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: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its combination product regulations to define ‘‘mode of action’’ (MOA) and ‘‘primary mode of action’’ (PMOA). Along with these definitions, the final rule sets forth an algorithm the agency will 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 final rule will 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 final 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: The regulation is effective [*insert date 90 days after date of publication in the* **Federal Register**].

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, 301–427–1934.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of May 7, 2004 (69 FR 25527), FDA published a proposed rule that proposed to define ‘‘mode of action’’ (MOA) and ‘‘primary mode of action’’ (PMOA) (the proposed rule). Along with these definitions, the proposal set forth an algorithm the agency proposed to 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 proposal put forth a requirement that a sponsor make 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.

As set forth in part 3 (21 CFR part 3), and as described in the proposed rule, 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 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 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. 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, to simplify the designation process for sponsors, and to enhance the transparency, predictability, and consistency of the agency's assignment of combination products, FDA is issuing this final rule to define ''mode of action'' and ''primary mode of action.'' This final rule will clarify and codify principles the agency has generally used since section 503(g) of the act was enacted in 1990.

II. Description of the Final Rule

A. Introduction

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

This final rule will fulfill the statutory requirement to assign products based on their PMOA, and will 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 with reasonable certainty 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 with reasonable certainty 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 will further MDUFMA's requirement that the agency ensure prompt assignment of combination products. Also, by issuing this final rule, the agency adheres to 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 will this final rule fulfill the objectives set forth in the preceding paragraph, it will do so in a way that remains consistent with agency practice regarding the assignment of combination products. This rulemaking will codify criteria the agency has generally used since 1990. The final rule will apply to RFD submissions received by the agency on or after its effective date.

B. Stakeholder Input Prior to Proposed Rulemaking

Before issuance of the proposed rule, 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 dockets for these meetings, 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 as well as others regarding the criteria for the assignment algorithm if PMOA could not be determined. 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 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 is 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 will consider the combination product as a whole when the agency cannot determine with reasonable certainty the most important therapeutic action of the product.

Another theme recurring in 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 further described in this document, mode of action is defined as the means by which a product achieves its intended therapeutic effect or action. 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 of disease, and its effect on the structure or function of the body. The agency intends to continue this practice, and has structured the PMOA definition to include consideration of the intended use of a combination product.

As with the definition for PMOA, several common themes emerged from the comments regarding possible criteria to be considered when the product's most important therapeutic action cannot be determined with reasonable certainty. 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 we have placed this criterion first in the algorithm's decisionmaking hierarchy. Therefore, if the agency cannot determine with reasonable certainty which mode of action provides the most important therapeutic effect, the agency will 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.

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 take that into account with the second criterion, which considers the most significant questions of safety and effectiveness presented by a combination product. Therefore, if the agency cannot determine the most important therapeutic action of a combination product, and there is no agency component that regulates combination products that as a whole present similar safety and effectiveness questions as the combination product at issue, the agency will

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 will assign the product to the agency component with the most expertise to evaluate the most significant safety and effectiveness issues raised by the product.

C. What are ''Mode of Action'' and ''Primary Mode of Action?''

1. Definitions

a. *Mode of action* is defined as ''the means by which a product achieves its 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.'' 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.

- 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.

- 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.

- 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* is defined as ‘‘the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action that is expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.’’ As with ‘‘mode of action,’’ for purposes of PMOA, ‘‘therapeutic’’ effect or action includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body.

2. Assignment Algorithm

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 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. To assign such products with as much consistency, predictability, and transparency as possible, the agency

is issuing an algorithm to determine PMOA in those instances, to be codified at § 3.4(b). 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), 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.

III. Comments on the Proposed Rule and FDA's Responses

A. Background

FDA received comments from 17 stakeholders on the proposal, and almost all comments supported the rule in whole or in part. For example, one comment said that ''[o]verall* * * FDA's approach to primary mode of action faithfully implements the statute'' and that ''* * * FDA did a remarkable job in listening to the comments on mode of action and primary mode of action expressed by stakeholders in prior hearings.'' Another comment ''agree[d] with FDA's proposed definition of primary mode of action'' and ''praise[d] FDA for the simplicity and consistency of the proposed assignment algorithm.''

A few general themes emerged from the comments. Though generally supportive, the comments asked that FDA provide the following clarification: (1) Clarification of the role of precedent in determining a combination product's PMOA; (2) clarification of the role of intended use in determining a combination product's PMOA; (3) clarification of the status of the Intercenter

Agreements established in 1991 and their role in determining a product's PMOA; and (4) more examples to show how the PMOA definition might be applied to assign an agency component with primary jurisdiction for regulatory oversight of a combination product.

After reviewing the comments, FDA made two changes to the codified portion of this rule. The differences between the language in the proposed and final rules are set forth in italics as follows:

PMOA PROPOSED RULE	PMOA FINAL RULE
3.2 (k) Mode of action is the means by which a product achieves a therapeutic effect.	3.2 (k) Mode of action is the means by which a product achieves its intended therapeutic effect or action.
3.2(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.	3.2(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.

The agency has included ''intended therapeutic effect'' in the MOA definition and ''overall intended therapeutic effects'' in the PMOA definition. FDA made these changes because the ''intended'' therapeutic effect is a basic premise upon which the PMOA analysis is prefaced.

B. MOA, PMOA, and the Assignment Algorithm

1. MOA Definition

(Comment 1) Two comments stated that the definitions of drug, device, and biological product MOAs meant that any product with a biological product component could never be a drug or a device. One comment was concerned that this definition will cause certain cellular and tissue-based combination products to be regulated as biological products, or impact the classification of single entity products. One comment stated that products relying on cell or gene therapy would not have a biological product MOA based on the definition provided.

