

*Contains Nonbinding Recommendations*

# Guidance for Industry and FDA Staff:

## How to Write a Request for Designation (RFD)

For questions regarding this document, contact:  
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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Office of the Commissioner  
Office of Combination Products**

August 2005

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## How to Write a Request for Designation (RFD)

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**U.S. Department of Health and Human Services  
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The information collection provisions in this guidance have been approved under OMB control number 0910-0523. This approval expires February 28, 2007.

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

13  
14 **I. PURPOSE**

15  
16 This guidance is intended to clarify the type of information the Office of Combination  
17 Products (OCP) recommends that a sponsor include in a Request for Designation (RFD). The  
18 goal of this guidance is to help a sponsor understand the type of information FDA needs to  
19 determine the regulatory identity of a product as a drug, device, biological product, or  
20 combination product, and to assign the product to the appropriate agency component for  
21 review and regulation. This guidance reflects the final rule defining the primary mode of  
22 action of a combination product (PMOA Final Rule) published in the Federal Register on  
23 August 25, 2005. The PMOA Final Rule is effective November 23, 2005.

24  
25 FDA's guidance documents, including this guidance, do not establish legally enforceable  
26 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and  
27 should be viewed only as recommendations, unless specific regulatory or statutory  
28 requirements are cited. The use of the word *should* in Agency guidances means that  
29 something is suggested or recommended, but not required.  
30  
31

32 **II. GENERAL INFORMATION REGARDING PRODUCT**  
33 **JURISDICTION/ASSIGNMENT OF SINGLE-ENTITY AND**  
34 **COMINATION PRODUCTS**

35 **A. What is a non-combination or “single-entity” product?**

36 A non-combination or “single-entity” product is a product that is either a drug, a device,  
37 or a biological product.

38 Section 201(g) of the Act defines a “drug” as an article intended for use in the  
39 diagnosis, cure, mitigation, treatment, or prevention of disease, or an article (other  
40 than food) intended to affect the structure or any function of the body.

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41 Section 201(h) of the Act defines a “device” as an instrument, apparatus, implement,  
42 machine, contrivance, implant, in vitro reagent, or other similar or related article,  
43 including any component, part, or accessory, which is intended for use in the  
44 diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or  
45 prevention of disease, or which is intended to affect the structure or function of the  
46 body. A device may not achieve its primary intended purposes through chemical  
47 action within or on the body of man or other animals, nor can it be dependent upon  
48 being metabolized for the achievement of its primary intended purposes.

49 21 CFR 600.3(h) and (i) define a biological product as a virus, therapeutic serum,  
50 toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product,  
51 or analogous product, or arsphenamine or derivative of arsphenamine (or any other  
52 trivalent organic compound), applicable to the prevention, treatment, or cure of a  
53 disease or condition of human beings.  
54

### 55 **B. Which Centers review non-combination or “single-entity” products?**

56 In general, single entity products that meet the definition of a drug are  
57 reviewed and regulated by the Center for Drug Evaluation and Research  
58 (CDER). Similarly, in general, single entity products that meet the definition  
59 of a device are reviewed by the Center for Devices and Radiological Health  
60 (CDRH). Certain devices that are used in the manufacture or delivery of  
61 biological products may be reviewed and regulated under the device  
62 provisions of the Act by the Center for Biologics Evaluation and Research  
63 (CBER).

64 CBER is responsible for the review of blood, blood components, plasma  
65 derived products, cellular and gene therapy products, vaccines, allergenic  
66 extracts, antitoxins, antivenins and venoms. In June 2003, FDA transferred  
67 the review and regulation of some types of therapeutic biological products  
68 from CBER to CDER. Additional information about the current assignment  
69 of biological products between CBER and CDER is available at  
70 <http://www.fda.gov/oc/combo/transfer.html>.

