

# DEPARTMENT OF HEALTH AND HUMAN SERVICES

## Food and Drug Administration

[Docket No. 2006N-0378]

### Review of Agreements, Guidances, and Practices Specific to Assignment of Combination Products in Compliance With the Medical Device User Fee and Modernization Act of 2002; Request for Comments

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Federal Food, Drug, and Cosmetic Act (the act) requires the Food and Drug Administration (FDA) to review each agreement, guidance, or practice that is specific to the assignment of combination products to agency centers and to determine whether the agreement, guidance, or practice is consistent with the requirements of the act. In carrying out the review, the agency is to consult with stakeholders and directors of the agency centers, and then determine whether to continue in effect, modify, revise, or eliminate such an agreement, guidance, or practice. The agency has completed its initial review of relevant agreements, guidances, and practices, and has consulted with directors of the agency centers. This document provides the preliminary results of the agency's review and requests stakeholder comments to fulfill the act's requirement for stakeholder consultation prior to the agency's final determination whether to continue the agreements, guidance, or practices in effect, or to modify, revise, or eliminate them.

**DATES:** Submit written or electronic comments by [*insert date 60 days after date of publication in the Federal Register*].

**ADDRESSES:** Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

**FOR FURTHER INFORMATION CONTACT:** Suzanne O’Shea, Office of Combination Products (HFG–3), Food and Drug Administration, 15800 Crabbs Branch Way, suite 200, Rockville, MD 20855, 301–427–1934, FAX: 301–427–1935, e-mail: [suzanne.oshea@fda.hhs.gov](mailto:suzanne.oshea@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:**

**I. Background**

In October 2002, the Medical Device User Fee and Modernization Act (MDUFMA) added section 503(g)(4)(F) (21 U.S.C. 353(g)(4)(F)) to the act. This new provision requires the Secretary of the Department of Health and Human Services (the Secretary), acting through the Office of Combination Products (OCP), to review each agreement, guidance, or practice of the Secretary that is specific to the assignment of combination products to agency centers and to determine whether the agreement, guidance, or practice is consistent with the requirements of section 503(g) of the act. In carrying out such a review, OCP is to consult with stakeholders and the directors of the agency centers. After such consultation, OCP is to determine whether to continue in effect, modify, revise, or eliminate such agreement, guidance, or practice, and publish in the **Federal Register** a notice of the availability of any modified or revised agreement, guidance, or practice.

This notice provides the preliminary results of OCP’s review of agreements, guidances, and practices that were in effect at the time section 503(g)(4)(F) of the act was enacted for their consistency with the act’s

requirement for the prompt assignment of combination products to agency centers on the basis of the products' primary mode of action (PMOA).<sup>1</sup> The directors of relevant agency centers have been consulted in this review. The agency now seeks stakeholder comment with respect to the following issues: (1) Whether the agency has identified all agreements, guidances, and practices specific to the assignment of combination products that should have been included in this review; (2) whether the agency's conclusions regarding the consistency of the agreements, guidances, and practices with the act's requirement that combination products be assigned promptly based on their PMOA is accurate; and (3) whether the identified agreements, guidances, and practices should be continued in effect, modified, revised, or eliminated.

Upon receipt and review of stakeholder input, the agency will publish another **Federal Register** notice announcing its determinations and the availability of any modified or revised agreements, guidances, or practices.

## **II. Primary Mode of Action—The Principle Underlying the Assignment of Combination Products to Agency Centers**

Section 503(g)(1) of the act requires that combination products be assigned to a lead agency center based upon the agency's determination of the product's PMOA. The agency published a final rule defining the PMOA of a combination product in the **Federal Register** of August 25, 2005 (70 FR 49848), after consulting with directors of the relevant agency centers and other agency officials, and obtaining stakeholder input through notice and comment rulemaking. As defined in the regulation, a combination product's PMOA is its single mode of action that provides the most important therapeutic action of the product (§ 3.2(m) (21 CFR 3.2(m))). The regulation includes an algorithm

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<sup>1</sup> Section 503(g)(1) of the act requires that combination products be assigned to an agency center for regulation and review on the basis of the product's PMOA. In addition, section 503(g)(4)(B) of the act directs OCP to ensure the prompt assignment of combination products to agency centers.

that will be followed when the most important therapeutic action of a combination product cannot be determined with reasonable certainty (§ 3.4(b)). The regulation 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. The regulation went into effect on November 23, 2005. A copy of the final rule is available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.htm>.

### **III. Agreements and Guidances Specific to the Assignment of Combination Products**

The agency has identified the three intercenter agreements (ICAs) as the agreements or guidances specific to the assignment of combination products described in section 503(g)(4)(F) of the act. The three ICAs were entered into in 1991 by the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH) shortly after Congress introduced the concept of combination products in the Safe Medical Devices Act of 1990 (SMDA). Although the three ICAs (i.e., the CDER–CDRH ICA, the CBER–CDER ICA, and the CBER–CDRH ICA) differ in content, format, and scope, they are all specific to the assignment of combination products because they explain how various categories of both combination and single entity products were classified<sup>2</sup> and assigned<sup>3</sup> to an agency center at the time the documents were developed. The ICAs constitute guidance that is not binding on the public or the agency (§ 3.5(a)(2)). The ICAs are available at <http://www.fda.gov/oc/combo/intercenter.html>.

