

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 3

Docket No. 2004N-0194

Definition of Primary Mode of Action of a Combination Product

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its combination product regulations to define "mode of action" and "primary mode of action" (PMOA). Along with these definitions, the proposed rule sets forth an algorithm the agency would use to assign combination products to an agency component for regulatory oversight when the agency cannot determine with reasonable certainty which mode of action provides the most important therapeutic action of the combination product. Finally, the proposed rule would also require a sponsor to base its recommendation of the agency component with primary jurisdiction for regulatory oversight of its combination product by using the PMOA definition and, if appropriate, the assignment algorithm. The proposed rule is intended to promote the public health by codifying the agency's criteria for the assignment of combination products in transparent, consistent, and predictable terms.

DATES: Submit written comments by July 6, 2004. See section IX of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: You may submit comments, identified by Docket No. 2004N-0194, by any of the following methods:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.
- Agency Web site: <http://www.fda.gov/dockets/ecomments>. Follow the instructions for submitting comments on the agency Web site.
- E-mail: fdadockets@oc.fda.gov. Include Docket No. 2004N-0194 in the subject line of your e-mail message.
- FAX: 301-827-6870.
- Mail/Hand delivery/Courier For paper, disk, or CD-ROM submissions: Division of Dockets Management, 5630 Fishers Lane,

rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and Docket No. 2004N-0194 for this proposed rulemaking. All comments received will be posted without change to <http://www.fda.gov/dockets/ecomments>, including any personal information provided. For detailed instructions on submitting comments and additional information on the proposed rulemaking process, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.fda.gov/dockets/ecomments> and/or the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Leigh Hayes, Office of Combination Products (HFG-3), Food and Drug Administration, 15800 Crabbs Branch Way, suite 200, Rockville, MD 20855, 301-827-9229.

SUPPLEMENTARY INFORMATION:

I. Introduction

As set forth in part 3 (21 CFR part 3), a combination product is a product comprised of any combination of a drug and a device; a device and a biological product; a biological product and a drug; or a drug, a device, and a biological product. A combination product includes: (1) A product comprised of two or more regulated components, i.e., drug/device, biological product/device, drug/biological product, or drug/device/biological product, 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.

Section 503(g) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 353(g)) requires that FDA assign a component of the agency to have primary jurisdiction for the premarket review and regulation of a combination product. That assignment must be based upon a determination of the PMOA of the combination product. For example, if the primary mode of action of a combination product is that of a biological product, the product is to be assigned to the FDA component responsible for the premarket review of that biological product. FDA issued a final rule in 1991 establishing the procedures (the "request for designation" (RFD) process) for determining the assignment of combination products under part 3.

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) further modified section 503(g) of the act to require the establishment of an office (Office of Combination Products) within the Office of the Commissioner. The purpose of the Office of Combination Products is to ensure the prompt assignment of combination products to agency components, the timely and effective premarket review of such products, and consistent and appropriate postmarket regulation of combination products. MDUFMA also requires the agency to review each agreement, guidance, or practice specific to the assignment of combination products to agency components, consult with stakeholders and the directors of the agency centers, and determine whether to continue in effect, modify, revise, or eliminate such agreements, guidances, or practices.

Currently, § 3.7 requires a sponsor submitting a request for designation to identify the PMOA of the combination product and recommend a lead agency component for its premarket review and regulation. The PMOA of a combination product, however, is not defined in the statute or regulations, and at times may be difficult to identify. Requests for assignment of combination products are usually submitted very early in a product's development. This practice is encouraged because it allows sponsors to begin working with an agency component as early in the development process as possible and to know the regulatory requirements for their products. For some products, though, the PMOA of the product is not readily apparent, to either FDA or the product sponsor, at the time the request for

assignment is submitted. Determining the PMOA of a combination product is also complicated for products that have two completely different modes of action, neither of which is subordinate to the other. In close cases, assignments may turn on subtle distinctions related to the determination of whether a mode of action is "primary," or not. The assignment process may appear to be unpredictable when two slightly different products are assigned to different agency components based on differences in their PMOAs.

To address these concerns, simplify the designation process for sponsors, and enhance the transparency, predictability, and consistency of the agency's assignment of combination products, FDA proposes to define "mode of action" and "primary mode of action." This proposal would merely clarify and codify principles the agency has generally used since section 503(g) of the act was issued in 1990.

