
Guidance for Industry

How to Write a Request for Designation (RFD)

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

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Guidance for Industry

How to Write a Request for Designation (RFD)

For questions regarding this document, contact:
Office of Combination Products (OCP) at 301-796-8930 or combination@fda.gov

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Guidance for Industry

How to Write a Request for Designation (RFD)

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. PURPOSE

This guidance is intended to clarify the type of information the Office of Combination Products (OCP) recommends that a sponsor include in a Request for Designation (RFD). The goal of this guidance is to help a sponsor understand the type of information FDA needs to determine the regulatory identity or classification of a product as a drug, device, biological product, or combination product,¹ and to assign the product to the appropriate Agency component for review and regulation.² This guidance addresses 21 CFR Part 3, as amended by the final rule defining the primary mode of action (PMOA) of a combination product (PMOA Final Rule).³ 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 guidances means that something is suggested or recommended, but not required.

¹ Section 563 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and 21 CFR Part 3.

² Section 503(g) of the FD&C Act.

³ 70 FR 49848 (Aug. 25, 2005); also available at <http://edocket.access.gpo.gov/2005/pdf/05-16527.pdf>. The PMOA Final Rule has been in effect since November 23, 2005.

II. GENERAL INFORMATION REGARDING THE REQUEST FOR DESIGNATION PROCESS FOR NON-COMBINATION AND COMBINATION PRODUCTS

A. What is a non-combination product?

A non-combination product is a product that is only either a drug, a device, or a biological product as each is defined in the FD&C Act. The term does not include combination products as defined in 21 CFR 3.2(e). In part, Section 201(g) of the FD&C Act (21 U.S.C. 321(g)) provides that the term “drug” means:

(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).

Section 201(h) of the FD&C Act (21 U.S.C. 321(h)) provides that the term “device” means:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Section 351(i) (as modified by the Patient Protection and Affordable Care Act) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(i)) provides that the term “biological product” means:

a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized

polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

B. What is a combination product?

A combination product is comprised of a combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, a device, and a biological product. Under 21 CFR 3.2(e), a combination product is defined to include:

1. 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;
2. 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;
3. 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); or
4. 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.

Examples of combination products are available at <http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm>.

C. What is a Request for Designation?

An RFD is also referred to as an applicant's letter of request (see 21 CFR 3.2(j)). It is a written submission to OCP. RFDs generally request a determination of (1) the regulatory identity or classification of a product as a drug, device, biological product, or combination product, and/or (2) either the component of FDA that will regulate the product if it is a non-combination product, or which Agency Center⁴ will have primary jurisdiction for premarket review and regulation if it is a combination product. A letter of designation, see 21 CFR 3.2(i), (alternatively referred to as a designation letter) is FDA's formal response to an RFD and is a binding determination with

⁴ Section 503(g) of the FD&C Act defines the term "agency center" as a center or alternative organizational component of the Food and Drug Administration.

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.⁵

D. When should an RFD be submitted?

It is not necessary to submit an RFD for every product. We recommend submitting an RFD when the classification of a product or the Agency Center to which it should be assigned is unclear or in dispute. Sponsors are encouraged to submit an RFD as soon as they have sufficient information for FDA to make a decision regarding classification or assignment of a product.

The RFD should be submitted before filing any investigational or marketing application for the product. This will avoid a potential stay of the review clock if the classification or assignment of the product under review is determined to be unclear or in dispute during the review process. See 21 CFR 3.10. This will also help you avoid expending unnecessary time and resources, by ensuring that whatever submission for investigational use or marketing approval you may ultimately make is of the appropriate type and to the appropriate Agency component.

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 RFD for each product.

E. Can I request a meeting with OCP to explain my product?

We encourage you to contact OCP before submitting your RFD if you have any questions, including if you are uncertain about the type of information to include or about the need to submit an RFD. However, it is not necessary to meet with OCP regarding most product classification and assignment questions or about an RFD submission.

In most cases, the Agency will be able to make its determination based on a well-written 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 prior to submitting an RFD. Such a request should include an explanation of the issues you would like to be addressed in the meeting. OCP will then decide whether to grant the request.