(Response) ‘‘Drug,’’ ‘‘device,’’ and ‘‘biological product’’ are defined by statute, and in defining MOA, FDA implemented those statutory definitions. The statute defines biological products based on their composition rather than their effects or mechanisms of action. FDA adhered to the definition of each article as set forth in the statutes, while focusing on the factors that the statutes identify as distinct for biological products, devices, and drugs. We followed this rationale because a biological product will also meet the statutory definition of drug or device, and a device will also meet the statutory definition of drug. Without mutually exclusive definitions of MOA, based on the unique characteristics of biological products and devices, it would be difficult to identify with certainty anything but a drug mode of action, since the statutory definition of drug is the broadest definition of the three. See, for example, 21 U.S.C. 321(g)(1)(C) (drug means articles other than food intended to affect the structure or any function of the body).

Additionally, it is important to keep in mind that this construction is used only to determine a product’s various modes of action to be considered in determining the PMOA. This construction does not necessarily determine how products will be regulated or the appropriate type of application for a combination product’s review.

Finally, we note that cell and gene therapy components typically have a biological product MOA. For example, certain cell and gene therapy components meet the definition of an ‘‘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 PHS Act.

(Comment 2) One comment stated that FDA should clarify that the definition of MOA relates only to the definition of each individual component.

The comment also provided alternative definitions for device MOA, drug MOA, and biological product MOA.

(Response) FDA agrees and clarifies that the definition of MOA relates only to the definitional status of each individual component. In addition, the comment suggested in part that FDA change ‘‘mode of action’’ to take into account a constituent part’s ‘‘‘intended’ therapeutic * * * effect * * *.’’ Because intended use is a basic tenet upon which the PMOA determination is premised, we agree, and have revised that definition accordingly. Another suggestion was that we change the word ‘‘action’’ to ‘‘function’’ in both the definition of MOA and PMOA. We have addressed that suggestion in the PMOA definition section. We have also addressed our rationale for the development of the definitions of device MOA, drug MOA, and biological product MOA in the response to comment 1 of this document.

(Comment 3) One comment stated that the proposed rule’s definition of mode of action ‘‘almost pre-supposes that a constituent part itself may be a combination of items,’’ and ‘‘a constituent part cannot itself be a combination product.’’

(Response) FDA agrees and here clarifies that constituent parts are components and not, in themselves, combination products.

(Comment 4) One comment stated that the definition of MOA of constituent parts should take into account the intended use of a combination product as a whole, and should not strictly rely on statutory definitions.

(Response) FDA agrees that the intended use of a combination product is an important factor in the PMOA analysis. Therefore, we have changed the codified definition of MOA to take into account a constituent part’s intended therapeutic effect or action. The MOA definition is subsumed into the PMOA

definition, where we take into account the combination product as a whole: ‘‘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*’’ (emphasis added).

(Comment 5) One comment stated that the statutory definitions of drug, device, and biological product should be updated to take into account emerging product technologies.

(Response) Revisions of the statutory definitions of drug, device, and biological product would require congressional action and are outside the scope of this rule.

(Comment 6) One comment stated that the language used to define device mode of action was inconsistent with the language defining drug mode of action.

(Response) FDA has reviewed the definitions, and disagrees. The agency believes that the language in the definitions clearly and consistently defines biological product, device, and drug modes of action for the purposes of part 3.

2. PMOA Definition

(Comment 7) One comment suggested that FDA change the word ‘‘action’’ in the MOA and PMOA definitions to ‘‘function.’’ The comment also suggested that the term ‘‘therapeutic’’ as in ‘‘therapeutic action’’ is more commonly used in connection with drugs and biological products. Consequently, the comment stated, use of the term ‘‘therapeutic action’’ might skew jurisdictional decisions away from devices and toward drugs and biological products.

(Response) FDA declines to make that change because we believe ‘‘action’’ is a more appropriate term than ‘‘function’’ as it pertains to the MOA and

PMOA definitions. The term ‘‘action’’ is intrinsic to ‘‘primary mode of action’’ and the term is therefore most closely tied to the statute.

Moreover, FDA stated in the May 2004 PMOA proposed rule that, for purposes of both the MOA and PMOA definitions, ‘‘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.’’ The term ‘‘therapeutic,’’ therefore, encompasses the actions or effects of drugs, biological products, and devices. As a result, the use of the term ‘‘therapeutic action’’ in the MOA and PMOA definitions will not cause jurisdictional determinations to be skewed toward drugs and biological products and away from devices.

(Comment 8) Two comments requested that FDA explain how it will determine the most important therapeutic action of a combination product.

(Response) As explained in new § 3.2(m), the most important therapeutic mode of action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. To make this determination, FDA would consider the intended use of the combination product as a whole, and how it achieves its overall intended therapeutic effect. Though not an exhaustive list (because each combination product presents different questions about its scientific characteristics and use), some other factors FDA would consider in determining a combination product’s most important therapeutic action include: 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, and any data or information provided by the applicant or 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.

(Comment 9) One comment requested that FDA clarify the meaning of ‘‘reasonable certainty.’’ Another comment expressed concern that the standard was subject to abuse.

(Response) In general, it would be possible to determine the PMOA of a combination product with ‘‘reasonable certainty’’ when the PMOA is not in doubt among knowledgeable experts, and can be resolved to an acceptable level in the minds of those experts based on the data and information available to FDA at the time an assignment is made. FDA believes that this standard provides adequate specificity and that it will be applied appropriately, not arbitrarily.

(Comment 10) Two comments stated that the PMOA definition should include the intended use of the product as a whole. In addition, one comment stated that, assuming we include intended use of the product as a whole and are guided by precedents, the use of the ‘‘reasonable certainty’’ standard is acceptable.

