

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. 02N-0445]

DMB

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Certifier D. Hawkins

**FDA Regulation of Combination Products; Public Hearing**

**AGENCY:** Food and Drug Administration.

**ACTION:** Notice of public hearing; request for comments.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing a public hearing to discuss the assignment, premarket review, and postmarket regulation of combination products. Combination products (defined in more detail later in this document) are products containing a combination of drugs, devices, or biological products. These products often are novel and have significant potential to enhance the public health. The purpose of the hearing is to solicit information and views from interested persons on the issues and concerns relating to the assignment, premarket review, and postmarket regulation of combination products. FDA is proposing specific questions, and the agency is interested in responses to these questions and any other pertinent information stakeholders would like to share.

**DATES:** The public hearing will be held on November 25, 2002, from 9 a.m. to 5 p.m. Submit written or electronic notices of participation by close of business on November 8, 2002. Written and electronic comments will be accepted until January 24, 2003.

**ADDRESSES:** The public hearing will be held at the DoubleTree Hotel, 1750 Rockville Pike, Rockville, MD. Directions to the hotel can be found at <http://www.doubletreerockville.com>.

Submit written or electronic notices of participation and comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852; or e-mail [FDADockets@oc.fda.gov](mailto:FDADockets@oc.fda.gov); or on the Internet at <http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm>. Transcripts of the hearing will be available for review at the Dockets Management Branch (see address in previous sentence) and on the Internet at <http://www.fda.gov/ohrms/dockets>.

**FOR FURTHER INFORMATION CONTACT:** Mark D. Kramer, Combination Products Program (HF-7), Food and Drug Administration, 5600 Fishers Lane, rm. 14B-03, Rockville, MD 20857, 301-827-3390, FAX 301-480-8039, e-mail: [mkramer@oc.fda.gov](mailto:mkramer@oc.fda.gov).

### **Registration Information and Requests for Oral Presentation**

Preregistration by written notice is necessary to ensure participation. The procedures governing the hearing are found in part 15 (21 CFR part 15). To register to attend the hearing, submit your name, title, business affiliation, address, telephone, fax number, and e-mail address. If you wish to make an oral presentation during the open public comment period of the hearing, you must state your intention on your registration form or with the registration contact person listed (see **FOR FURTHER INFORMATION CONTACT**). You must submit a written statement at the time of registration for each discussion question you wish to address, the names and addresses of all individuals that plan to participate, and the approximate time requested to make your presentation. Electronic registration for this hearing is available at <http://www.accessdata.fda.gov/scripts/oc/dockets/meetings/meetingdocket.cfm>. Registrations will be accepted on a first-come, first-served basis. Individuals

who register to make an oral presentation will be notified of the scheduled time for their presentation prior to the hearing. Depending on the number of presentations, FDA may need to limit the time allotted for each presentation. All participants are encouraged to attend the entire day. Presenters must submit two copies of each presentation given. If you need special accommodations due to a disability, please inform the registration contact person when you register. Presentations will be limited to the questions and subject matter identified in section III of this document.

#### **SUPPLEMENTARY INFORMATION:**

### **I. Background**

The Safe Medical Devices Act (SMDA) of 1990 explicitly recognized the existence of products that “constitute a combination of a drug, device, or biological product” and provided a mechanism for determining which agency component would be assigned the administrative responsibility of regulating a particular combination product (21 U.S.C. 353(g)). The Food and Drug Administration Modernization Act of 1997 (FDAMA) further refined the assignment process by providing a mechanism to request that FDA classify a product as a drug, biological product, device, or a combination product, in addition to determining which agency component will be assigned to regulate the product (21 U.S.C. 360bbb-2).

As defined in § 3.2(e) (21 CFR 3.2(e)), the term combination product means a product comprised of two or more different regulated components, e.g., drug, device, or biologic (for example, a syringe prefilled with a drug); or two or more separate products packaged together as one unit (for example, a kit containing drapes, needles, a syringe, a local anesthetic and a topical

antiseptic). A combination product is also defined to include a product that is intended for use only with an approved product where both are required to achieve the intended use, indication, or effect, and the labeling of the approved product needs to be changed to reflect this use. For example, if a device to aerosolize medication works only with a specific aerosolized drug, the device would be labeled for use with this drug and the two products would be a combination product. Finally, the combination product definition includes any investigational product that is intended to be used only with another investigational product where both are required to achieve the intended use, indication, or effect.