71 OCP’s website has a variety of information on product jurisdiction to help  
72 sponsors understand what types of products are reviewed by CBER, CDER  
73 and CDRH.  
74

### 75 **C. What is a combination product?**

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

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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;
- 84  
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86
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;
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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
- 95  
96  
97  
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99
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.
- 100

### 101 **D. What are some examples of combination products?**

102 Examples of combination products where the components are physically,  
103 chemically or otherwise combined (21 CFR 3.2(e)(1)):

- 104
- Monoclonal antibody conjugated to a therapeutic drug
  - Device coated or impregnated with a drug or biologic
    - Drug-eluting stent; pacing lead with steroid-coated tip; catheter with antimicrobial coating; condom with spermicide
    - Skin substitutes with cellular components; orthopedic implant with growth factors
  - Prefilled syringes, insulin injector pens, metered dose inhalers, transdermal patches
- 105  
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112 Examples of combination products where the components are packaged  
113 together (21 CFR 3.2(e)(2)):

- 114
- Drug or biological product packaged with a delivery device
  - Surgical tray with surgical instruments, drapes, and antimicrobial swabs
- 115

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116 Examples of combination products where the components are separately  
117 provided but labeled for use together (21 CFR 3.2(e)(3) or (e)(4)):

- 118 • Photosensitizing drug and activating laser/light source
  - 119 • Iontophoretic drug delivery patch and controller
- 120

### 121 **E. How are combination products assigned for review?**

122 A combination product is assigned to an Agency center<sup>1</sup> that will have primary  
123 jurisdiction for its premarket review and regulation. Under section 503(g)(1) of the Act,  
124 assignment to a “lead center” is based on a determination of the “primary mode of action”  
125 (PMOA) of the combination product. For example, if the PMOA of a combination product  
126 is that of a biological product, then the combination product would be assigned to the  
127 Agency component responsible for premarket review of that biological product.

128  
129 A final rule defining the primary mode of action of a combination product (PMOA Final  
130 Rule) was published in the August 25, 2005, Federal Register, and is available at  
131 <http://www.fda.gov/oc/combination/default.htm>. The final rule, which is effective  
132 November 23, 2005, defines primary mode of action as “the single mode of action of a  
133 combination product that provides the most important therapeutic action of the  
134 combination product. The most important therapeutic action is the mode of action  
135 expected to make the greatest contribution to the overall intended therapeutic effects of  
136 the combination product.”

137  
138 In some cases, neither FDA nor the sponsor can determine the most important  
139 therapeutic action of a combination product at the time a RFD is submitted. A  
140 combination product may also have two independent modes of action, neither of which  
141 is subordinate to the other. The final rule described an algorithm FDA will follow to  
142 determine the center assignment for these types of combination products. The algorithm  
143 first directs the assignment based on consistency with the assignment of other  
144 combination products raising similar questions of safety and effectiveness questions  
145 with respect to the combination product as a whole. When there are no such prior  
146 products (e.g., it is the first such combination product, or differences in its intended use,  
147 design, formulation, etc. present different safety and effectiveness questions), the  
148 algorithm directs the assignment to the agency component with the most expertise  
149 related to the most significant safety and effectiveness questions raised by the  
150 combination product.

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<sup>1</sup> Section 503(g) of the Act defines the term “agency center” as a center or alternative organizational component of the Food and Drug Administration.

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### **F. How do I determine which Center will review my combination or non-combination/single-entity product?**

The regulatory identity of a product as a drug, device, biological product, or combination product is often clear. Similarly, the primary mode of action of a combination product is often clear. On occasion, however, the regulatory identity of the product, or the Center with jurisdiction to review and regulate the product may be unclear, or may be the subject of a disagreement between the Agency and the sponsor. In these cases, sponsors may request a determination of the classification and/or assignment of a product.

Requests for classification (a determination of the regulatory identity of a product as a drug, device, biological product, or combination product) or assignment of a combination product to an Agency Center, may be handled formally or informally.

A formal request is made through the Request for Designation (RFD) process, which is described in this guidance in detail. However, when FDA has had enough experience with similar products, an informal determination may suffice. Rather than submitting an RFD, sponsors may request an informal determination of jurisdiction by telephone or by e-mail. Informal jurisdictional determinations are not binding on the agency.