(Response) As stated in the proposal, FDA reviewed the vast majority of our prior jurisdictional determinations and found that those assignments would not have changed based on the definition of PMOA finalized here. The definition set forth here is intended to clarify and codify the principles that FDA has used since 1990 in making jurisdictional assignments. FDA agrees that intended use plays an important role in the PMOA analysis. Consequently, the revised definition of MOA will read: ‘‘*Mode of action* is the means by which a product achieves its intended therapeutic effect or action.’’ The MOA definition is subsumed into the PMOA definition, where we take into account

the combination product as a whole. Furthermore, we have revised the PMOA definition to include intended use as well: ‘‘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’’ (emphasis added).

(Comment 11) One comment stated that the intended use of a product should dictate its PMOA. In turn, PMOA should determine assignment of the product to an agency component for review and regulation, as well as the regulatory authorities to be applied. This comment also stated that the algorithm should be used only when PMOA cannot be determined, and if the algorithm is used to determine the jurisdiction of the product, two applications and two separate approvals would be necessary for its review.

(Response) As described previously in this document, FDA agrees that intended use plays an integral role in the PMOA analysis, and we have revised the MOA and PMOA definitions accordingly.

However, we do not require in this rule that PMOA dictates the regulatory authorities to be applied to a combination product’s review and regulation. The application of regulatory authorities to a combination product is outside the scope of this rule. The Safe Medical Devices Act of 1990 (SMDA) established a rule determining which ‘‘persons’’ would be responsible for regulating combination products. See 21 U.S.C. section 353(g)(1). This law addresses the agency component responsible for regulating a combination product, but does not address which authorities, including which application schemes, the persons identified must use to regulate the combination product.

Under this SMDA provision, the agency would decide the following: (1) Whether to recommend that a single application for the combination product

be used, and if so, what kind of application should be used new drug application (NDA), abbreviated new drug application (ANDA), biologics license application (BLA), 510(k), or premarket approval application (PMA); or (2) whether to require more than one application; for example, a BLA for the biological product component, and a PMA for the device component of a combination product. (See 21 CFR 3.4(b) (''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.''))

It also appears that the comment presupposes that FDA would not identify a PMOA if there are two independent modes of action. FDA disagrees. A combination product may have two independent modes of action, yet FDA still may be able to determine the product's most important therapeutic action with reasonable certainty. However, FDA's experience in evaluating combination products has shown that for a small subset of products, the most important therapeutic action is not determinable with reasonable certainty. Therefore, FDA needs a mechanism to ensure that these types of products are assigned with consistency, transparency, and predictability. Out of necessity and with the authority granted to the agency by Congress, FDA established the algorithm to accomplish these goals. Once an assignment is made under the algorithm, FDA will decide the number (one or more), and type, of applications that are necessary.

(Comment 12) One comment asked that FDA clarify whether PMOA determined designation only, or whether it also determined the controlling regulatory authorities and the degree of collaboration between Centers.

(Response) As stated in the response to Comment 11 of this document, FDA here clarifies that PMOA is determinative of assignment only.

3. Assignment Algorithm

a. *First criterion*.

(Comment 13) One comment suggested that we clarify that the term ‘‘direct experience,’’ as set forth in the proposed rule’s explanation of the algorithm, is not part of the analysis at the first tier of the algorithm.

(Response) The term ‘‘direct experience’’ is not part of the codified language used to describe the first tier of the algorithm to be used when the agency is unable to determine the PMOA with reasonable certainty. FDA here clarifies that its use of the term ‘‘direct experience’’ in the proposed rule’s explanation of the algorithm was simply a reference to the first criterion of the algorithm, which states that the agency will assign a 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.

(Comment 14) One comment asked how FDA will determine whether a product presents similar safety and effectiveness questions.

(Response) FDA will consider products the agency has already reviewed as well as products that are currently under review to determine whether a product presents similar safety and effectiveness questions. Though the examples are not intended to be exhaustive, FDA includes in the response to Comment 16 of this document the types of questions that FDA may consider, as appropriate, when making the determination of whether a combination product presents questions of safety and effectiveness that are similar to questions presented by other combination products.

b. *Second criterion*.

(Comment 15) One comment suggested that our use of the term ‘‘expertise’’ might cause divisiveness within FDA and industry. The comment recommended that the focus be on safety and effectiveness issues rather than ‘‘expertise.’’ In considering the most significant safety and effectiveness questions, the comment recommended that FDA make these judgments on a case-by-case basis.

(Response) FDA agrees that the focus here should be on the most significant safety and effectiveness issues presented by a combination product. Use of the term ‘‘expertise’’ is not meant to be divisive or imply a value judgment. Instead, the ‘‘expertise’’ criterion at this level is used merely as the most appropriate means to direct the assignment of a combination product based on the most significant safety and effectiveness issues it presents when no agency component has direct experience in the review of the product as a whole. FDA also agrees with the comment that significant safety and effectiveness issues should be considered on a case-by-case basis. As with jurisdictional determinations made prior to the issuance of this rule, FDA intends to make assignments by considering the unique issues raised by each individual combination product.

(Comment 16) Three comments asked that FDA explain how it would determine the most significant safety and effectiveness issues presented by the product. One comment suggested that the preamble to the proposal implied that FDA intended to base these determinations primarily on an assessment of the product’s ‘‘relative risks.’’ Another comment asked that FDA issue a guidance document to clarify the agency’s determination of the most significant safety and effectiveness issues.

(Response) FDA agrees that risk is not always the driving factor in determining appropriate jurisdiction; rather it is one factor that the agency may consider.