In accordance with section 503(g)(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 353(g)(1)), the agency is required to assign premarket review responsibility for combination products based on the product's "primary mode of action." The designation of an agency component does not preclude consultations with other agency components, and when such consultation is used, the involvement of more than one center in the premarket review process presents unique challenges in review management. In addition, where the agency finds it is appropriate, the agency reserves the option to require separate applications to be approved (by either the lead center or separate agency components) for the individual components of a combination product. FDA recognizes that requiring the approval of a second agency component may present additional issues for the applicant and in those instances strives to coordinate the reviews to the greatest extent possible.

A number of issues have been raised regarding FDA's regulation of combination products. These include concerns about the consistency, predictability, and transparency of the assignment (jurisdiction) process; issues

related to the management and timeliness of the review process when two (or more) FDA centers have review responsibilities for a combination product; lack of clarity about the postmarket regulatory controls applicable to combination products; and the lack of clarity regarding certain agency policies, such as when applications to more than one agency component are needed.

FDA recognizes the need to have policies and procedures that will ensure the efficient and effective review and regulation of combination products, and has established a Combination Products Program within the Office of the Ombudsman to provide support to the Centers for these activities. In addition to serving as a point of contact for industry and the FDA centers on combination products issues, the Combination Products Program is working with the centers to develop a variety of initiatives to improve the review and regulation of combination products. These initiatives include the development of standard operating procedures to improve the management of the intercenter review process, centralized monitoring of the progress of premarket reviews of combination products, and the development of guidance on policy issues that relate to combination products.

## **II. Purpose and Scope of the Hearing**

The agency recognizes the importance of protecting the public health by facilitating the introduction of safe and effective new products. New technologies and products that result from the combination of components that would otherwise be regulated under different regulatory authorities raise not only unique scientific questions, but also regulatory challenges related to where and how such products should be regulated in order to ensure adequate and consistent regulatory oversight.

FDA is calling this meeting to discuss the agency's processes for the assignment, premarket review, and postmarket regulation of combination products in general. The meeting is another step in the agency's continuing effort to elicit information helpful to the refinement of the agency's policies on combination products, and will build upon the June 24, 2002, part 15 hearing held to discuss the assignment and premarket review of wound healing products comprised of living human cells in combination with a device matrix. The hearing is limited to discussion of combination products as defined in § 3.2(e). Combinations of two devices, two drugs, or two biologics are not considered combination products under § 3.2(e) and are beyond the scope of this meeting. Discussion of the assignment of specific types of combination products, or of premarket review or testing requirements for specific products, is also beyond the scope of the meeting. Examples of issues raised for particular products may, however, be appropriate for illustration purposes.

### **III. Issues for Discussion**

Combination products often involve cutting edge, novel technologies that raise unique scientific, technical, policy and regulatory issues. Multi-center responsibility for the premarket review and regulation of combination products creates special challenges with respect to both the scientific and administrative aspects of review management. In addition, the combination of components that would normally be regulated under different regulatory authorities introduces additional factors to consider in the formulation of appropriate regulatory requirements. FDA recognizes the need to have policies and procedures that will ensure the efficient and effective review and regulation of combination products, and is holding this meeting to obtain stakeholders'

views on the issues raised by, and suggestions for, the review and regulation of combination products.

To assist in the development of consistent policies on assignment of these products and appropriate premarket and postmarket regulatory policies, the agency invites information and comments on the issues and questions listed in the next section of this document.

#### *A. Assignment and Intercenter Agreements*

##### Issue:

One goal of FDA's regulatory process has been the establishment of a credible, consistent and predictable ("transparent") framework for the assignment and review of human drugs, biologics, and devices to the appropriate centers. Prior to 1991, confusion over product jurisdiction was a frequently cited complaint by regulated industry.

