to supplement your background information package with any new or modified information after this date, we may have to reschedule the meeting or delay our feedback on discussion topics related to the new or updated information. While it is important to provide a complete background package, submission of extraneous information can be counterproductive. In order for us to provide the most efficient and beneficial advice to you, please keep your background information targeted and focused on the issues in your Pre-RFD that you would like us to consider.

D. How do I submit a Pre-RFD for my product?

Part III of this document addresses the recommended format and specific content of a Pre-RFD in detail. You may submit a Pre-RFD, and include any relevant data pertaining to your product, which should be clearly labeled as such, to combination@fda.gov or to the address listed below in Section IV.E.

E. How promptly will FDA review my Pre-RFD?

Within 5 business days of its receipt of a Pre-RFD, OCP aims to review the Pre-RFD submission to ensure that it has adequate information for us to make our preliminary assessment. OCP will then either send you an acknowledgement email that our assessment will proceed, or we will detail the additional information needed before we can begin our assessment.

OCP's goal is to provide feedback on a Pre-RFD within 60 calendar days after we receive complete information to begin our review. However, please keep in mind that the speed of the review depends on the quality and adequacy of the information submitted. Furthermore, if you

choose to submit a large amount of data for FDA to consider, it may be necessary for us to take longer than our goal of 60 calendar days to fully consider the information provided.

F. May I withdraw my Pre-RFD after submission?

Yes, you may withdraw your Pre-RFD by notifying OCP in writing, via email or correspondence sent to the address below in section IV.E., any time after its submission and before FDA issues its preliminary assessment.

G. What if I disagree with OCP's preliminary assessment?

If you disagree with OCP's preliminary assessment of your product, you may contact our office to discuss our findings. After receiving our feedback, should you wish to present additional information or new data that was not presented in the original Pre-RFD, we encourage you to contact our office to discuss such additional information. We will be happy to provide you with assistance before you submit a new Pre-RFD. Once you submit a new Pre-RFD to us, OCP will consider this Pre-RFD a new submission and provide it with a new review and thorough assessment.

Alternatively, you can submit an RFD for our consideration (see 21 CFR Part 3 and the guidance document "How to Write an RFD" for additional information on the necessary information, format, and page limit for an RFD). Once your RFD has been reviewed for completeness and accepted for filing, we will review the RFD and provide, within 60 calendar days of filing, a binding determination with respect to classification and/or center assignment that may be changed under conditions specified in section 563 of the FD&C Act and 21 CFR 3.9 in the regulations. If you disagree with the RFD decision, you may appeal that decision in accordance with 21 CFR 10.75.

H. How can I contact OCP?

Contact information for OCP, including mailing address, e-mail address, phone number, and fax number are listed below in Part IV.E.

I. Where can I find more information?

More information about product classification and assignment, as well as the regulation of combination products, is available on the OCP website at https://www.fda.gov/CombinationProducts/default.htm.

IV. WHAT INFORMATION SHOULD I INCLUDE IN A PRE-RFD?

A. What is the basic information that I should include in my Pre-RFD?

1. Contact information including your name, company's name, email address, and telephone number.

2. A complete description of the product and, if applicable, the following information.

    a. The 510(k), Premarket Approval (PMA), New Drug Approval (NDA), Abbreviated New Drug Approval (ANDA), Biologics License Application (BLA), or any other FDA regulatory submission number associated with the product.
    b. Name of the product and all component products; and
    c. A photo/diagram of the product

3. For products sourced from biologically-derived materials, describe how the material was processed and a characterization of the identity of the final product.

4. An explanation of how the product works. And, though optional, you may include additional information describing details (i.e., study conditions/methods, identification of controls, results and conclusions) of relevant testing that supports how the product works. Please be aware that comparisons to other products or biocompatibility testing are typically not helpful in understanding how the product works.

5. An explanation of how the product will be marketed. For instance, will the product have separately marketed constituent parts that are to be labeled for use together, or will it have components that either will be physically or chemically combined to make a single entity or will be co-packaged?

6. A listing of all components/ingredients, including the amount and reasoning for including each component/ingredient, in the product. If the product contains a solution/liquid/gel/powder, please provide a listing of all ingredients (active and inactive), their amount/concentration, and the reason for including the ingredient in the product.

7. Proposed use/intended use/indications for use statement.

8. Instructions for use/conditions of use.

9. All known methods of action and the mechanism(s) by which each is achieved.

10. For products that might be combination products, any information that you might have, if any, to support the relative contribution of different components to the overall intended therapeutic/diagnostic effects of the combination product. Though optional, you may provide a detailed description of any supporting tests/studies if such information is available and you would like FDA to consider the information.