II. Description of the Proposed Rule

A. Introduction

FDA proposes to amend its combination product regulations to create new definitions in § 3.2 of "mode of action" and "primary mode of action." This proposal also sets forth a two-tiered assignment algorithm in § 3.4, which the agency would use to determine assignment when it cannot determine which mode of action of a combination product provides the most important therapeutic action of the product. Finally, the rule proposes to require that sponsors base their recommendation of the agency component with primary jurisdiction for regulatory oversight of its product in terms of the PMOA definition and, if appropriate, the assignment algorithm.

This proposal would fulfill the statutory requirement to assign products based on their PMOA, and would use safety and effectiveness issues, as well as consistency with the regulation of similar products, to guide the assignment of products when the agency cannot determine which mode of action provides the most important therapeutic action of the combination product. It ensures that like products would be similarly assigned, and it allows new products for which the most important therapeutic action cannot be determined to be assigned to the most appropriate agency component based on the most significant safety and effectiveness issues they present. In addition, by providing a more defined framework for the assignment process, a codified definition of PMOA would further MDUFMA's requirement that the agency

ensure prompt assignment of combination products. Also, by issuing this proposal, the agency furthers MDUFMA's requirement that it review practices specific to the assignment of combination products, consult with stakeholders and center directors, and make a determination whether to modify those practices.

Not only would this proposal fulfill the objectives set forth in the preceding paragraph, it would do so in a way that remains consistent with agency practice regarding the assignment of combination products. This rulemaking would thus codify criteria the agency has generally used since 1991. The proposed rule, when finalized, will affect RFD submissions received by the agency on or after the effective date of any final rule issued as a result of this proposed rule.

B. What Are "Mode of Action" and "Primary Mode of Action"

1. Definitions

a. *Mode of action* would be defined as "the means by which a product achieves a therapeutic effect." For purposes of this definition, "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. 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.

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(a) 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 (21 U.S.C.321(h)(1) to (h)(3)), 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.

b. *Primary mode of action* would be defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product." This would be the mode of action that is expected to make the greatest contribution to the overall 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.

2. Stakeholders' Comments

FDA held public hearings on May 15, 2002, and on November 25, 2002, and a public workshop on July 8, 2003, to discuss various issues pertaining to combination products, including the assignment of products to an agency component for regulatory oversight. Stakeholders also provided a number of written comments to the docket, which FDA opened to further facilitate the discussion of PMOA issues. The agency received many thoughtful comments from the stakeholders who participated in those discussions, as well as from stakeholders who submitted written comments to the docket, including some pertaining to a definition of PMOA. The November 2002 meeting in particular addressed questions regarding assignment. Some questions raised at the meeting were:

- What factors should FDA consider in determining the PMOA of a combination product?
- In instances where the PMOA of the combination product cannot be determined with certainty, what other factors should the agency consider in assigning primary jurisdiction?
- Is there a hierarchy among these additional factors that should be considered in order to ensure adequate review and regulation (e.g., which component presents greater safety questions?)

Several common themes emerged from these comments regarding the agency's definition of PMOA. For instance, many stakeholders felt that the agency should base any proposed definition of PMOA on the combination product as a whole. FDA agrees, and has crafted the definition so that PMOA would be based on the most important therapeutic action of the combination product as a whole. Furthermore, as

detailed in the section regarding the assignment algorithm, the agency expects to consider the combination product as a whole when the agency cannot determine with reasonable certainty the most important therapeutic action of the product.

Another recurring theme among a number of comments concerned the intended use of the product. Several stakeholders expressed their desire that FDA construct a definition of PMOA around this concept. As stated previously, mode of action would be defined as the means by which a product achieves a therapeutic effect. For over a decade, the agency has considered in its determination of PMOA an assessment of the product's intended use, as well as its effect on the diagnosis, cure, mitigation, treatment, or prevention disease, and its effect on the structure or function of the body. The agency intends to continue this practice, and has structured the proposed definition of PMOA to include consideration of the intended use of a combination product.

C. What If We Are Unable to Determine Which Mode of Action of a Combination Product is its Most Important Therapeutic Action? Assignment Algorithm (For easy reference, a diagram of the assignment algorithm is included at the end of this preamble.)