Due to a mandatory short timeframe for reviewing RFDs, in general, OCP will not grant a request for a meeting after the RFD is submitted. Meeting requests may be submitted by writing to OCP at the address listed in Part III.C of this guidance document or by e-mail to combination@fda.gov. Please label your correspondence as a “Meeting Request.”

⁵ Though a designation letter is generally binding as to classification and/or assignment of a particular product, that determination pertains only to the product described in the designation letter. Further, if there is a change in, for example, an intended use or component of the product, or if the sponsor or Agency becomes aware of additional information that reveals that the mode or modes of action differ from what was originally described in the RFD, a new determination may be appropriate.

F. How do I submit an RFD for a combination or non-combination product?

The RFD process is outlined in 21 CFR Part 3. The regulation addresses (1) who should file; (2) when to file; (3) what to file; and (4) where to file an RFD. Part III of this document addresses the recommended format and specific content of an RFD in detail. The required information to include in an RFD is described in 21 CFR 3.7 (available at <http://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm109108.htm>).

G. How promptly will FDA review my RFD?

Within 5 business days of its receipt of an RFD, OCP will review the submission for completeness and determine whether the RFD contains the required information. See 21 CFR 3.8(a). OCP will then either send the sponsor an acknowledgement letter confirming the filing date of the RFD, or notify the sponsor that the RFD was not filed, and identify the information needed to make the RFD complete for filing. For filed RFDs, the acknowledgement letter will also identify the date by which FDA plans to respond to the RFD.

If FDA does not issue a designation letter within 60 calendar days of the filing of the RFD, as required by 21 CFR 3.8(b), the sponsor's recommendation for the classification or assignment of the product will become the designated classification or assignment. See Section 563 of the FD&C Act and 21 CFR 3.8(b).

H. May I withdraw my RFD after submission?

Yes, you may withdraw your RFD by notifying OCP in writing any time after its submission and before FDA issues its letter of designation. When FDA issues its letter of designation, it constitutes an Agency determination that may only be changed in accordance with 21 CFR 3.9(b). See also section 563 of the FD&C Act. Once the date-stamped letter of designation is issued by FDA, you may not withdraw your RFD.

I. What if I disagree with OCP's jurisdictional determination?

If you disagree with OCP's jurisdictional determination, 21 CFR Part 3 provides a mechanism for you to request that OCP reconsider its decision. Under 21 CFR 3.8(c), you may request reconsideration of a decision within 15 calendar days of receipt of the designation letter. A request for reconsideration under 21 CFR 3.8(c) cannot exceed five pages, and cannot include any new information that was not contained in your original RFD. FDA will review and act in writing within 15 calendar days of our receipt of the request for reconsideration.⁶

If you wish to present additional information or new data that was not presented in the RFD, you may submit a new RFD containing this information. OCP will consider this RFD a new submission.

⁶ As with any agency decision, a review may be requested under 21 CFR 10.75.

J. How can I contact OCP?

Contact information for OCP, including mailing address, e-mail address, and phone number, are listed on the front page of this guidance document and in Parts III.C and D below.

K. Where can I find more information?

More information about product classification and assignment and regarding the regulation of combination products is available on the OCP website at <http://www.fda.gov/CombinationProducts/default.htm>.

III. WHAT INFORMATION MUST I INCLUDE IN AN RFD?

A. What information must I include in my RFD?

According to 21 CFR 3.7(c), you are required to include the following information in your RFD, as applicable. Section III.E of this guidance further clarifies FDA's recommendations for the information that should be provided for each of these sections.