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<sup>2</sup> Classification refers to the determination of a product's regulatory identity as a drug, device, biological product, or combination product.

<sup>3</sup> Assignment refers to the determination of the agency center that will have primary jurisdiction for the review and regulation of a product.

The agency has reviewed the ICAs and preliminarily determined that they are generally consistent with the requirements of section 503(g) of the act in that the principles used to assign combination products described in the ICAs are based on a product's PMOA. The ICAs were developed following the enactment of the statutory PMOA criterion used to assign combination products to an agency center, and were developed using the PMOA principle.

For example, the CDER–CDRH ICA 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. This 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 CBER–CDER ICA assigns 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.

FDA recognizes that, since the ICAs were written in 1991, new products have been developed, new uses for existing products have been devised, and additional laws, regulations, and guidances are in effect. During this period, FDA has continued to classify and assign many new products not specifically

covered by the ICAs. In addition, some jurisdictional decisions made since 1991 cover products that appear to be part of a broad class of product included in an ICA, but are classified and/or assigned in a way different from the class of product because of the particular product's specific characteristics or use. Many of these decisions have been made through the formal Request for Designation (RFD) process. For these reasons, the body of jurisdictional decisions has grown over time, and the ICAs have become incomplete statements.

Moreover, in 2003 the agency administratively transferred many therapeutic biological products from CBER to CDER. For this reason, the CBER–CDER ICA is out of date.

#### **IV. Preliminary Proposal to Continue in Effect the CDER–CDRH and CBER–CDRH ICAs, and to Rescind the CBER–CDER ICA**

The agency believes it is very important to provide transparency in jurisdictional decisionmaking. Such transparency ensures predictability and consistency of decisions, and decreases ambiguity and uncertainty about agency perspectives. Moreover, as the bases for agency decisionmaking become clearer, the need for formal RFDs and informal inquiries covering specific products may diminish, which should conserve resources for the industry and the agency.

##### *A. CDER–CDRH and CBER–CDRH ICAs*

The agency has reviewed the CDER–CDRH and CBER–CDRH ICAs and preliminarily determined that they continue to provide helpful nonbinding guidance, and so proposes to continue them in effect, with the understanding that they should not be independently relied upon as the most current, complete jurisdictional statements.

The agency considered updating the CDER–CDRH and CBER–CDRH ICAs as a way to continue to provide transparency to its jurisdictional decisionmaking. After consideration, however, the agency believes that the goal of transparency can be achieved more effectively by other means. The process of updating the ICAs would be time consuming, and given the quick pace of product development, the updated ICAs would soon be out of date as well. The agency believes that transparency is better served by articulating the principles upon which it bases determinations of a combination product’s PMOA, and by frequently issuing jurisdictional information on particular classes of products as that information becomes available. The agency suggests that persons wishing to get the most current information about jurisdictional determinations consult the numerous other sources of information about jurisdictional determinations described in this document, as well as the ICAs.

#### *B. CBER–CDER ICA*

The 2003 administrative transfer of many therapeutic biological products from CBER to CDER has rendered the CBER–CDER ICA out of date. For this reason, the agency preliminarily proposes to rescind the CBER–CDER ICA. A statement of the current assignment of biological products to CBER and CDER is available at <http://www.fda.gov/oc/combination/transfer.html>.

### **V. Actions Taken to Increase Transparency of Jurisdictional Decisionmaking**

Since the enactment of MDUFMA, the agency has implemented, or is developing, the following actions to increase the transparency of jurisdictional decisionmaking:

#### *A. Regulatory Definition of PMOA*

As described previously in this document, the agency recently published a final rule defining “primary mode of action,” which is the basis for assigning

a combination product to a lead center for review. The regulation includes an algorithm that will be followed when the most important therapeutic action of a combination product cannot be determined with reasonable certainty. This clarification of the PMOA principle is expected to significantly increase the transparency of the reasoning underlying the agency's assignment of combination products to an agency center.

*B. Guidance for Industry and FDA Staff: How to Write a Request for Designation (RFD)*

The goal of the guidance is to provide recommendations regarding the type of information a sponsor should submit in order for the agency to determine the regulatory identity of a product as a drug, device, biological product, or combination product, and to assign the product to the appropriate agency component for review and regulation. The guidance reflects the final rule defining the PMOA of a combination product, and is expected to increase the transparency of the RFD process by clarifying the kind of information that enables the agency to make a prompt and appropriate assignment decision. The guidance is available at <http://www.fda.gov/oc/combination/howtowrite.html>.

*C. Jurisdictional Determinations*

The agency has made available on the OCP Web site more than 220 capsular descriptions of prior RFD decisions. In selecting which jurisdictional determinations were appropriate to summarize and make public in this way, the agency considered the extent to which the product could be suitably described, the extent to which the existence and description of the product or similarly described products have been made public, and related factors. The agency will continue to update the list of capsular descriptions as new

decisions are made and as information on these products becomes publicly available. The capsular descriptions are available at <http://www.fda.gov/oc/combination/determinations.html>.