In certain cases, it is not possible for either FDA or the product sponsor to determine, at the time a request is submitted, which mode of action of a combination product provides the most important therapeutic effect. 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. To assign such products with as much consistency, predictability, and transparency as possible, the agency proposes the application of an algorithm to determine PMOA in those instances, to be codified at § 3.4(b). In those cases, the agency would 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), the agency would assign the combination product

to the agency component with the most expertise to evaluate the most significant safety and effectiveness questions presented by the combination product.

1. Stakeholders' Comments

As previously mentioned, FDA held public hearings on May 15, 2002, and on November 25, 2002, and a public workshop on July 8, 2003, to discuss various issues pertaining to combination products, including the assignment of products to an agency component for regulatory oversight. Stakeholders also provided a number of written comments to the docket, which FDA opened to further facilitate the discussion of PMOA issues.

As with the definition for PMOA, several common themes emerged from these comments regarding possible criteria for the algorithm. For example, several stakeholders suggested that the agency consider similarly situated products when assigning a combination product to a lead agency component. We agree that both precedent and expertise are important when assigning a combination product to a particular agency component, and propose that this criterion be placed first in the algorithm's decisionmaking hierarchy. Therefore, if the agency could not determine with reasonable certainty which mode of action provides the most important therapeutic effect, the agency would assign the combination product to the agency component that regulates combination products that present similar safety and effectiveness questions for the product as a whole. In other words, FDA would consider whether there is an agency component with direct experience related to the combination product in question. We note, too, that application of this criterion would require consideration of the product as a whole, rather than by its constituent parts, which is another common recommendation of stakeholders.

Another factor many stakeholders asked the agency to consider when developing an assignment algorithm relates to the relative risks of a particular combination product. We agree that this is an important consideration, and propose that the second criterion take into account the most significant questions of safety and effectiveness presented by a combination product. Therefore, if the agency cannot determine which mode of action makes the greatest contribution to its overall therapeutic effects, and the agency has no direct experience with combination products that as a whole present similar safety and effectiveness

questions as the combination product at issue, the agency would assign the product to the agency component with the most expertise related to the most significant questions of safety and effectiveness of the product. In situations where the new product is the first such combination product, or where another combination product exists but the intended use, design, formulation, etc. for this combination product raise different safety and effectiveness questions, FDA would assign the product to the agency component with the most expertise to evaluate the most significant safety and effectiveness issues raised by the product.

2. Application of Proposed Definitions and Proposed Algorithm: Examples¹

If the suggested definitions in the preceding section were applied to these products, the results would be as follows:

a. *Conventional drug-eluting stent*—a vascular stent provides a mechanical scaffold to keep a vessel open while a drug is slowly released from the stent to prevent the buildup of new tissue that would re-occlude the artery.

PMOA Analysis—Which Mode of Action Provides the Most Important Therapeutic Action of the Combination Product?

In this case, the product has two modes of action. One action of the vascular stent is to provide a physical scaffold to be implanted in a coronary artery to improve the resultant arterial luminal diameter following angioplasty. Another action of the product is the drug action, with the intended effect of reducing the incidence of restenosis and the need for target lesion revascularization.

Assignment of Lead Agency Component: Center for Devices and Radiological Health (CDRH)—The product's PMOA is attributable to the device component's function of physically maintaining vessel lumen patency, while the drug plays a secondary role in reducing restenosis caused by the proliferative response to the stent implantation, augmenting the safety and/or effectiveness of the uncoated stent. Accordingly, FDA would assign the product to CDRH for premarket review and regulation because the device component provides the most important therapeutic action of the product. It is unnecessary to proceed to the assignment algorithm because it is possible to determine which mode of action provides the most important

¹ As stated previously, a copy of the proposed algorithm is attached at the end of this preamble.

therapeutic action of this particular combination product.

b. *Drug eluting disc*—a surgically implanted disc contains a drug that is slowly released for prolonged, local delivery of chemotherapeutic agents.

PMOA Analysis—Which Mode of Action Provides the Most Important Therapeutic Action of the Combination Product?

In this case, the product has two modes of action. This product has a device mode of action because it is surgically implanted in the body and is designed for controlled drug release, thus affecting the structure of the body and treating disease. Another mode of action is the drug action, with the intended effect of preventing tumor recurrence at the implant site.