1. The identity of the sponsor, including company name and address, establishment registration number, company contact person and telephone number (3.7(c)(1)).
2. A description of the product, including:
 - i. Classification, name of the product and all component products, if applicable (3.7(c)(2)(i));
 - ii. Common, generic, or usual name of the product and all component products (3.7(c)(2)(ii));
 - iii. Proprietary name of the product (3.7(c)(2)(iii));
 - iv. Identification of any component of the product that already has received premarket approval, is marketed as not being subject to premarket approval, or has received an investigational exemption, the identity of the sponsors, and the status of any discussions or agreements between the sponsors regarding the use of this product as a component of a new combination product (3.7(c)(2)(iv));
 - v. Chemical, physical, or biological composition (3.7(c)(2)(v));
 - vi. Status and brief reports of the results of developmental work, including animal testing (3.7(c)(2)(vi));
 - vii. Description of the manufacturing processes, including the sources of all components (3.7(c)(2)(vii));
 - viii. Proposed use or indications (3.7(c)(2)(viii));
 - ix. Description of all known modes of action, the sponsor's identification of the single mode of action that provides the most important therapeutic action of the product, and the basis for that determination (3.7(c)(2)(ix));

- x. Schedule and duration of use (3.7(c)(2)(x));
 - xi. Dose and route of administration of drug or biologic (3.7(c)(2)(xi));
 - xii. Description of related products, including the regulatory status of those related products (3.7(c)(2)(xii)); and
 - xiii. Any other relevant information (3.7(c)(2)(xiii)).
3. The sponsor's recommendation as to which Agency component should have primary jurisdiction (3.7(c)(3)).

B. What format should I follow for my RFD?

We recommend that you follow the format and organization described in 21 CFR 3.7(c)(1)-(3). We recommend that you identify each required section of an RFD, in the order presented in the regulation, followed by your response. We recommend you use a standard typeface (e.g., Times New Roman), which should be in an easily readable font size (e.g., 12).

As explained in 21 CFR 3.7(c), RFDs are limited in length to 15 pages, including attachments.

C. How should my RFD be addressed?

You should submit your original RFD, and two copies, to:

*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 RFD to be sent to the correct location, the envelope should be clearly marked as a "Request for Designation."

D. Does FDA accept electronic submissions for RFDs?

Yes. You may submit your original RFD by e-mail to combination@fda.gov⁷ in a common electronic format, such as a Portable Document Format (PDF) in addition to two copies sent to the address listed in part C. above.

E. What information does FDA recommend that sponsors provide in RFD submissions?

Sponsors must provide the information required in 21 CFR 3.7. FDA recommends including the following information to ensure sufficient information is available for FDA to determine the regulatory identity and most appropriate assignment of the product:

⁷ RFDs submitted to other e-mail accounts will not be accepted.

1. Contact Information. Section 3.7(c)(1)

In addition to the required information, such as your name and your company's name, its street address, company establishment registration number (if applicable), and telephone number, we recommend you also include your fax number, e-mail address, and alternate company contact person and contact information.

2. Product Name. Sections 3.7(c)(2)(i), 3.7(c)(2)(ii), and 3.7(c)(2)(iii)

You must identify the classification, common, generic and/or usual names of your product and of all components of your product (if applicable). If you have chosen a proprietary name for your product, you must include that in your RFD. If any of this information is not known, please state this.

3. Description of the Product. Section 3.7(c)(2)

You must include a description of your product as outlined in 3.7(c)(2). It may be helpful to provide descriptive diagrams for complex products. For combination products with separate constituent parts (i.e., the drug, device, and/or biological product of which your combination product is comprised are not combined into a single entity), you should also explain how you intend to market your product. For example, describe whether the constituent parts will be provided in a kit or co-package, or, if sold separately, how they will be labeled for use together.

4. Prior Approvals and Agreements. Section 3.7(c)(2)(iv)

This provision requires you to identify any component of the product that:

- has received premarket approval/clearance;
- is marketed as not being subject to individual premarket approval/clearance (e.g., under an over-the-counter drug monograph, as a human cellular/tissue product subject only to section 361 of the PHS Act, or as a device exempt from the premarket notification requirements in section 510(k) of the FD&C Act); or
- has received an investigational exemption.

Furthermore, Section 3.7(c)(2)(iv) requires you to identify the sponsor of any such component.

You must also include the status of any discussions or agreements that you have had with the sponsor(s) regarding the use of the product(s) as a component of a new combination product.

