

(1) If the petition is to add use of a noninvestigational product, the petitioner must submit compelling evidence that:

(i) Substantial technical barriers exist to formulating the product without ODSs;

(ii) The product will provide an unavailable important public health benefit; and

(iii) Use of the product does not release cumulatively significant amounts of ODSs into the atmosphere or the release is warranted in view of the unavailable important public health benefit.

(2) If the petition is to add use of an investigational product, the petitioner must submit compelling evidence that:

(i) Substantial technical barriers exist to formulating the investigational product without ODSs;

(ii) A high probability exists that the investigational product will provide an unavailable important public health benefit; and

(iii) Use of the investigational product does not release cumulatively significant amounts of ODSs into the atmosphere or the release is warranted in view of the high probability of an unavailable important public health benefit.

(g) Any person may file a petition under part 10 of this chapter to request that FDA initiate rulemaking to amend paragraph (e) of this section to remove an essential use. FDA may initiate notice-and-comment rulemaking to remove an essential use on its own initiative or in response to a petition, if granted. If the petition is to remove an essential use from paragraph (e) of this section, the petitioner must submit compelling evidence of any one of the following criteria:

(1) The product using an ODS is no longer being marketed; or

(2) After January 1, 2005, FDA determines that the product using an ODS no longer meets the criteria in paragraph (f) of this section after consultation with a relevant advisory committee(s) and after an open public meeting; or

(3) For individual active moieties marketed as ODS products and represented by one new drug application (NDA):

(i) At least one non-ODS product with the same active moiety is marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the ODS product containing that active moiety;

(ii) Supplies and production capacity for the non-ODS product(s) exist or will exist at levels sufficient to meet patient need;

(iii) Adequate U.S. postmarketing use data is available for the non-ODS product(s); and

(iv) Patients who medically required the ODS product are adequately served by the non-ODS product(s) containing that active moiety and other available products; or

(4) For individual active moieties marketed as ODS products and represented by two or more NDAs:

(i) At least two non-ODS products that contain the same active moiety are being marketed with the same route of delivery, for the same indication, and with approximately the same level of convenience of use as the ODS products; and

(ii) The requirements of paragraphs (g)(3)(ii), (g)(3)(iii), and (g)(3)(iv) of this section are met.

[67 FR 48384, July 24, 2002, as amended at 71 FR 70873, Dec. 7, 2006; 70 FR 17192, Apr. 4, 2005; 75 FR 19241, Apr. 14, 2010; 73 FR 69552, Nov. 19, 2008]

EFFECTIVE DATE NOTE: At 75 FR 19241, Apr. 14, 2010, §2.125 was amended by removing and reserving paragraphs (e)(2)(iv) and (e)(4)(viii) effective Dec. 31, 2013.

PART 3—PRODUCT JURISDICTION

Subpart A—Assignment of Agency Component for Review of Premarket Applications

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Subpart B [Reserved]

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AUTHORITY: 21 U.S.C. 321, 351, 353, 355, 360, 360c–360f, 360h–360j, 360gg–360ss, 360bbb–2, 371(a), 379e, 381, 394; 42 U.S.C. 216, 262, 264.

SOURCE: 56 FR 58756, Nov. 21, 1991, unless otherwise noted.

Subpart A—Assignment of Agency Component for Review of Premarket Applications

§ 3.1 Purpose.

This regulation relates to agency management and organization and has two purposes. The first is to implement section 503(g) of the act, as added by section 16 of the Safe Medical Devices Act of 1990 (Public Law 101–629) and amended by section 204 of the Medical Device User Fee and Modernization Act of 2002 (Public Law 107–250), by specifying how FDA will determine the organizational component within FDA designated to have primary jurisdiction for the premarket review and regulation of products that are comprised of any combination of a drug and a device; a device and a biological; a biological and a drug; or a drug, a device and a biological. This determination will eliminate, in most cases, the need to receive approvals from more than one FDA component for such combination products. The second purpose of this regulation is to enhance the efficiency of agency management and operations by providing procedures for determining which agency component will have primary jurisdiction for any drug, device, or biological product where such jurisdiction is unclear or in dispute. Nothing in this section prevents FDA from using any agency resources it deems necessary to ensure adequate review of the safety and effectiveness of any product, or the substantial equivalence of any device to a predicate device.