Sponsors wishing to discuss jurisdictional issues informally may contact:

- **OCP Product Assignment Officer (for assignment of a combination product to an Agency Center):**  
Leigh Hayes, at 301-427-1934
- **OCP Product Classification Officer (for classification of a product as a drug, device, biological product or combination product):**  
Suzanne O'Shea at 301-427-1934
- **OCP e-mail address:**  
[combination@fda.gov](mailto:combination@fda.gov)

The Center jurisdictional officers of the Center you believe would review and regulate your product can also assist you in determining the appropriate Center:

- **Center for Biologics Evaluation and Research (CBER):**  
Sheryl Lard-Whiteford, Ph.D., 301-827-0379
- **Center for Devices and Radiological Health (CDRH):**  
Eugene Berk, 301-594-1190
- **Center for Drug Evaluation and Research:**  
Warren Rumble, 301-594-5480

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### **G. What is a Request for Designation, and at what point in product development should I submit it?**

A Request for Designation is an applicant's written submission to the agency's Product Jurisdiction Officer (the Office of Combination Products) seeking the designation of the agency component with primary jurisdiction for a product. An RFD is the mechanism by which sponsors can request a formal determination of either (1) the regulatory identity of a product as a drug, device, biological product, or combination product, or (2) which Center will have primary jurisdiction for premarket review and regulation of a combination product. FDA's formal response to an RFD is a binding jurisdictional determination with respect to center assignment that may be changed only under conditions specified in 21 CFR 3.9 and Section 563 of the Act.<sup>2</sup>

As explained in Section F above, it is not necessary to submit an RFD for every product. An RFD should be submitted when the jurisdiction of a combination or non-combination product 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 assignment of a product. The RFD should be submitted before filing any investigational or marketing application for the product.

### **H. How do I submit a Request for Designation for a combination or non-combination/single-entity product?**

The Request for Designation (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. The specific information to be included in an RFD is described in 21 CFR 3.7, which can be accessed at <http://www.fda.gov/oc/ombudsman/part3&5.htm#request>. Part III of this document addresses the recommended format and content of an RFD in detail.

### **I. How promptly will FDA review my RFD?**

Within 5 days of its receipt of an RFD, OCP will review the submission for administrative completeness and determine whether the RFD contains the information FDA needs to make its jurisdictional determination.<sup>3</sup> OCP will then either send the sponsor an acknowledgement letter confirming the filing date of an RFD, or notify the sponsor that the RFD was not filed, and identify the information needed to make the RFD complete. For filed RFD's, the acknowledgement letter will also identify the date by which FDA will respond to the RFD. If FDA does not issue a designation letter within 60 days of the

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<sup>2</sup> Though a designation letter is binding as to assignment of a particular product, that assignment pertains only to the product described in the designation letter. If that product's configuration, composition, modes of action, intended use, or other key aspect changes after the designation letter issues, it may be necessary to submit a new RFD to determine the new product's appropriate assignment.

<sup>3</sup> The checklist we currently use to screen RFD's for filing is provided as an Appendix.

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241 filing of the RFD, as required by 21 CFR 3.8(b), the sponsor's recommendation of the  
242 agency component with primary jurisdiction will become the designated agency  
243 component. Information regarding FDA's timeliness in reviewing RFD's is posted on our  
244 website at <http://www.fda.gov/oc/combo>. This information is updated periodically.  
245  
246

### **J. May I withdraw my RFD after submission?**

247  
248  
249 Yes, you may withdraw your RFD by notifying OCP in writing any time after its  
250 submission and before FDA issues its jurisdictional determination. After FDA issues its  
251 determination, the assignment decision is binding, and you may not withdraw your RFD.  
252

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

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254  
255  
256 If you disagree with OCP's jurisdictional determination, you may request that OCP  
257 reconsider its decision. According to 21 CFR 3.8(c), you may request reconsideration of  
258 a decision within 15 days of receipt of the designation letter. By regulation, a request for  
259 reconsideration cannot exceed five pages, and you may not include any new information  
260 in your request for reconsideration that was not contained in your original RFD. FDA  
261 will review and act in writing within 15 days of FDA's receipt of the request for  
262 reconsideration. If you disagree with FDA's response to your request for reconsideration,  
263 you may request further internal Agency review in accordance with 21 CFR 10.75. There  
264 is no time limit to submitting such an appeal.  
265