If you have previously submitted information about your product to the Agency under a provision of the FD&C Act or an FDA regulation (e.g., under a request for device classification in accordance with section 513(g) of the FD&C Act, a 510(k) premarket notification, a new drug application (NDA) under section 505 of the FD&C Act or an investigational new drug application (IND) under 21 CFR 312, etc.), please reference any identifying number that is associated with that submission.

If there are no prior approvals, clearances, or agreements, please state so.

5. Chemical, Physical or Biological Composition. Section 3.7(c)(2)(v)

A fundamental part of your product's description is its chemical, physical and/or biological composition. You must include this information in your submission according to 21 CFR 3.7(c)(2)(v). Please identify all of the components or the ingredients, the purpose of each, and their concentration or amount. It may be helpful to provide this information in a tabular format.

6. Developmental Work and Testing. Section 3.7(c)(2)(vi)

This section requires that you include the status and brief reports of the results of developmental work, including animal testing. See 21 CFR 3.7(c)(2)(vi). We recommend that you summarize any available preclinical and clinical studies, with particular emphasis on those studies which establish the mode(s) of action and (for a combination product) the PMOA of the product. Information demonstrating the mode(s) of action of a product (e.g., whether or not a product or a component of a product works by chemical action or by being metabolized), and the PMOA of a combination product are important for the appropriate classification and jurisdictional assignment of your product.

7. Manufacturing Information. Section 3.7(c)(2)(vii)

You must include a description of the processes that will be used to manufacture your product, including the sources of all components. See 21 CFR 3.7(c)(2)(vii). A brief description and/or flowchart will generally suffice.

8. Proposed Use or Indications. Section 3.7(c)(2)(viii)

Like the explanation of the composition of your product, the proposed use or indications section is a critical section of your RFD. You are required to submit this information under 21 CFR 3.7(c)(2)(viii). You should state concisely and clearly the proposed use(s) or indication(s) for your product. This information can be relevant both to the classification and assignment of your product.

9. Modes of Action and Primary Mode of Action. Section 3.7(c)(2)(ix)

This is the cornerstone of the RFD submission. The modes of actions of products are typically critical to FDA's determination of whether a product is a drug, device, biological product, or combination product, and to the Agency's determination of the PMOA for a combination product upon which an assignment depends. The regulation requires that you provide a description of all known modes of action, and, for combination products, identify the PMOA, and the basis for that determination. See 21 CFR 3.7(c)(2)(ix). Additional information on modes of action and PMOA is provided below.

Modes of Action. 21 CFR 3.2(k) defines “mode of action” as: the means by which a product achieves an intended therapeutic effect or action. For purposes of this definition, “therapeutic” action or effect includes any effect or action of a combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body.

Because combination products are comprised of more than one type of regulated article (biological product, device, or drug), and each constituent part contributes a mode of action, combination products will have more than one mode of action.

Under 21 CFR 3.7(c)(2)(ix), your RFD must include a description of each mode of action of your product and should explain how each mode of action is achieved and which components or ingredients are responsible for each mode of action. You should also state whether each mode of action contributes a drug, device, or biological product mode of action, and explain the basis for your conclusion. It may be helpful to cite published literature⁸ or the developmental work and testing you provided under Section 3.7(c)(2)(vi) to support your explanation.

Primary Mode of Action.⁹ 21 CFR 3.2(m) defines “primary mode of action” (PMOA) as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.” As with “mode of action,” for purposes of PMOA, “therapeutic” effect or action includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body.

If your product is a combination product, under 21 CFR 3.7(c)(2)(ix) and 3.7(c)(3), you must identify the mode of action that you believe to be the single mode of action that provides the most important therapeutic action of the combination product; i.e. the PMOA. You must also include the basis for why you think that action is the most important. Literature references are often helpful in supporting your argument or you may wish to refer to any data you provided in your response to Section 3.7(c)(2)(vi).