The questions listed in this response to comment 16 of this document are intended to further illustrate the kinds of issues FDA would consider when determining the most significant safety and effectiveness questions presented by a combination product, or whether a new combination product presents similar safety and effectiveness issues as a previous product. We note that the list of factors is not all-inclusive. FDA considers its ability to continue to assess the individual characteristics of particular products to be essential. This will allow the agency to respond to technological developments, scientific understanding, factual information concerning a specific product, or the composition, mechanism of action or intended use of a particular product. As described previously in this document, the need to consider appropriate issues on a case-by-case basis was supported by some of the comments. The questions are not listed in order of importance; indeed some factors may be weighted more than others depending on various issues presented by each individual combination product.

- What is the intended use of the product?
- What is the therapeutic effect of the product as a whole?
- Does the device component incorporate a novel or complex design or have the potential for clinically significant failure modes?
- Is this a new molecular entity or new formulation?
- Has the drug previously been approved as a generic drug?
- Does the drug have a narrow therapeutic index?
- Is the biological product component a particularly fragile molecule?

- How well understood are the product's components? Is one component relatively routine, while the other presents more significant safety and effectiveness issues due to the risks it poses, its effectiveness, or novelty?
- Which component raises greater risks?
- Has either of the components been previously approved or cleared?
- Is there a new indication, route of administration or a significant change in dose or use of one of the components, or are only secondary aspects of the labeling affected?

FDA is not issuing a guidance document on this topic at this time. However, FDA will take the suggestion under advisement, and will reconsider issuance of such guidance if it becomes apparent after implementation of the final rule that more clarification is needed.

(Comment 17) One comment recommended that FDA consider the ''least burdensome'' requirements of the device provisions of the act, as well as the ''Improving Innovation in Medical Technology'' and ''Critical Path to New Medical Products'' initiatives, which are specifically intended to advance innovation of new medical technologies by, among other things, use of a variety of premarket resources and tools (e.g., early collaboration meetings, 100–day meetings, modular reviews, etc.).

(Response) As stated in the response to Comments 11 and 12 of this document, assignment only directs a product to an agency component, and does not dictate the regulatory authorities that will be used.

4. *Miscellaneous Algorithm Questions*

(Comment 18) One comment suggested that FDA add the sponsor's recommendation of assignment to the algorithm.

(Response) FDA agrees that the sponsor's recommendation of jurisdictional assignment plays a significant role in the process of making jurisdictional determinations. Indeed, the sponsor's recommendation of assignment is a required element of an RFD under § 3.7(c)(3). FDA takes into account the information provided by the sponsor as well as the sponsor's recommendation of jurisdictional assignment not only when it is necessary to use the algorithm, but also when FDA initially decides whether the PMOA of a product can be determined with reasonable certainty. We note, too, that if FDA fails to make a jurisdictional determination within 60 days, the combination product would then automatically be assigned to the agency component recommended by the sponsor. FDA believes that the final codified language, together with the regulations currently in place, adequately takes into account a sponsor's recommendation of jurisdictional assignment of its combination product.

5. Flow Chart

(Comment 19) Two comments suggested that FDA include the flow chart in a guidance rather than the final rule.

(*Response*) FDA has not included the flow chart in the codified section of the final rule. However, we believe that the flow chart is a useful tool to illustrate how the PMOA process works; therefore, we included it in the preamble of the proposed rule merely for its instructional use.

(Comment 20) One comment suggested that FDA replace the reference in the flow chart to ''an agency component with responsibility for that type of device'' by the ''agency component with responsibility for devices'' to ensure that CDRH has primary jurisdiction.

(Response) FDA included the phrasing as written because it encompasses the subsets of drugs and devices regulated by the Center for Biologics

Evaluation and Research (CBER) and biological products regulated by the Center for Drug Evaluation and Research (CDER). While most devices are regulated by the Center for Devices and Radiological Health (CDRH), certain devices, such as those related to blood collection and processing, have long been regulated by CBER, and while most biological products are regulated by CBER, certain therapeutic biological products are now regulated by CDER. A drug-device combination product with a device PMOA, where the device is regulated by CBER, would be assigned to CBER. Similarly, a biological product-device combination product with a biological product PMOA, where the biological product is regulated by CDER, would be assigned to CDER.

C. Status of Intercenter Agreements

(Comment 21) Several comments asked that FDA confirm that the Intercenter Agreements (ICAs) remain viable in helping FDA determine the appropriate agency component for premarket review and regulation of products, or update the Agreements to encompass types of combination products developed after the Agreements were written in 1991.

(Response) FDA confirms that the ICAs referenced at § 3.5(a)(1) continue to provide helpful guidance related to product jurisdiction, including the assignment of some types of combination products. The ICAs were developed following the enactment of the PMOA criterion used to make assignments of combination products. Consequently, PMOA principles were used in the ICAs' development. For example, the ICA between CDER and CDRH assigns to CDRH products such as a ''device incorporating a drug component with the combination product having the primary intended purpose of fulfilling a device function.'' The premise underlying the assignment to CDRH is that the device component of such a product provides the most important therapeutic

action of the product. The CDER–CDRH ICA assigns to CDER prefilled delivery systems, such as a ‘‘device with primary purpose of delivering or aiding in the delivery of a drug and distributed containing a drug.’’ The premise of this assignment to CDER is that the device’s primary purpose in delivering or aiding in the delivery of a drug is subordinate to the most important therapeutic action provided by the drug product. Similarly, the ICA between CBER and CDER assigned to CDER ‘‘combination products that consist of a biological component and a drug component where the biological component enhances the efficacy or ameliorates the toxicity of the drug product.’’ The premise underlying this assignment is that the drug product provides the most important therapeutic action of the product, while the biological product has a subordinate role in enhancing such action. These principles are preserved by the definition described in this rule.