[56 FR 58756, Nov. 21, 1991, as amended by 68 FR 37077, June 23, 2003]

§ 3.2 Definitions.

For the purpose of this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act.

(b) *Agency component* means the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Drug

Evaluation and Research, or alternative organizational component of the agency.

(c) *Applicant* means any person who submits or plans to submit an application to the Food and Drug Administration for premarket review. For purposes of this section, the terms “sponsor” and “applicant” have the same meaning.

(d) *Biological product* has the meaning given the term in section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)).

(e) *Combination product* includes:

(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.

(f) *Device* has the meaning given the term in section 201(h) of the act.

(g) *Drug* has the meaning given the term in section 201(g)(1) of the act.

(h) *FDA* means Food and Drug Administration.

(i) *Letter of designation* means the written notice issued by the product

jurisdiction officer specifying the agency component with primary jurisdiction for a combination product.

(j) *Letter of request* means an applicant's written submission to the product jurisdiction officer seeking the designation of the agency component with primary jurisdiction.

(k) *Mode of action* is 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 combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body. When making assignments of combination products under this part, the agency will consider three types of mode of action: The actions provided by a biological product, a device, and a drug. 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 identifiable mode of action.

(1) A constituent part has a biological product mode of action if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings, as described in section 351(i) of the Public Health Service Act.

(2) A constituent part has a device mode of action if it meets the definition of device contained in section 201(h)(1) to (h)(3) of the act, it does not have a biological product mode of action, and it does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and is not dependent upon being metabolized for the achievement of its primary intended purposes.

(3) A constituent part has a drug mode of action if it meets the definition of drug contained in section 201(g)(1) of the act and it does not have a biological product or device mode of action.

(l) *Premarket review* includes the examination of data and information in an application for premarket review described in sections 505, 510(k), 513(f), 515, or 520(g) or 520(l) of the act or section 351 of the Public Health Service Act of data and information contained in any investigational new drug (IND) application, investigational device exemption (IDE), new drug application (NDA), biologics license application, device premarket notification, device reclassification petition, and premarket approval application (PMA).

(m) *Primary mode of action* is 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.

(n) *Product* means any article that contains any drug as defined in section 201(g)(1) of the act; any device as defined in section 201(h) of the act; or any biologic as defined in section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)).

(o) *Product jurisdiction officer* is the person or persons responsible for designating the component of FDA with primary jurisdiction for the premarket review and regulation of a combination product or any product requiring a jurisdictional designation under this part.

(p) *Sponsor* means "applicant" (see § 3.2(c)).

[56 FR 58756, Nov. 21, 1991 as amended at 64 FR 398, Jan. 5, 1999; 64 FR 56447, Oct. 20, 1999; 68 FR 37077, June 23, 2003; 70 FR 49861, Aug. 25, 2005]

§ 3.3 Scope.

This section applies to:

- (a) Any combination product, or
- (b) Any product where the agency component with primary jurisdiction is unclear or in dispute.

§ 3.4 Designated agency component.

(a) To designate the agency component with primary jurisdiction for the premarket review and regulation of a combination product, the agency shall determine the primary mode of action

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of the product. Where the primary mode of action is that of:

(1) A drug (other than a biological product), the agency component charged with premarket review of drugs shall have primary jurisdiction;

(2) A device, the agency component charged with premarket review of devices shall have primary jurisdiction;

(3) A biological product, the agency component charged with premarket review of biological products shall have primary jurisdiction.