### **L. How can I contact OCP?**

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267  
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269 You may e-mail OCP at [combination@fda.gov](mailto:combination@fda.gov), or call OCP at (301) 427-1934. Our  
270 mailing address is 15800 Crabbs Branch Way, Suite 200 (HFG-3), Rockville, MD  
271 20855. Our fax number is (301) 427-1935.  
272

## **273 III. WHAT INFORMATION MUST I INCLUDE IN AN RFD?**

### **274 A. What information must I include in my RFD?**

275  
276 According to 21 CFR § 3.7(c), you are required to include the following information in  
277 your RFD. Section III.E of this guidance further clarifies FDA's recommendations for  
278 the information that should be provided for each of these sections.  
279

- 280 (1) The identity of the sponsor, including company name and address, establishment  
281 registration number, company contact person and telephone number (3.7(c)(1)).  
282
- 283 (2) A description of the product, including:

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- 284 (i) Classification, name of the product and all component products, if  
285 applicable (3.7(c)(2)(i));
- 286 (ii) Common, generic, or usual name of the product and all component  
287 products (3.7(c)(2)(ii));
- 288 (iii) Proprietary name of the product (3.7(c)(2)(iii));
- 289 (iv) Identification of any component of the product that already has received  
290 premarket approval, is marketed as not being subject to premarket  
291 approval, or has received an investigational exemption, the identity of the  
292 sponsors, and the status of any discussions or agreements between the  
293 sponsors regarding the use of this product as a component of a new  
294 combination product (3.7(c)(2)(iv));
- 295 (v) Chemical, physical, or biological composition (3.7(c)(2)(v));
- 296 (vi) Status and brief reports of the results of developmental work, including  
297 animal testing (3.7(c)(2)(vi));
- 298 (vii) Description of the manufacturing processes, including the sources of all  
299 components (3.7(c)(2)(vii));
- 300 (viii) Proposed use or indications (3.7 (c)(2)(viii));
- 301 (ix) Description of all known modes of action, the sponsor's identification of  
302 the single mode of action that provides the most important therapeutic  
303 action of the product, and the basis for that determination (3.7(c)(2)(ix));
- 304 (x) Schedule and duration of use (3.7(c)(2)(x));
- 305 (xi) Dose and route of administration of drug or biologic (3.7(c)(2)(xi));
- 306 (xii) Description of related products, including the regulatory status of those  
307 related products (3.7(c)(2)(xii)); and
- 308 (xiii) Any other relevant information (3.7(c)(2)(xiii)).
- 309
- 310 (3) The sponsor's recommendation as to which agency component should have primary  
311 jurisdiction.
- 312
- 313

### **B. What format should I follow for my RFD?**

314 We recommend that you follow the format and organization described in 21 CFR § 3.7(c)(1)-  
315 (3). We recommend that you identify each required section of an RFD, in the order presented  
316 in the regulation, followed by your response. As explained in 21 CFR 3.7(c), RFD's are  
317 limited in length to 15 pages, including attachments.

318

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### **C. How should my RFD be addressed?**

322 You should submit your original RFD to the Office of Combination Products, 15800 Crabbs  
323 Branch Way, Suite 200 (HFG-3), Rockville, MD 20855. We recommend that the envelope be  
324 marked as a "Request for Designation."