Nonetheless, the Intercenter Agreements were developed in 1991 and do not address many types of combination products developed since that time. Furthermore, we note that, although the ICAs were developed before the regulations governing good guidance practices, the Agreements constitute guidance, which is not binding. See 21 CFR 10.115(d)(1). Moreover, the ICAs describe sometimes broad categories of products, and because PMOA might vary depending on a combination product’s specific characteristics and use, the ICA recommendations may not be appropriate for every single product within a broad category. FDA is actively considering whether to continue in effect, modify, revise, or eliminate the ICAs and plans in the near future to further clarify the role of the ICAs in light of other available information, such as this rule and more recent jurisdictional information made available on the Office of Combination Products (OCP’s) Internet site. FDA believes the

issuance of this final rule will help clarify jurisdiction for combination products generally.

D. Role of Precedents

(Comment 22) Several comments asked that FDA clarify the role of precedent in the jurisdictional determination of a combination product.

(Response) FDA believes that precedent plays a very important role in determining the assignment of a combination product. First, the definition of PMOA finalized here is based on past practice and will preserve precedent. FDA has long considered a product's most important therapeutic action in determining the primary mode of action of a combination product and the concept of ''most important therapeutic action'' also underlies the assignments of combination products outlined in the Intercenter Agreements. In addition, the role of precedent is encompassed in the first criterion of the assignment algorithm, for use when the agency cannot determine a combination product's PMOA with reasonable certainty. That criterion directs FDA to assign a combination product to the agency component that regulates other combination products that present similar safety and effectiveness questions with regard to the product as a whole.

E. Application of Regulatory Authorities in the Review of Combination Products

(Comment 23) A few stakeholders asked FDA to clarify which good manufacturing practices and adverse event reporting authorities would apply to the regulation of a combination product. Other comments asked whether single or separate marketing applications would be appropriate for certain types of combination products, and how user fees are handled for combination products.

(Response) As explained previously in this document, this final rule applies only to the jurisdictional assignment of combination products to an agency component for review and regulatory oversight. The specific regulatory authorities to be applied to a combination product are outside the scope of this rule.

F. Review of Specific Types of Products

(Comment 24) One comment requested that FDA clarify how the rule affects general-purpose drug delivery devices. Another comment asked FDA to clarify the applicability of a particular principle described in the CDER–CDRH ICA related to unfilled drug delivery devices. The pertinent section of that ICA states that a device with the primary purpose of delivering or aiding in the delivery of a drug that is distributed without a drug (i.e., unfilled), where the drug and device would be developed and used together as a system, would be assigned to a lead Center after considering whether the drug or device had been previously approved and the dominance of the drug or device issues. A third comment asked for clarification that delivery devices that are distributed unfilled and determined not to require conforming changes to drug labeling are devices. For instance, the comment asked for clarification of the regulatory status of closed loop insulin delivery systems and catheters to deliver clot-busting drugs, which also act physically to dissolve the clot.

(Response) In order to be a combination product, a product must meet one of the definitions found in § 3.2(e). By their general nature, unfilled, general-purpose drug delivery devices typically do not meet the definition of a combination product because they are not physically combined or packaged with, or tied by labeling to a particular drug, so such products are regulated as devices. The specific types of products mentioned in comment 24 of this

document could be single-entity devices as long as they are provided without the drugs, and the labeling of the drugs does not need to change to reflect their use. The assignment of delivery devices that are not combination products as defined by § 3.2(e) is outside the scope of this rule.

(Comment 25) One comment asked FDA to clarify how several variables would impact PMOA. These questions were as follows: What if the drug component is an old, generic, off-patent drug? What if the mode of administration and dosage of the drug are changed only slightly? What if the drug indication remains the same? What if only secondary aspects of drug labeling (e.g., precautions, instructions for use) change?

(Response) These questions would not affect the determination of PMOA (i.e., the most important therapeutic action of a combination product), but they are factors FDA would consider, as appropriate, at the second tier of the algorithm, when FDA assesses the most significant safety and effectiveness questions presented by the combination product.

(Comment 26) One comment stated that, without additional clarification of the role of precedents, the PMOA analysis as applied to pharmacogenomic drug/diagnostic device products might lead to uncertain results. The comment also identified a number of products and suggested that they would not be considered under the PMOA rule as precedents because historically they have not been designated as combination products. In addition, the comment expressed concern that after this rule's enactment, the device component of these types of products would no longer be reviewed separately by CDRH, as historically has been the case.

(Response) FDA has clarified the role of precedents earlier in this section of the document. With regard to the application of the PMOA analysis to

pharmacogenomic drug/diagnostic device products, the comment is correct in noting that not all such products are combination products, and when they are not, the drug and device would be regulated as separate entities.

(Comment 27) One comment asked that OCP continue its role in the regulatory oversight of drug/biological product combinations, even when CDER has regulatory responsibility for both the drug and biological product components.

(Response) A drug-biological product remains a combination product even if both components are reviewed by the same Center. FDA agrees that OCP continues to have oversight responsibility, consistent with 21 USC 353(g)(4) and the regulations set forth in 21 CFR Part 3, for drug/ biological product combination products even when both the drug and biological product components are regulated by CDER. FDA's jurisdictional update on drug-biological product combination products, available at *http://www.fda.gov/oc/combination/biologic.html*, provides more information.

(Comment 28) One comment asked that over-the-counter (OTC) drug and dietary supplement combinations be classified as combination products.

(Response) Under 21 U.S.C. 353(g) and 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. Classification of OTC drug and dietary supplement combinations is outside the scope of this rule.

(Comment 29) One comment asked that FDA clarify whether tissue-engineered products, such as human-derived fibroblasts cultured in vitro on a synthetic scaffold, are considered to be combination products.

(Response) While classification of particular products is outside the scope of this rule, we note that many tissue engineered products, such as the product described in comment 29 of this document, are comprised of biological product and device components, and therefore meet the definition of a combination product as defined in § 3.2(e).