(b) In some situations, it is not possible to determine, with reasonable certainty, which one mode of action will provide a greater contribution than any other mode of action to the overall therapeutic effects of the combination product. In such a case, 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, the agency will 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.

(c) The designation of one agency component as having primary jurisdiction for the premarket review and regulation of a combination product does not preclude consultations by that component with other agency components or, in appropriate cases, the requirement by FDA of separate applications.

[56 FR 58756, Nov. 21, 1991, as amended at 70 FR 49861, Aug. 25, 2005]

§ 3.5 Procedures for identifying the designated agency component.

(a)(1) The Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Drug Evaluation and Research have entered into agreements clarifying product jurisdictional issues. These guidance documents are on display in the Division of Dockets Management (HFA-305), Food and Drug Ad-

ministration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and are entitled “Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health;” “Intercenter Agreement Between the Center for Devices and Radiological Health and the Center for Biologics Evaluation and Research;” “Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research.” The availability of any amendments to these intercenter agreements will be announced by FEDERAL REGISTER notice.

(2) These guidance documents describe the allocation of responsibility for categories of products or specific products. These intercenter agreements, and any amendments thereto, are nonbinding determinations designed to provide useful guidance to the public.

(3) The sponsor of a premarket application or required investigational filing for a combination or other product covered by these guidance documents may contact the designated agency component identified in the intercenter agreement before submitting an application of premarket review or to confirm coverage and to discuss the application process.

(b) For a combination product not covered by a guidance document or for a product where the agency component with primary jurisdiction is unclear or in dispute, the sponsor of an application for premarket review should follow the procedures set forth in § 3.7 to request a designation of the agency component with primary jurisdiction before submitting the application.

[56 FR 58756, Nov. 21, 1991, as amended at 68 FR 24879, May 9, 2003]

§ 3.6 Product jurisdiction officer.

The Office of Combination Products (Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, rm. 5129, Silver Spring, MD 20993-0002, 301-796-8930, e-mail: *combination@fda.gov*, is the designated product jurisdiction officer.

[68 FR 37077, June 23, 2003, as amended at 71 FR 16033, Mar. 30, 2006; 75 FR 13678, Mar. 23, 2010]

§ 3.7 Request for designation.

(a) Who should file: the sponsor of:

(1) Any combination product the sponsor believes is not covered by an intercenter agreement; or

(2) Any product where the agency component with primary jurisdiction is unclear or in dispute.

(b) When to file: a sponsor should file a request for designation before filing any application for premarket review, whether an application for marketing approval or a required investigational notice. Sponsors are encouraged to file a request for designation as soon as there is sufficient information for the agency to make a determination.

(c) What to file: an original and two copies of the request for designation must be filed. The request for designation must not exceed 15 pages, including attachments, and must set forth:

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

(2) A description of the product, including:

(i) Classification, name of the product and all component products, if applicable;

(ii) Common, generic, or usual name of the product and all component products;

(iii) Proprietary name of the product;

(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.

(v) Chemical, physical, or biological composition;

(vi) Status and brief reports of the results of developmental work, including animal testing;

(vii) Description of the manufacturing processes, including the sources of all components;

(viii) Proposed use or indications;

(ix) Description of all known modes of action, the sponsor's identification of the single mode of action that pro-

vides the most important therapeutic action of the product, and the basis for that determination.

(x) Schedule and duration of use;

(xi) Dose and route of administration of drug or biologic;

(xii) Description of related products, including the regulatory status of those related products; and

(xiii) Any other relevant information.

(3) 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. If the sponsor cannot determine with reasonable certainty which mode of action provides the most important therapeutic action of the combination product, the sponsor's recommendation must be based on the assignment algorithm set forth in § 3.4(b) and an assessment of the assignment of other combination products the sponsor wishes FDA to consider during the assignment of its combination product.