Though not an exhaustive list (because each combination product presents different questions about its scientific characteristics and use), some factors that we consider when determining PMOA are provided below. We recommend that you consider and address these as appropriate when explaining the PMOA of your combination product:

- The proposed use(s) or indication(s) for the product;

⁸ When possible, you should cite published literature that is readily available. If you choose to cite “in press” literature or other published literature that you believe would be difficult for the Agency to obtain, you should provide copies of the referenced material with your RFD. We do not intend to count this type of supporting material toward the 15 page limit of your RFD. However, information or data which is only available in your company’s internal research report(s) should be included in the 15 page RFD.

⁹ If your product is a non-combination product, then you would not need to identify a PMOA for the product. However, if there is reason to believe that your product might be a combination product (i.e., it may have two or more ingredients or components whose modes of action may be different), you should identify which mode of action makes the greatest contribution to the overall intended therapeutic effect of the product, and explain the basis for your conclusion.

- How it achieves its overall intended therapeutic effect(s);
- The relative contribution of each constituent part to the proposed use(s) or indication(s), and to the overall intended therapeutic effect(s) of the product;
- The duration of the contribution of each constituent part toward the intended therapeutic effect(s) of the product; and
- Any data or information provided by you or that is available in scientific literature that describes and supports the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the product.

If OCP does not have enough information to determine the PMOA of your product directly or cannot determine the PMOA with reasonable certainty, OCP will assign the combination product in accordance with the assignment algorithm at 21 CFR 3.4(b).

Assignment Algorithm. For some combination products, it may not be possible for you or us to determine with reasonable certainty which mode of action of the product provides the most important therapeutic action. Determining the PMOA of a combination product is also complicated for products where the product has two completely distinct therapeutic effects achieved by completely different modes of action, neither of which is subordinate to the other (e.g., vision-correcting contact lenses impregnated with a drug for treating glaucoma). In such an instance, 21 CFR 3.7(c)(3) requires the sponsor to recommend which Agency component should have primary jurisdiction based on the assignment algorithm at 21 CFR 3.4(b).

The algorithm has two steps. Under the first step, if there are other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole, the Agency will assign the combination product to the Agency component that regulates those other combination products. See 21 CFR 3.4(b).

However, there may be no other combination products that present such similar questions of safety and effectiveness. For example, the RFD might present the first such combination product, or the combination product presented might differ in its intended use, design, formulation, etc., such that it presents different safety and effectiveness questions than existing combination products. In such cases, we would turn to the second step, under which we would assign the combination product to the Agency component with the most expertise related to the most significant safety and effectiveness questions presented by the combination product. *Id.*

Factors relevant to application of the algorithm. The factors listed below are intended to further illustrate the kinds of issues that may be relevant when determining whether a new combination product presents safety and effectiveness issues similar to those presented by a previous combination product, or which are the most significant safety and effectiveness questions presented by a combination product. We note that the list of factors below is not all-inclusive. Also, FDA may consider individual characteristics of the specific product. Such case-by-case analysis allows the Agency to take into account, for example, technological developments, evolving scientific understanding, and specific factual information concerning the particular product, such as its composition, or mechanism of action for achieving an intended use.

The following questions are not listed in order of importance; indeed some factors may be weighted more than others depending on various issues presented by each individual combination product. If you believe FDA may need to consider the algorithm in the assignment of your product (i.e., if your product's most important therapeutic action cannot be determined with reasonable certainty), then we recommend you consider and address these and/or other safety and effectiveness issues, as applicable, for your product:

- What is the intended use(s)/indication(s) for use of the product?
- What is the overall therapeutic effect(s) of the product as a whole?
- Does a device constituent part incorporate a novel or complex design or have the potential for clinically significant failure modes?
- Is a drug constituent part a new molecular entity or new formulation?
- Has a generic version of the drug been approved under section 505(j) of the FD&C Act?
- Does the drug have a narrow therapeutic index?
- Is the biological product constituent part a particularly fragile molecule?
- How well understood are the product's constituent parts? Is one constituent part relatively common, while another presents more significant safety and effectiveness issues relating to the risks it poses, its effectiveness, or its novelty?
- Which constituent part raises greater risks?
- Have any of the constituent parts been previously approved or cleared for the same or a similar use?
- Is there a new indication, route of administration or a significant change in dose or use of one of the constituent parts?