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- 330 **D. Does FDA accept electronic submissions for RFD's?**  
331  
332 Yes. You may submit an RFD electronically to [combination@fda.gov](mailto:combination@fda.gov) in a common  
333 electronic format, such as a word processing file or in Portable Document Format (PDF).  
334 You must concurrently submit your original RFD as described in Section C above.  
335  
336
- 337 **E. What information does FDA recommend that sponsors provide in RFD submissions?**  
338  
339 We recommend sponsors provide the following information to satisfy the requirements of 21  
340 CFR 3.7 and to ensure sufficient information is available for FDA to determine the regulatory  
341 identity and most appropriate assignment of the product:  
342
- 343 **1. Contact Information.** Section 3.7(c)(1)  
344  
345 You should include enough information for OCP to contact you, including your name  
346 and your company's name, its street address, company establishment registration  
347 number (if applicable), telephone number, and alternate company contact person and  
348 contact information (if applicable). We also recommend you provide your fax number  
349 and email address.  
350
- 351 **2. Product Name.** Sections 3.7(c)(2)(i), 3.7(c)(2)(ii), and 3.7(c)(2)(iii)  
352  
353 You should identify the classification, common, generic and/or usual names of your  
354 product and of all component products (if applicable). If you have chosen a  
355 proprietary name for your product, you should include that in your RFD.  
356
- 357 **3. Prior Approvals and Agreements.** Section 3.7(c)(2)(iv)  
358  
359 This provision requires you to identify:  
360
  - any component of the product that has received premarket approval, or
  - is marketed as not being subject to premarket approval (e.g., OTC monograph,  
362 Section 361 human cellular/tissue product or 510(k) exempt), or
  - has received an investigational exemption, and the identity of the sponsors.  
364  
365 You should also include the status of any discussions or agreements that you have had  
366 regarding the use of the product as a component of a new combination product.  
367
- 368 **4. Chemical, Physical or Biological Composition.** Section 3.7(c)(2)(v)  
369  
370 A fundamental part of your product's description is its chemical, physical and/or  
371 biological composition. In other words, you should fully describe your product and its  
372 constituent parts. If OCP does not have enough information to understand the  
373 composition of your product, we will not be able to determine its regulatory identity or  
374 appropriate assignment.  
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### **5. 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. We recommend that you summarize any available preclinical and clinical studies. Since the focus of an RFD is to establish the mode(s) of action and (for a combination product) the PMOA of a product, information demonstrating whether a product or a component of a product works by chemical or metabolic action, and the PMOA of a combination product usually are very helpful.

### **6. Manufacturing Information.** Section 3.7(c)(2)(vii)

We recommend that you include a description of the processes that will be used to manufacture your product, including the sources of all components. A brief description and/or flowchart will generally suffice.

### **7. 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 should state concisely and clearly the intended use and indications for use of your product. OCP considers both the intended use and indications for use of your product when making an assignment to an agency Center for premarket review and regulation.

### **8. Modes of Action.** Section 3.7(c)(2)(ix)

This is the cornerstone of the RFD submission. A product's modes of action are often critical to FDA's determination of the regulatory identity of a single entity product, and a combination product's primary mode of action determines its assignment. The regulation requires that you provide a description of all known modes of action, and, for combination products, identify the single mode of action that provides the most important therapeutic action of the product, and the basis for that determination. Additional information on modes of action and PMOA is provided below.

**Modes of Action.** The PMOA Final Rule 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 the product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body.

Products may have a drug, biological product, or device mode of action. Because combination products are comprised of more than one type of regulated article (biological product, device, or drug), and each constituent part contributes a biological product, device, or drug mode of action, combination products will typically have more than one mode of action. While the definitions below specifically apply to the

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421 constituent parts of a combination product, they may also be helpful in determining  
422 the modes of action of non-combination/single-entity products:

- 423  
424 • A constituent part of a combination product has a biological product mode of  
425 action if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine,  
426 blood, blood component or derivative, allergenic product, or analogous product  
427 applicable to the prevention, treatment, or cure of a disease or condition of human  
428 beings, as described in subsection 351(i) of the Public Health Service Act.  
429
- 430 • A constituent part of a combination product has a device mode of action if it meets  
431 the definition of device contained in section 201(h)(1)-(3) of the act, it does not  
432 have a biological product mode of action, and it does not achieve its primary  
433 intended purposes through chemical action within or on the body of man or other  
434 animals and is not dependent upon being metabolized for the achievement of its  
435 primary intended purposes.  
436
- 437 • A constituent part of a combination product has a drug mode of action if it meets  
438 the definition of drug contained in section 201(g)(1) of the act and it does not have  
439 a biological product or device mode of action.  
440