(d) Where to file: all communications pursuant to this subpart shall be addressed to the attention of the product jurisdiction officer. Such a request, in its mailing cover should be plainly marked "Request for Designation." Concurrent submissions of electronic copies of Requests for Designation may be addressed to *combination@fda.gov*.

[56 FR 58756, Nov. 21, 1991, as amended at 68 FR 37077, June 23, 2003; 70 FR 49861, Aug. 25, 2005]

§ 3.8 Letter of designation.

(a) Each request for designation will be reviewed for completeness within 5 working days of receipt. Any request for designation determined to be incomplete will be returned to the applicant with a request for the missing information. The sponsor of an accepted request for designation will be notified of the filing date.

(b) Within 60 days of the filing date of a request for designation, the product jurisdiction officer will issue a letter of designation to the sponsor, with copies to the centers, specifying the agency component designated to have primary jurisdiction for the premarket review and regulation of the product at issue,

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and any consulting agency components. The product jurisdiction officer may request a meeting with the sponsor during the review period to discuss the request for designation. If the product jurisdiction officer has not issued a letter of designation within 60 days of the filing date of a request for designation, the sponsor's recommendation of the center with primary jurisdiction, in accordance with §3.7(c)(3), shall become the designated agency component.

(c) Request for reconsideration by sponsor: If the sponsor disagrees with the designation, it may request the product jurisdiction officer to reconsider the decision by filing, within 15 days of receipt of the letter of designation, a written request for reconsideration not exceeding 5 pages. No new information may be included in a request for reconsideration. The product jurisdiction officer shall review and act on the request in writing within 15 days of its receipt.

§3.9 Effect of letter of designation.

(a) The letter of designation constitutes an agency determination that is subject to change only as provided in paragraph (b) of this section.

(b) The product jurisdiction officer may change the designated agency component with the written consent of the sponsor, or without its consent to protect the public health or for other compelling reasons. A sponsor shall be given 30 days written notice of any proposed nonconsensual change in designated agency component. The sponsor may request an additional 30 days to submit written objections, not to exceed 15 pages, to the proposed change, and shall be granted, upon request, a timely meeting with the product jurisdiction officer and appropriate center officials. Within 30 days of receipt of the sponsor's written objections, the product jurisdiction officer shall issue to the sponsor, with copies to appropriate center officials, a written determination setting forth a statement of reasons for the proposed change in designated agency component. A nonconsensual change in the designated agency component requires the concur-

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rence of the Principal Associate Commissioner.

[56 FR 58756, Nov. 21, 1991, as amended at 68 FR 37077, June 23, 2003]

§3.10 Stay of review time.

Any filing with or review by the product jurisdiction officer stays the review clock or other established time periods for agency action for an application for marketing approval or required investigational notice during the pendency of the review by the product jurisdiction officer.

Subpart B [Reserved]

PART 4—REGULATION OF COMBINATION PRODUCTS

EFFECTIVE DATE NOTE: 78 FR 4321, Jan. 22, 2013, Part 4 was added, effective July 22, 2013.

Subpart A—Current Good Manufacturing Practice Requirements for Combination Products

Sec.

- 4.1 What is the scope of this subpart?
- 4.2 How does FDA define key terms and phrases in this subpart?
- 4.3 What current good manufacturing practice requirements apply to my combination product?
- 4.4 How can I comply with these current good manufacturing practice requirements for a co-packaged or single-entity combination product?

Subpart B [Reserved]

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360b-360f, 360h-360j, 360l, 360hh-360ss, 360aaa-360bbb, 371(a), 372-374, 379e, 381, 383, 394; 42 U.S.C. 216, 262, 263a, 264, 271.

SOURCE: 78 FR 4321, Jan. 22, 2013, unless otherwise noted.

Subpart A—Current Good Manufacturing Practice Requirements for Combination Products

§4.1 What is the scope of this subpart?

This subpart applies to combination products. It establishes which current good manufacturing practice requirements apply to these products. This