(Comment 30) One comment asked FDA to note that the review timelines of combination products would be consistent with the performance goals of the primary review Center. Another comment asked FDA to address the review timelines for a combination product in which the agency has required that the sponsor submit separate marketing applications.

(Response) Review timelines are outside the scope of this rule. We note that review timeframes are associated with the type of marketing application, rather than the reviewing Center. Further information on these issues, as well as other information regarding the timeliness of reviews, is discussed in FDA's guidance document on dispute resolution available at *http://www.fda.gov/oc/combination/*.

(Comment 31) One comment asked that FDA clarify how the agency would evaluate new uses for a product using the PMOA analysis.

(Response) FDA is required by statute to assign a product to an agency component for review based on its PMOA. Stakeholders have urged, and FDA agrees, that determination of a product's PMOA should take into account the product's intended use. Therefore, it is possible that a single product, intended for two different purposes, may be assigned to different agency components for review of those different uses if the PMOA for each use directs the assignment to a different agency component. However, FDA will strive to minimize the impact of these assignments where possible.

(Comment 32) One comment was concerned that the PMOA definition would direct all drug delivery devices combined with a drug product to CDER. The comment mentioned a specific example of an approved drug product in its approved container, with no change to the route of administration, combined with an innovative delivery device. Additionally, the comment stated that the same device combined with different drug products may be assigned to different divisions within CDER, which could result in confusing or conflicting requirements for the release testing or labeling of the device.

(Response) As stated previously in this document, FDA is required by statute to assign a product to an agency component for review based on its PMOA. FDA has developed a Standard Operating Procedure (SOP) to help ensure efficient and effective consultation and collaboration between the Centers on such reviews. Such consultation and collaboration will also help to ensure uniformity in approaches by the review divisions. This review process is outlined in further detail in the FDA SOP for Intercenter Consultative/Collaborative Review Process, available at *http://www.fda.gov/oc/ombudsman/intercentersop.pdf*.

Examples

(Comment 33) Several comments asked that FDA provide more examples, particularly examples illustrating how drug and biological product combination products would be reviewed. One comment recommended that FDA include examples of copackaged and cross-labeled combination products.

(Response) FDA agrees, and we provide 11 hypothetical examples in this section of the document, three of which were also provided in the proposal. We note that the interferon/ribavirin combination product is an example where the two components may be either copackaged or separately provided but

labeled to be used together; the same assignment would result in either situation. In addition, we have posted a list of selected capsular descriptions illustrating many prior jurisdictional determinations, which is available on our website at *http://www.fda.gov/oc/combination/determinations.html*. FDA believes these descriptions also help to illustrate the jurisdictional determination process.

(Comment 34) One comment listed a number of hypothetical products, and asked that FDA explain how it would review and regulate them, so that stakeholders would have a better understanding of the process FDA uses when making assignments of combination products.

(Response) FDA notes that some of the comment's examples are not combination products and, therefore, fall outside the scope of the rule, while other examples lack sufficient detail for FDA to work through as a hypothetical exercise. However, FDA used or adapted some of the examples suggested and developed additional hypothetical examples. FDA believes the examples provided in this response to comment 34 of this document, along with the capsular descriptions of prior jurisdictional determinations posted on OCP's website, and the types of questions FDA considers when making assignments of combination products, further illustrate the process FDA uses when making assignments.

Examples Repeated From Proposed Rule

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 reocclude 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: CDRH*

The product's primary mode of action 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 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 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 to a tumor site.

- *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: CDER*

Though the product has a device mode of action, the product's primary mode of action 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 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 algorithm.

- *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 more routine. It should also be noted that CDER has expertise in the review of other drugs delivered using a contact lens. Based on the application of this criterion, this product would be assigned to CDER because CDER has the most expertise related to these issues.

d. *Contact Lens Combined With Drug to Treat Glaucoma*. This product is identical to the product described in example c. in all material respects. The RFD was filed after the designation of the product in example c. Since it is not possible to determine which mode of action provides the greatest contribution to the overall therapeutic effects of the combination product, we would apply the assignment algorithm. This product would be assigned to CDER under the first criterion of the assignment algorithm, since the product described in example c. presents similar questions of safety and effectiveness with respect to the combination product as a whole and is already assigned to CDER.

Additional Examples-These hypothetical examples further illustrate the designation process.

e. *Spinal fusion device coated with a therapeutic protein intended to treat degenerative disc disease*. A spinal fusion cage soaked in a solution of a therapeutic protein to coat the inside surfaces of the device. In this hypothetical example, the fusion cage, a permanent implant, maintains the spacing and stabilizes the diseased region of the spine, while the protein is

used to encourage the formation of bone within the fusion cage to further stabilize this portion of the spine as well as the cage itself.

- *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 is the device component's action to mechanically maintain the intervertrebral spacing and stabilize the diseased region of the spine. Another action is the therapeutic protein's action to encourage the formation of bone within the fusion cage to further stabilize the cage and this portion of the spine.

Assignment of Lead Agency Component: CDRH

The product's PMOA is attributable to the device component's action to mechanically maintain the intervertebral spacing and stabilize the diseased region of the spine, while the therapeutic protein's action to encourage bone formation within and around the cage plays a secondary role. In this hypothetical example, the therapeutic protein does not have the mechanical properties necessary to maintain the spacing and stabilize the spine if used alone. Furthermore, clinically successful spinal fusion, i.e., pain reduction and stability of the spine, can be achieved even in the absence of bone growth within the cage. Accordingly, FDA would assign the product to CDRH for 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 therapeutic action of this particular combination product.

f. *Chemotherapeutic drug and monoclonal antibody for targeted cancer treatment*. The monoclonal antibody is intended to improve the drug's effectiveness by directly targeting the drug to receptors on cancer tumor cells.