Addressing the assignment algorithm in your RFD. If you cannot determine with reasonable certainty the most important therapeutic action of your combination product, you must recommend an assignment for your product based on the assignment algorithm at 21 CFR 3.4(b). See 21 CFR 3.7(c)(3). Under the first step, you should consider whether FDA regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole. In other words, you should consider whether an FDA Center has direct experience with a combination product similar to yours. You should identify any such other combination products that you are aware of that you believe FDA should consider in determining the assignment of your product, and explain how your product is similar. For example, if you have developed a new drug for treating glaucoma that will be combined with a contact lens, and you are aware of other products reviewed by FDA that consist of a contact lens and another drug for this intended use, you should identify those products.

If you do not believe that your product as a whole is similar to other combination products that a Center has already reviewed or that you are aware a Center is currently reviewing, you should address the second step of the algorithm. Even if you believe your product is similar to another, we recommend that you explain how you think we should assign your product should we find it necessary to move to this second step in the algorithm. For this part of the algorithm, you should identify the most significant safety and effectiveness questions presented by your combination product, and explain, in your opinion, which Center has the most expertise related to those questions. For example, if this is the first time the Agency is presented with a vision-correcting contact lens containing a glaucoma drug, then, using the factors described above, you should

explain, in your opinion, which Center has more expertise to answer these questions. In this case, you might explain that the most significant safety and effectiveness questions are related to the characterization, manufacturing, and clinical performance of the drug component, while the safety and effectiveness questions raised by the vision-correcting contact lens are considered more routine. Based on these criteria, you might recommend that CDER has the most expertise related to these issues.

10. Schedule and Duration of Use. Section 3.7(c)(2)(x)

You must briefly explain how often and for how long your product is intended to be used. For example, if your product is a non-combination device that would be implanted in the body during one surgical procedure, you should state the duration for which it is implanted or if it will be implanted with the expectation that, as long as the device functions, it will remain in the body indefinitely. In other cases, such as with a wound dressing, for instance, an RFD might explain that the dressing should be used over a four-hour period, after which a change of dressing would occur if needed, with a maximum of six dressings to be used over a 24-hour time period. Another example would be that your product is a drug to be delivered by a device every twelve hours over a period of time not to exceed 10 days.

11. Dose and Route of Administration. Section 3.7(c)(2)(xi)

As applicable, you should briefly explain the dose (amount) of the drug or biological product (or constituent part) to be used, and how it will be used in or on the body. For example, for a combination product wound dressing consisting of a drug and device delivery system, you would identify the specific amount of the drug contained in the device, and that it would be applied topically to the specific type of wound your product is intended to treat. If your product is an injectable drug, you would explain that the delivery device would be used to inject a specific dose of the drug intramuscularly, intravenously, etc.

Even if you believe your product is a device (containing no drug or biological products), it may be helpful to provide information about the dose or route of administration for the product. For example, if your product is an injectable product, such as a wrinkle filler, you should describe the amount of product being injected and the site of the injection.

12. Related Products. Section 3.7(c)(2)(xii)

If you think there are other products like yours, or other products with related components, you must briefly explain what they are, how they are regulated, and their regulatory status (e.g., approved, investigational, etc.) so that we can consider them when classifying and/or making the assignment for your product. Please include the product application numbers when available (e.g., 510(k) or NDA number). You should explain any similarities or differences between these products and your product and state how these are relevant to the classification and/or assignment of your product.

If you are not aware of other products like yours or other products with related components, please state this.

13. Other Relevant Information. Section 3.7(c)(2)(xiii)

If you think there is anything else we should consider when determining the appropriate classification and/or assignment of your product, you should explain that in this portion of your RFD. For example, literature references describing the product, its components, and its modes of action are often helpful.

14. Sponsor's Recommendation. Section 3.7(c)(3)

The final section of an RFD must include your recommendation for the classification (drug, device, biological product, or combination product) and assignment (CBER, CDER, or CDRH) of your product.