#### *D. Jurisdictional Updates*

Jurisdictional updates are more detailed statements of the classification and assignment of various product classes. They reflect past agency decisions, and are not intended to be policy statements. Jurisdictional updates generally contain information about the basis for the assignment and classification decisions that have been made. The agency selects product classes to be the subject of jurisdictional updates based on the agency's perception of the current level of interest in the jurisdictional issue, the extent to which the class of products can be clearly described, the extent to which the existence and description of the class of products has been made public, and related factors. Additional jurisdictional updates will be issued as appropriate. Jurisdictional updates are available at <http://www.fda.gov/oc/combination/updates.html>.

#### *E. RFD Decision Letters*

The agency posts on the OCP Web site RFD decision letters for products that have been approved or cleared. These letters have been redacted to remove trade secret and confidential commercial information in accordance with the Freedom of Information Act. It should be noted that, in some cases, products undergo changes in name, sponsor, design, or other key aspects following the agency's issuance of an RFD decision. The agency will post RFD decision letters when it is certain that the covered product has been approved or cleared, but it should be recognized that the posting may be incomplete. Posting of these letters, which generally include the agency's reasoning behind the RFD decision, is intended to provide additional transparency on the

jurisdictional process. The letters are available at <http://www.fda.gov/oc/combination/rfd.html>.

#### *F. Chemical Action*

In the course of assigning combination products to an agency center, OCP must often determine whether a product is a combination product—a determination that may turn on whether a constituent part of the product is properly classified as a device. Section 201(h) of the act (21 U.S.C. 321(h)) states that a device cannot achieve its primary intended purposes through chemical action within or on the body of man, or be dependent on being metabolized to achieve its primary intended purposes. The agency plans to develop guidance and/or regulations to further clarify what is meant by “chemical action within or on the body.” When final, such guidance and/or regulations should be helpful to sponsors in determining whether a product is a combination product.

#### *G. Devices Regulated by CBER*

Certain single entity (i.e., noncombination) devices are regulated under the device provisions of the act by CBER, rather than CDRH. One of the main purposes of the CBER–CDRH ICA is to identify categories of devices regulated by CBER. The agency believes, however, that additional guidance describing the assignment of devices that process human cellular and tissue products would be helpful. This product area was not fully envisioned at the time the CBER–CDRH ICA was developed. The agency plans to develop such guidance to assist sponsors in determining whether certain devices would be regulated by CDRH or CBER.

## *H. Combination Product Regulation*

For some types of combination products, the CDER–CDRH ICA addresses good manufacturing practices, registration and listing, labeling, and other product regulation issues. The agency is developing guidance and/or regulations to address these and other significant areas of combination product regulation, and when final, these documents will ultimately update the limited information provided in the CDER–CDRH ICA on these topics.

## **VI. Practices Specific to Assignment of Combination Products**

The agency has reviewed its practices specific to the assignment of combination products to ensure that they are in compliance with the requirement of section 503(g)(4)(B) of the act that the agency promptly assign a combination product to an agency center with primary jurisdiction in accordance with section 503(g)(1) of the act.

The agency has refined its processing of jurisdictional requests to ensure that the agency makes its assignments promptly. For example, section 503(g)(4)(A) of the act requires OCP, in determining whether a product is appropriately classified as a combination product, to consult with the component within the Office of the Commissioner that is responsible for such determinations. In the **Federal Register** of June 23, 2003 (68 FR 37075), the agency issued a final rule announcing that to enhance the efficiency of agency operations, OCP assumed responsibility from the Office of the Ombudsman for designating the component of FDA with primary jurisdiction for the premarket review and regulation of any product requiring a jurisdictional determination under part 3 (21 CFR part 3). This change consolidated the jurisdiction program within OCP, eliminated the requirement for consultation about the classification of a product as a combination product, and made the

RFD program more efficient to administer. The final rule also provided for the electronic submission of RFDs (§ 3.7(d)).

Similarly, OCP has refined its internal processes and practices to ensure that all RFDs are resolved within the 60-day timeframe requirement of section 563(b) of the act (21 U.S.C. 360bbb-2(b)) (§ 3.8(b)). All RFDs submitted to OCP since its inception have been resolved within the 60-day period. Furthermore, all requests for reconsideration were responded to within the 15-day timeframe (§ 3.8(c)). For the period from the establishment of OCP through March 31, 2006, FDA's average RFD processing time for assignments of combination products is 37.7 days (median 40 days, range 11-59 days). Accordingly, the agency has preliminarily determined that its practices are consistent with the requirement contained in section 503(g)(4)(B) of the act that it promptly assign combination products to an agency center based on the product's PMOA. FDA plans to continue in effect the process improvements needed to maintain the prompt assignment of combination products, and plans to continue to work to refine its processes further.

## **VII. Comments**

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of

this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 22, 2006.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

[FR Doc. 06-????? Filed ??-??-06; 8:45 am]

**BILLING CODE 4160-01-S**