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

In this hypothetical case, the product has two modes of action. One action is the chemotherapeutic drug component's action to treat cancer. Another action is the monoclonal antibody's (biological product) action to target the drug to receptors on cancer tumor cells, thereby delivering the drug directly to the tumor site.

Assignment of Lead Agency Component: CDER

The product's PMOA is attributable to the drug component's cytotoxic action on cancer cells, while the biological product component's action to target the drug to the receptors on the cancer cells enhances the efficacy of the drug. Accordingly, FDA would assign the product to CDER for 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 combination product. Note that in June 2003, FDA transferred to CDER the regulation of certain therapeutic biological products, including monoclonal antibodies, which had been regulated by CBER. Although CDER now has regulatory responsibility over both the chemotherapeutic drug and monoclonal antibody described in this hypothetical example, this example is provided for illustrative purposes. For further information about the drug and biological product consolidation, see

the **Federal Register** of June 26, 2003 (68 FR 38067), and the OCP website at *http://www.fda.gov/oc/combination/transfer.html*.

g. *Scaffold seeded with autologous cells for organ replacement*. The hypothetical product has the shape of the target organ, and the autologous cells are intended to allow the product to ultimately function like the target organ in the patient.

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 product is the action of the biological product component to help form new tissue that will ultimately function like the native organ. Another action of the product is the device component's action to provide a scaffold on which the new organ tissue will form.

Assignment of Lead Agency Component: CBER

The product's PMOA is attributable to the biological product component's action to help form new organ tissue that will ultimately function like the native organ. The device component's action to provide a scaffold upon which the new tissue will form is secondary. Though the scaffold is necessary to create the new tissue and provide the necessary shape, the creation of a functioning organ is primarily dependent upon the role of the cells to provide the tissue organization and muscular layer needed to function like the native organ. Accordingly, FDA would assign the product to CBER for regulation because the biological product 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 combination product.

h. *Menstrual tampon impregnated with genetically modified bacteria*. The hypothetical product is intended for use throughout menstruation both in the collection of menstrual fluid and to treat and/or prevent recurrence of bacterial vaginosis.

- *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 product is the action of the biological product component to act upon the vaginal mucus membrane to produce antimicrobial factors that will control opportunistic pathogens. Another action of the product, like other menstrual tampons, is the device component's action to collect menstrual fluid. 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 tampons; CBER regulates bacterial products and genetically modified cells. In this hypothetical example, no combination product intended both to collect menstrual fluid and to treat and/or prevent recurrence of bacterial vaginosis through the actions of a genetically modified

organism has previously been reviewed by the agency. Though both CDRH and CBER 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: CBER

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 case, the menstrual tampon component presents generally routine safety and effectiveness questions, similar to those of other menstrual tampons. In contrast, the biological product component raises more significant safety and effectiveness questions, such as those related to bacterial strain selection and dose; bacterial purity, potency and metabolic activity, including the impact of genetic modifications; bacterial adherence potential, microbial strain interactions, and constitutive production of ancillary antimicrobial substances. Based on the application of this criterion, this product would be assigned to CBER because CBER has the most expertise related to these issues.

i. *Interferon and Ribavirin Combination Therapy*. The product is intended for use in the treatment of chronic hepatitis C. Interferon is approved under the licensing provisions of the Public Health Service Act as a stand-alone product for treatment of chronic hepatitis C. Clinical studies show that ribavirin when used alone to treat chronic hepatitis C can improve liver function, but most patients relapse with treatment of ribavirin alone. However, data show that ribavirin, when used in conjunction with interferon, produces a more efficacious response than when interferon is used alone to treat chronic hepatitis C. The drug and biological product components may be copackaged or are provided separately but cross-labeled for use together.

- *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 product is the action of the biological product component to treat chronic hepatitis C, which produces a dose-dependent decline in hepatitic C virus ribonucleic acid (RNA) titers. Another action of the product is the ribavirin tablet's action to enhance the efficacy of the biological product.

Assignment of Lead Agency Component: CDER

The product's PMOA is attributable to the biological product component's function, while the drug component works to enhance its efficacy. Note that interferons are now reviewed in CDER following the transfer of therapeutic biological products to CDER in 2003. CDER is now the agency component responsible for review of such biological products (see example e. in this section of the document).

j. *Implantable device with local chemotherapeutic drug*. Embolization device coated with a chemotherapeutic agent intended to treat hypervascularized tumors.

- *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 is the device component's action to physically occlude the tumor's blood supply. Another action is the drug component's action as it elutes from the device to the tumor where it has a cytotoxic effect. The embolization device is a permanent implant, while the drug component is a short-term acting chemotherapeutic.

Assignment of Lead Agency Component: CDRH

In this hypothetical example, the product's PMOA is attributable to the device component's role in the physical occlusion of the blood supply to the tumor site through embolization, while the drug component plays a subordinate role in causing apoptosis in any remaining proliferating tumor cells. In this hypothetical example, data indicate that the effectiveness of the embolization device alone for the stated indication is much greater than the effectiveness of the drug component when delivered directly to the tumor site without use of the embolization agent. Accordingly, FDA would assign the product to CDRH for 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 therapeutic action of this particular combination product. In this hypothetical example, the PMOA was attributable to the device component. However, we note such a product used for another indication, or with another drug, could have a drug PMOA depending on the

relative effectiveness of the drug and device components in providing the most important therapeutic action for the new use.

k. *Vertebroplasty Implant With Extended-Release Analgesic*. This hypothetical product is intended to provide spinal stabilization in patients with spinal bone metastases who also require palliative relief of pain.

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

One action of the product is the device action, to stabilize the fractured spinal vertebral body bone. Another action of the product is the drug action, to provide for extended analgesic delivery as an alternative to oral medication in patients expected to continue to require long-term pain management despite the stabilization implant. In this hypothetical example, both actions of the product are independent, and neither is clearly 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.