If you believe your product is a non-combination product, you should state whether you believe it meets the statutory definition of a drug, device, or biological product and your rationale for this recommendation. Your classification recommendation should be based on the composition, mode(s) of action, and intended use(s) of your product. Based on this recommended classification, you should then state your recommendation as to which Center (CBER, CDER, or CDRH) should regulate your product.

If you believe your product is a combination product, you should state what type of combination product it may be (e.g., drug/device) and your rationale for this recommendation. Next, you should explain which Center (CBER, CDER, or CDRH) should have primary jurisdiction (the "lead") for regulation of your product. This explanation should be based on the composition, intended use(s), modes of action, and PMOA of the product. If you cannot determine which single mode of action provides the most important therapeutic action of the product, you must use the algorithm set forth in 21 CFR 3.4(b) to make your recommendation of "lead" Center (see Section 9 above).

If you are unclear whether your product is a combination product or a non-combination product, we recommend you provide an analysis for the product being a combination product and for being a non-combination product.

F. How can I limit my submission to 15 pages including attachments as required by the regulation, and still provide all the information FDA needs to make its decision?

In FDA's experience, a comprehensive RFD submission, addressing all the information required by the regulation and needed by FDA to make its jurisdictional determination, can be accomplished within the 15-page requirement. The most important sections of an RFD are summarized in Section IV below.

IV. CONCLUSION

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

- A complete description of the product, including its composition (what is your product?);
- The intended use/indications of the product (why would your product be used?);
- The mode(s) of action of the product (how does your product work?);
- The PMOA of the product (what is your combination product's most important therapeutic action?);
- The basis for your PMOA determination (including any literature references and a summary of any developmental work or testing that helps describe your product's modes of action and/or PMOA);
- The assignment algorithm; and
- Your classification and assignment recommendations (how do you think your product should be classified and assigned, and why?).

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

Appendix: RFD Screening Checklist

_____: Original RFD not exceeding 15 pages, including attachments (21 CFR 3.7(c))

_____: The identity of the sponsor, including company name and address, establishment registration number, company contact person, and telephone number (3.7(c)(1))

_____: Description of the product (3.7(c)(2))

_____: Classification, name of the product, and all component products, if applicable (3.7(c)(2)(i))

_____: Common, generic, or usual name of the product and all component products (3.7(c)(2)(ii))

_____: Proprietary name of the product (3.7(c)(2)(iii))

_____: Identification of any component of the product that already has received premarket approval, is marketed as not being subject to premarket approval, or has received an investigational exemption. The identity of the sponsors, and the status of any discussions or agreements between the sponsors regarding the use of this product as a component of a new combination product (3.7(c)(2)(iv))

_____: Chemical, physical, or biological composition (3.7(c)(2)(v))

_____: Status and brief reports of the results of developmental work, including animal testing (3.7(c)(2)(vi))

_____: Description of the manufacturing processes, including the sources of all components (3.7(c)(2)(vii))

_____: Proposed use or indications (3.7(c)(2)(viii))

_____: Description of all known modes of action, the sponsor's identification of the single mode of action that provides the most important therapeutic action of the product, and the basis for that determination (3.7(c)(2)(ix))

_____: Schedule and duration of use (3.7(c)(2)(x))

_____: Dose and route of administration of drug or biologic (3.7(c)(2)(xi))

_____: Description of related products, including the regulatory status of those related products (3.7(c)(2)(xii))

_____: The sponsor's recommendation as to which Agency component should have primary jurisdiction based on the mode of action that provides the most important therapeutic action of the combination product. (3.7(c)(3))

_____: For combination products where the mode of action that provides the most important therapeutic action cannot be determined with reasonable certainty, the sponsor's recommendation must be based on the assignment algorithm and an assessment of the assignment of other combination products the sponsor wishes FDA to consider during the assignment of its combination product. (3.7(c)(3))

_____: 1st step of assignment algorithm: assignment of other combination products presenting similar safety and effectiveness questions

_____: 2nd step of assignment algorithm: most expertise related to the most significant safety and effectiveness questions