Assignment of Lead Agency Component: Center for Drug Evaluation and Research (CDER)—Though the product has a device mode of action, the product's PMOA is attributable to the drug component's function of preventing tumor recurrence at the implant site. Accordingly, we would assign the product to CDER for premarket review and regulation because the drug component provides the most important therapeutic action of the product. It is unnecessary to proceed to the assignment algorithm because it is possible to determine which mode of action provides the most important therapeutic action of this particular product.

c. *Contact lens combined with drug to treat glaucoma*—in this case, a contact lens is placed in the eye to correct vision. The contact lens also contains a drug to treat glaucoma that will be delivered from the lens to the eye.

PMOA Analysis—Which Mode of Action Provides the Most Important Therapeutic Action of the Combination Product?

This product has two modes of action. One action of the product is the device action, to correct vision. Another action of the product is a drug action, to treat glaucoma. Though administration through a contact lens is not necessary for the drug's delivery, the combination product allows a patient requiring vision correction to receive glaucoma treatment without having to undertake a more complicated daily drug regimen. Here, both actions of the product are independent, and neither appears to be subordinate to the other.

Because it is not possible to determine which mode of action provides the greatest contribution to the overall therapeutic effects of the combination product, it is necessary to apply the assignment algorithm.

Assignment Algorithm:

Is There an Agency Component That Regulates Other Combination Products That Present Similar Questions of Safety and Effectiveness With Regard to the Combination Product as a Whole?

CDRH regulates devices intended to correct vision. CDER regulates drugs intended to treat glaucoma. In this hypothetical example, no combination product intended to treat these different conditions simultaneously has yet been submitted to the agency for review. Though both CDER and CDRH regulate products that raise similar safety and effectiveness questions with regard to the constituent parts of the product, neither agency component regulates combination products that present similar safety and effectiveness questions with regard to the product as a whole.

Because there is no agency component that regulates products that present similar safety and effectiveness questions with regard to the product as a whole, it is necessary to apply the second criterion of the hierarchy.

Which Agency Component Has the Most Expertise Related to the Most Significant Safety and Effectiveness Questions Presented by the Combination Product?

Assignment of Lead Agency Component: CDER—Because there is no agency component that regulates combination products that present similar safety and effectiveness issues with regard to the product as a whole, the agency would consider which agency component has the most expertise related to the most significant safety and effectiveness questions presented by the product. In this hypothetical example, 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 routine. Based on the application of this criterion, this product would be assigned to CDER because CDER has the most expertise related to these issues.²

D. How Will the PMOA Definition and Assignment Algorithm Affect the Contents of My RFD Submission?

A sponsor would continue to submit its assessment of PMOA and its recommendation of lead agency component for regulatory oversight of

² Had this been the second such product, it would be assigned to CDER based on the first criterion, assuming the first such product had also been assigned to CDER using the second criterion.

its combination product. These requirements are not new; they are currently codified at § 3.7(c)(2)(ix) and (c)(3). Under this rule, however, a sponsor would present its recommendation of lead agency component in accordance with the PMOA definition of proposed § 3.2(m) and, if appropriate, the assignment algorithm of proposed § 3.4(b). Because this definition and the algorithm set forth a more defined framework on which to base a recommendation, the agency believes that these provisions will make it easier for sponsors to present their analysis of a product's PMOA.

III. Legal Authority

The agency derives its authority to issue the regulations found in part 3 from 21 U.S.C. 321, 351, 353, 355, 360, 360c–360f, 360h–360j, 360gg–360ss, 371(a), 379e, 381, 394; 42 U.S.C. 216, 262, and 264 as stated in the Code of Federal Regulations. As stated previously in this document, Congress expressly directed FDA to assign combination products to the appropriate agency component for premarket review and regulation based on the agency's assessment of PMOA as set forth in section 503(g) of the act. Under section 701 of the act (21 U.S.C. 371) and for the efficient enforcement of the act, FDA has the authority to define and codify "mode of action" and PMOA and to issue the assignment algorithm.

IV. Environmental Impact

FDA has determined under 21 CFR 25.30(a) and (k), and 25.32(g) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Paperwork Reduction of 1995

FDA tentatively concludes that the changes to the regulations on combination products proposed in this document are not subject to review by the Office of Management and Budget (OMB) because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The information collected under part 3 is currently approved under OMB control number 0910–0523. This proposal does not constitute an additional paperwork burden.