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 vertebroplasty implants. CDER regulates analgesic drug products. In this hypothetical example, no product combining a vertebroplasty implant and an extended-release analgesic has yet been submitted to the agency for review, therefore 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 algorithm.

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: CDRH

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. Although important safety and effectiveness questions are presented by this new route of administration of an analgesic and its extended release from the device, and would need to be addressed, in this hypothetical example, the most significant safety and effectiveness questions associated with the combination product as a whole are related to the mechanical strength, wear, and clinical performance of the vertebroplasty implant. Based on the application of this criterion in the algorithm, this product would be assigned to CDRH because CDRH has the most expertise related to these issues. CDRH would consult or collaborate with CDER on the safety and effectiveness issues raised by the analgesic component.

Miscellaneous Comments

(Comment 35) Several comments asked that FDA post precedents on the Web, so that stakeholders could better understand the process FDA used when making jurisdictional determinations for combination products submitted to FDA prior to implementation of this final rule.

(Response) FDA has complied with these requests and has published a list of capsular descriptions of selected previous jurisdictional determinations, and is working to publish additional such descriptions. They are available on OCP's Web site at: *http://www.fda.gov/oc/combination/determinations.html*.

(Comment 36) A few comments suggested that FDA issue various guidances on PMOA, either before issuance of the final rule, concurrently with issuance of the final rule, or after issuance of the final rule.

(Response) FDA believes that it has provided sufficient explanation and examples, both in the preamble to the proposed and final PMOA rules and on the PMOA analysis codified here, to render additional guidance unnecessary at this time. Nonetheless, FDA will reconsider if implementation of this rule gives rise to a need for development of a guidance on this topic.

(Comment 37) One comment suggested that FDA repropose the rule after FDA issued a guidance.

(Response) FDA declines to repropose the rule. First, the majority of comments were supportive of the rule in whole or in part, and only two minor changes have been made to the codified language. Second, the majority of stakeholders that commented in public meetings held prior to issuance of the proposal stressed to FDA the need to define PMOA and MOA in a timely manner. We have done so here in a manner that, as one comment stated, ''faithfully implements the statute.''

(Comment 38) One comment suggested that FDA withdraw the rule because it would hinder the assignment process and because the algorithm is not set forth in the statute. The comment was primarily concerned that the criteria used in the algorithm did not adequately explain how FDA would

determine the most significant as well as similar safety and effectiveness questions.

(Response) FDA believes that it has adequately addressed how it will determine these issues by providing in this preamble numerous examples as well as examples of factors FDA considers when making these determinations. Additionally, we have published on the OCP Web site an extensive list of capsular descriptions of actual assignment decisions. The agency believes the issuance of this rule will not hinder the assignment process but rather improve it. FDA declines to withdraw this rule for the reasons stated in comment 38 of this document. Furthermore, FDA's experience in evaluating combination products has shown that for a small subset of products, the most important therapeutic action is not determinable with reasonable certainty, even by the product's developer. Therefore, FDA needs a mechanism to ensure that these types of products are assigned with consistency, transparency, and predictability to an appropriate agency component. Out of necessity, FDA established the algorithm to accomplish these goals.

Implementation

(Comment 39) Several comments asked FDA to clarify whether the rule would affect prior RFD determinations. One comment also asked that FDA clarify whether the final rule is intended to change prior jurisdictional decisions made outside the RFD process.

(Response) The rule is prospective in nature and will apply only to assignments FDA makes 90 days after the rule is published in the **Federal Register**. This final rule is not intended to affect RFD determinations made prior to its implementation. For prior jurisdictional assignments of combination products made outside the RFD process, FDA would consider the

facts and principles governing PMOA before moving such a product to another agency component.

IV. 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, 360bbb–2, 371(a), 379e, 381, 394; 42 U.S.C. 216, 262, and 264 as stated in the Code of Federal Regulations. Congress expressly directed FDA to assign combination products to the appropriate agency component for 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.

V. 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.

VI. Paperwork Reduction Act of 1995

FDA concludes that the changes to the regulations on combination products finalized 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.

VII. Federalism

FDA has analyzed this final 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.

VIII. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the final 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, 109 Stat. 48). 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). The final rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. No further analysis is required under the Regulatory Flexibility Act because the agency has determined that these final rule amendments have no compliance costs and will not have a significant impact on a substantial

number of small entities. Therefore, the agency certifies the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ‘‘any rule that includes any Federal mandate that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted annually for inflation) in any one year.’’ The current threshold after adjustment for inflation is $115 million, using the most current (2003) implicit price deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

B. The Rationale Behind This Final Rule

The purpose of the final rule 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, as stated in the proposed rule, many stakeholders have requested that the agency issue 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 this final rule and its preamble address the significant concerns stakeholders have expressed regarding the assignment process, and address the significant concerns expressed in the comments to the proposal. Moreover, we have incorporated into the codified section of this

final rule suggestions provided by the comments to the proposal regarding the MOA and PMOA definitions.

The codification of these principles will 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. The finalization of this rule will allow a sponsor 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 final rule, as well as in the proposed rule, the amendments finalized here will fulfill the statutory requirement to assign products based on their PMOA, and will 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. The final rule ensures that like products will 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 will further MDUFMA's requirement that the agency ensure prompt assignment of combination products. Also, by issuing this final rule, 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.

The agency believes the final rule will have no compliance costs and poses no additional burden to industry.

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, 21 CFR part 3 is 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, 360bbb–2, 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 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.

* * * * *

(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.

* * * * *

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. 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.

* * * * *

4. Section 3.7 is amended by revising paragraph (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.

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Dated: August 9, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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