441  
442 **Primary Mode of Action.** If your product is a combination product,<sup>4</sup> the PMOA  
443 Final Rule requires that you identify the single mode of action that you believe  
444 provides the most important therapeutic action of the combination product. The  
445 PMOA Final Rule defines “primary mode of action” (PMOA) as “the single mode of  
446 action of a combination product that provides the most important therapeutic action of  
447 the combination product. The most important therapeutic action is the mode of action  
448 that is expected to make the greatest contribution to the overall intended therapeutic  
449 effects of the combination product.” As with “mode of action,” for purposes of  
450 PMOA, “therapeutic” effect or action includes any effect or action of the combination  
451 product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the  
452 structure or any function of the body.  
453

454 When explaining the mode of action that you believe to be the single mode of action  
455 that is expected to make the greatest contribution to the overall intended therapeutic  
456 effects of the combination product, you should include the reasons why you think that  
457 action is the most important, and why the other mode(s) of action are secondary to it.  
458 You may also refer to any data you provided in your response to Section 3.7(c)(2)(vi).  
459 Literature references are often helpful.

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<sup>4</sup> If your product is a non-combination or single-entity product, then you would not need to explain the product’s primary mode of action. We note that in some cases RFDs are submitted to determine whether a product is a single entity or a combination product. In those cases, we recommend that you address both possibilities. For instance, you should first explain why you believe your product meets the definition of a drug, a device, or a biological product, and is therefore a single-entity product. We also recommend that you consider the possibility that we may find that your product is a combination product. In so doing, you would explain what the modes of action of your product are, its PMOA, and which Center would be most appropriate to regulate the product based on its PMOA or the assignment algorithm.

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Though not an exhaustive list (because each combination product presents different questions about its scientific characteristics and use), some questions 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 intended use of the product as a whole
- How it achieves its overall intended therapeutic effect
- The intended therapeutic effect of each constituent part
- The duration of the contribution of each constituent part toward the therapeutic effect of the product as a whole
- Any data or information provided by you or that is available in scientific literature that describe the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.

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**Assignment Algorithm.** For some products, it may not be possible for you or for us to determine, at the time your RFD is submitted, which one mode of action of a combination 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 different modes of action, neither of which is subordinate to the other. The agency promulgated an assignment algorithm in the PMOA Final Rule (21 CFR 3.4(b)) to assign such products with as much consistency, predictability, and transparency as possible.

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In those cases, the agency will assign the combination product to the agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole. When there are no other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole (e.g., it is the first such combination product, or differences in its intended use, design, formulation, etc. present different safety and effectiveness questions), 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.

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If you cannot determine the most important therapeutic action of your combination product, you should use the assignment algorithm. First, 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 product similar to yours. You should identify other combination products you wish FDA to consider during the assignment of your product.

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If you do not believe that your product as a whole is similar to others that FDA has already reviewed or is currently reviewing, you should address the second criterion 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

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506 necessary to move to the second step in the algorithm. For this part of the algorithm,  
507 you should consider the most significant safety and effectiveness questions presented  
508 by your combination product, and which Center has the most expertise related to those  
509 questions.

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511 The factors listed below are intended to further illustrate the kinds of issues we may  
512 consider, as appropriate, when determining the most significant safety and  
513 effectiveness questions presented by a product, or whether a new combination product  
514 presents similar safety and effectiveness issues as a previous product. We note that  
515 the list of factors below is not all-inclusive. FDA considers to be essential its ability to  
516 continue to assess the individual characteristics of particular products. This will allow  
517 the agency to respond to technological developments, scientific understanding, factual  
518 information concerning a specific product, or the composition, mechanism of action or  
519 intended use of a particular product. The questions are not listed in order of  
520 importance; indeed some factors may be weighted more than others depending on  
521 various issues presented by each individual combination product. If you believe FDA  
522 may need to consider the algorithm in the assignment of your product (i.e., if its most  
523 important therapeutic action cannot be determined with reasonable certainty), then we  
524 recommend you consider and address these and/or other safety and effectiveness  
525 issues, as appropriate, for your product:  
526