11. A list of claims that you intend to make or have made regarding the product.

B. What if I have additional information about my product that I would like to share with FDA in my Pre-RFD?

In addition to the above requested information needed for FDA to conduct a Pre-RFD review, you may also choose to provide additional information about a product. Information beyond that which is listed in Section IV.A is optional. However, in the event that you have prepared other information that you wish us to consider, we would be happy to do so. This information might include, for example, a recommendation for lead Center, if your product is a combination product, or any products that you believe may be similar to your product, or any other information that you consider relevant for us to consider during our preliminary assessment.[5]

C. What format should I follow for my Pre-RFD?

We recommend that you concisely provide the information identified in the screening checklist in the Appendix and explained in detail in the above sections. It would be helpful if you include for each section of the Pre-RFD a separate heading that corresponds to the headings listed in the screening checklist followed by your response. We also recommend you use a standard typeface (e.g., Times New Roman), which should be in an easily readable font size (e.g., 12).

D. Does FDA accept electronic submissions for Pre-RFDs?

Yes. You may submit your Pre-RFD by e-mail to combination@fda.gov in a common electronic format, such as a Portable Document Format (PDF) or a Word Document. As explained in the preceding section, only one electronic submission is necessary.

E. How should my Pre-RFD be addressed if I submit it via standard mail?

We encourage you to submit your Pre-RFD electronically to our inbox at combination@fda.gov. However, if you choose to submit your Pre-RFD via standard mail, you should send it to the following address:

[5] We note that to the extent any information a sponsor provides in a Pre-RFD is trade secret or confidential commercial information, such information is protected by the same confidentiality laws as those that protect such information provided in an RFD.

Office of Combination Products
Office of the Commissioner
Food and Drug Administration
WO32 Hub/Mail Room #5129
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

In order for the Pre-RFD to be sent to the correct location, the envelope should be clearly marked as a "Pre-Request for Designation." Only one Pre-RFD submission is necessary. In other words, no copies of your original Pre-RFD submission are required.

F. Is there a page limit for Pre-RFDs?

No, there is no page limit for Pre-RFDs (nor is there a word limit for emailed Pre-RFD submissions that are not in PDF or Word format). However, we encourage you to limit your Pre-RFD to a succinct summary of information relevant for OCP to make its preliminary assessment.

V. CONCLUSION

This guidance provides our recommendations for the format and content of a Pre-RFD submission. We recommend you pay particular attention to these sections of your Pre-RFD, as applicable:

- A complete description of the product, including its composition (what is your product?);
- The intended use/indications for use of the product (why would your product be used?);
- The methods of action of the product (how does your product work?);
- If your product may be a combination product, information you may have, if any, regarding the relative contribution of each of its components to the overall intended therapeutic/diagnostic effects of the combination product; and
- Any claims you have made or plan to make about your product.

OCP is always available as a resource to you. We strongly encourage you to contact OCP before submitting your Pre-RFD if you have any questions, or if you are uncertain about the type of information to include.

VI. Paperwork Reduction Act of 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average 13 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0845 (expires October 31, 2020).

VII. Appendix:

A. Pre-RFD Screening Checklist:

1. Contact information including your name, company's name, email address, and telephone number.

2. A complete description of the product and, if applicable, the following information.

    a. The 510(k), PMA, NDA, ANDA, BLA, or any other FDA regulatory submission number associated with the product.
    b. Name of the product and all component products; and
    c. A photo/diagram of the product

3. For products sourced from biologically-derived materials, describe how the material was processed and a characterization of the identity of the final product.

4. An explanation of how the product works. Though optional, you may provide additional information describing details (i.e., study conditions/methods, identification of controls, results, and conclusions) of relevant testing that supports how the product works. Please be aware that comparisons to other products or biocompatibility testing are typically not helpful in understanding how the product works.

5. An explanation of how the product will be marketed (e.g., kit configuration). For instance, will the product have separately marketed constituent parts that are to be labeled for use together, or will it have components that will be physically or chemically combined to make a single entity or co-package?

6. A listing of all components/ingredients, including the amount and purpose for including each component/ingredient, in the product. If the product contains a solution/liquid/gel/powder, please provide a listing of all ingredients (active and inactive), their amount/concentration, and the reason for including each ingredient in the product.

7. Proposed use/intended use/indications for use statement.

8. Instructions for use/conditions of use.

9. All known methods of action and the mechanism(s) by which each is achieved.

10. For products that might be combination products, information that you might have, if any, to support the relative contribution of different components to the overall intended therapeutic/diagnostic effects of the combination product. Though optional, you may provide detailed description of any relevant

tests/studies if such information is available and you would like FDA to consider the information.

11. A list of claims that you have made or plan to make regarding the product.

B. Pre-RFD Process Flow