VI. Federalism

FDA has analyzed this proposed rule in accordance with the principles set

forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VII. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation) in any one year. Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the agency must analyze whether a rule may have a substantial impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact.

The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive order and these two statutes. The proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. No further analysis is required under the Regulatory Flexibility Act because the agency has determined that these proposed rule amendments have no compliance costs and will not have a significant effect on a substantial number of small entities. Therefore the agency certifies they will

not have a significant economic impact on a substantial number of small entities.

This proposed rule also does not trigger the requirements for a written statement under section 202(a) of the Unfunded Mandates Reform Act because it does not impose a mandate that results in expenditure of \$100 million or more by State, local, and tribal governments in the aggregate, or by the private sector in any one year.

B. The Rationale Behind This Proposed Rule

The purpose of the proposed rule amendments is twofold: (1) To codify the definition of PMOA, a criterion the agency has used for more than a decade when assigning combination products to agency components for regulatory oversight; and (2) to simplify the designation process by providing a defined framework that sponsors may use when recommending and/or considering the PMOA and assignment of a combination product.

Indeed, many stakeholders have requested that the agency propose a rule defining PMOA because, without a definition of this statutory criterion, the assignment process has at times appeared to lack transparency. We believe that the proposal addresses many of the concerns stakeholders have expressed regarding the assignment process. Moreover, we have incorporated many of the suggestions stakeholders have provided regarding the PMOA definition and assignment algorithm.

The codification of these principles would also simplify the designation process for sponsors. For years, a sponsor has been required to determine PMOA and make a recommendation of lead agency component for regulatory oversight of its combination product, without a codified definition of PMOA. When the rule is finalized, a sponsor would be able to base its determination of PMOA and recommendation of lead agency component for regulatory oversight of its product on defined factors.

As mentioned previously in this proposal, the amendments proposed here would fulfill the statutory requirement to assign products based on their PMOA, and would use safety and effectiveness issues as well as consistency with the regulation of similar products to guide the assignment of products when the agency cannot determine which mode of action provides the most important therapeutic action of a combination product. It ensures that like products would be similarly assigned and regulated, and it

allows new products for which the most important therapeutic action cannot be determined to be assigned to the most appropriate agency component based on the most significant safety and effectiveness issues they present. In addition, by providing a more defined framework for the assignment process, a codified definition of PMOA would further MDUFMA's requirement that the agency ensure prompt assignment of combination products. Also, by issuing this proposal, the agency furthers MDUFMA's requirement that it review practices specific to the assignment of combination products, consult with stakeholders and center directors, and make a determination whether to modify those practices.

In general, the agency believes the proposed rule will have no compliance costs and pose no additional burden to industry.

VIII. Request for Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

IX. Proposed Effective Date

The agency is proposing that any final rule that may issue based upon this proposed rule become effective 90 days after its date of publication in the **Federal Register**.

List of Subjects in 21 CFR Part 3

Administrative practice and procedure, Biologics, Drugs, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 3 be amended as follows:

PART 3—PRODUCT JURISDICTION

1. The authority citation for 21 CFR part 3 is revised to read as follows:

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

2. Section 3.2 is amended by redesignating paragraph (k) as paragraph (l), paragraph (l) as paragraph (n), paragraph (m) as paragraph (o),

paragraph (n) as paragraph (p); and by adding new paragraphs (k) and (m) to read as follows:

§ 3.2 Definitions.

(k) Mode of action is the means by which a product achieves a therapeutic effect. 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.

(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 therapeutic effects of the combination product.

3. Section 3.4 is amended by redesignating paragraph (b) as paragraph (c) and by adding a new paragraph (b) to read as follows:

§ 3.4 Designated agency component.

(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. Then, 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.

4. Section 3.7 is amended by revising paragraphs (c)(2)(ix) and (c)(3) to read as follows:

§ 3.7 Request for designation.

(c) * * *

(2) * * *

(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) 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.

Dated: May 3, 2004.

William K. Hubbard, Associate Commissioner for Policy and Planning.

Note: The following appendix will not appear in the Code of Federal Regulations.

PRIMARY MODE OF ACTION ASSIGNMENT ALGORITHM