- 527 • What is the intended use of the product?
- 528 • What is the therapeutic effect of the product as a whole?
- 529 • Does the device component incorporate a novel or complex design or have the  
530 potential for clinically significant failure modes?
- 531 • Is this a new molecular entity or new formulation?
- 532 • Has the drug previously been approved as a generic drug?
- 533 • Does the drug have a narrow therapeutic index?
- 534 • Is the biological product component a particularly fragile molecule?
- 535 • How well understood are the product's components? Is one component  
536 relatively routine, while the other presents more significant safety and  
537 effectiveness issues due to the risks it poses, its effectiveness, or novelty?
- 538 • Which component raises greater risks?
- 539 • Has either of the components been previously approved or cleared?
- 540 • Is there a new indication, route of administration or a significant change in  
541 dose or use of the one of the components, or are only secondary aspects of the  
542 labeling affected?

### **9. Schedule and Duration of Use.** Section 3.7(c)(2)(x)

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545 You should briefly explain how often and for how long your product is intended to be  
546 used. For example, if your product is a single-entity device, it may be the type that  
547 would be implanted in the body during one surgical procedure with the expectation  
548 that, as long as the device functions, it will remain in the body indefinitely. In other  
549 cases, such as with a wound dressing, for instance, an RFD might explain that the  
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552 dressing should be used over a four hour period, after which a change of dressing  
553 would occur if needed, with a maximum of six dressings to be used over a 24-hour  
554 time period. Yet another example would be if your product is a drug to be delivered  
555 by a device every twelve hours over a period of time not to exceed 10 days.  
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### **10. Dose and Route of Administration.** Section 3.7(c)(2)(xi)

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559 You should briefly explain the dose (amount) of the drug or biological product (or  
560 component) to be used, and how it will be used in or on the body. Using the examples  
561 mentioned above, you would explain that your product is implanted in the body during  
562 a single surgical procedure, and it is intended to remain in the body permanently. For  
563 a wound dressing containing both drug and device components, you would identify the  
564 specific amount of the drug contained in the device, and that it would be applied  
565 topically to the specific type of wound your product is intended to treat. Finally, if  
566 your product is an injectable drug, you would explain that the delivery device would  
567 be used to subcutaneously (intramuscularly, intravenously, etc.) inject a specific dose  
568 of the drug.  
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### **11. Related Products.** Section 3.7(c)(2)(xii)

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572 If you think there are other products like yours, or other products with related  
573 components, you should briefly explain what they are, how they are regulated, and  
574 their regulatory status (e.g., approved, investigational, etc.) so that we can consider  
575 them when making the assignment of your product. If you are not aware of other  
576 products like yours or other products with related components, you should state this in  
577 a sentence.  
578

### **12. Other Relevant Information.** Section 3.7(c)(2)(xiii)

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581 If you think there is anything else we should consider when determining the  
582 appropriate classification and/or assignment of your product, you should explain that  
583 in this portion of your RFD. For example, literature references describing the product,  
584 its components, and its modes of action are often helpful.  
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### **13. Sponsor's Recommendation.** Section 3.7(c)(3)

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588 The final section of an RFD provides you the opportunity to recommend the  
589 jurisdictional assignment of your product.  
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591 If your product is a single-entity (non-combination) product, you should explain why  
592 your product meets the statutory definition of a drug, device, or biological product.  
593 Based on this recommended classification, you should then state your  
594 recommendation whether CBER, CDER, or CDRH should regulate it. Your  
595 classification recommendation should be based on the composition, modes of action,  
596 and intended use of your product. OCP's website has a variety of information on

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597 product jurisdiction to help sponsors understand what types of products are regulated  
598 by CBER, CDER and CDRH.

599  
600 If your product is a combination product, you should explain which Center (CBER,  
601 CDER, or CDRH) should have the “lead” in the review of your product. This  
602 explanation should be based on the composition, intended use, modes of action, and  
603 the single mode of action that provides the most important therapeutic action of the  
604 product. If you do not believe that your combination product has a single mode of  
605 action that provides the most important therapeutic action of the product, then you  
606 should use the algorithm set forth in the PMOA Final Rule to make your  
607 recommendation of “lead” center (see Section 8 above).

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

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

616

## 617 **IV. CONCLUSION**

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

- 620 • A complete description of and/or composition of the product (what is your product?);
- 621 • The intended use/indications of the product (why would your product be used?);
- 622 • The modes of action of the product (how does your product work?);
- 623 • The PMOA of a combination product (what is your product’s most important  
624 therapeutic action?);
- 625 • The basis for your PMOA determination (including a summary of any developmental  
626 work or testing that helps describe your product’s modes of action and/or PMOA);
- 627 • The assignment algorithm (if appropriate); and
- 628 • Your jurisdictional recommendation (how do you think your product should be  
629 assigned, and why?).

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

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### **Appendix: RFD Screening Checklist**

- 634  
635  
636 \_\_\_\_: Original RFD not exceeding 15 pages, including attachments (3.7(c))  
637  
638 \_\_\_\_: The identity of the sponsor, including company name and address, establishment registration number,  
639 company contact person, and telephone number (3.7(c)(1))  
640  
641 \_\_\_\_: Description of the product (3.7(c)(2))  
642  
643 \_\_\_\_: Classification, name of the product, and all component products, if applicable (3.7(c)(2)(i))  
644  
645 \_\_\_\_: Common, generic, or usual name of the product and all component products (3.7(c)(2)(ii))  
646  
647 \_\_\_\_: Proprietary name of the product (3.7(c)(2)(iii))  
648  
649 \_\_\_\_: Identification of any component of the product that already has received premarket approval, is  
650 marketed as not being subject to premarket approval, or has received an investigational exemption. The  
651 identity of the sponsors, and the status of any discussions or agreements between the sponsors regarding the  
652 use of this product as a component of a new combination product (3.7(c)(2)(iv))  
653  
654 \_\_\_\_: Chemical, physical, or biological composition (3.7(c)(2)(v))  
655  
656 \_\_\_\_: Status and brief reports of the results of developmental work, including animal testing (3.7(c)(2)(vi))  
657  
658 \_\_\_\_: Description of the manufacturing processes, including the sources of all components (3.7(c)(2)(vii))  
659  
660 \_\_\_\_: Proposed use or indications (3.7(c)(2)(viii))  
661  
662 \_\_\_\_: Description of all known modes of action, the sponsor's identification of the single mode of action that  
663 provides the most important therapeutic action of the product, and the basis for that determination  
664 (3.7(c)(2)(ix))  
665  
666 \_\_\_\_: Schedule and duration of use (3.7(c)(2)(x))  
667  
668 \_\_\_\_: Dose and route of administration of drug or biologic (3.7(c)(2)(xi))  
669  
670 \_\_\_\_: Description of related products, including the regulatory status of those related products  
671 (3.7(c)(2)(xii))  
672  
673 \_\_\_\_: The sponsor's recommendation as to which agency component should have primary jurisdiction based  
674 on the mode of action that provides the most important therapeutic action of the combination product.  
675 (3.7(c)(3))  
676  
677 \_\_\_\_: For combination products where the mode of action that provides the most important therapeutic  
678 action cannot be determined with reasonable certainty, the sponsor's recommendation must be based on the  
679 assignment algorithm and an assessment of the assignment of other combination products the sponsor wishes  
680 FDA to consider during the assignment of its combination product. (3.7(c)(3))  
681 \_\_\_\_: 1<sup>st</sup> step of assignment algorithm: assignment of other combination products presenting similar safety  
682 and effectiveness questions  
683 \_\_\_\_: 2<sup>nd</sup> step of assignment algorithm: most expertise related to the most significant safety and  
684 effectiveness questions