As described in section I of this document, SMDA required that FDA assign combination products to the FDA components based on the product's primary mode of action. Furthermore, in 1991, the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Center for Drug Evaluation and Research (CDER) developed working agreements ("Intercenter Agreements") addressing the assignment and regulatory pathways for specified products or classes of products, including some types of combination products. The Agreements identify the lead center that will be responsible for regulating particular types of products, and in some instances, the applicable regulatory authority. While the Intercenter Agreements continue to provide useful guidance, the evolution in technology and scientific knowledge about the mode of action of medical products has in some cases pushed the usefulness of the current Intercenter

Agreements past their limits. FDA recognizes the need to revise and update the Intercenter Agreements to reflect decisions made since 1991 and an appropriate division of labor among the centers.

Stakeholders have voiced concern about a perceived lack of consistency in the assignment of combination products. This perception is sometimes attributed to potential differences in the interpretation of a combination product's "primary mode of action," a term that is not defined in the statute. The assignment process may also appear to be inconsistent if two products that appear to be similar in nature are assigned to different centers based on differences in their primary mode of action. When review responsibility for particular products of a given type is split between two centers, it may lead to inconsistencies in the type of premarket regulatory authorities applied, review policies, postmarket regulatory controls, and other factors relevant to product regulation.

Another complaint frequently cited about the assignment of combination products is the lack of transparency. In an effort to keep stakeholders apprised of significant jurisdictional decisions, FDA has begun to post a series of "jurisdictional updates" on its Combination Products Web site <http://www.fda.gov/oc/ombudsman/combination.html>. These jurisdictional updates report prior agency decisions only and are not policy statements. In determining whether Web publication of a jurisdictional update is appropriate for a product, FDA will take into account 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. In cases where it is not possible to adequately describe the subject of a jurisdictional decision and still

protect confidential and trade secret information, jurisdictional updates will not be available.

Questions:

1. What types of guiding scientific and policy principles should FDA use in its revisions to the existing Intercenter Agreements that allocate review responsibility for human medical products?

2. What factors should FDA consider in determining the primary mode of action of a combination product? In instances where the primary mode of action 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)?

### *B. Marketing Applications*

The SMDA required that the primary mode of action of a combination product must determine which FDA center would be responsible for premarket review, but did not address which authorities, including which type of marketing application, should be used to review the combination product, beyond authorizing FDA to use any resources necessary to ensure an adequate premarket review. The selection of regulatory authorities to be applied to a combination product is intended to ensure appropriate review and regulation, but may also affect the potential for generic competition and the availability of certain regulatory mechanisms or processes (e.g., a device component of a combination product regulated solely under the new drug application (NDA) or biological license application (BLA) authorities would not be eligible for

reclassification or review under section 510(k) of the act premarket notification).

As stated in 21 CFR 3.4(b), FDA may require separate applications for the different components of a combination product (“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.”). This flexibility is important because the most appropriate regulatory approach for a given combination product may need to be tailored to the associated scientific and policy issues. Some applicants have questioned the need for separate marketing applications for the components of a combination product, perhaps based on the perception that the regulatory burden would be less with a single application. On the other hand, some applicants have objected to FDA’s decision to require only a single application because separate applications were considered to be advantageous for future development and/or marketing opportunities. While no single approach is universally preferred or most appropriate from a regulatory perspective, the agency recognizes that it is important to have established criteria for determining whether one application or two would be more appropriate.

Questions:

3. What are the general scientific and policy principles that should be followed in selecting the premarket regulatory authorities to be applied to combination products? Is one premarket review mechanism (e.g., premarket approval (PMA), premarket notification (510(k)), new drug application (NDA),

or biologic licensing application (BLA)) more suitable than another for regulating combination products?

4. Recognizing the need to ensure product safety and effectiveness, what criteria should FDA use to determine whether a single application or separate applications for the individual components would be most appropriate for regulation of a combination product? For example, FDA may determine that it is necessary to apply elements of different regulatory authorities to a combination product to ensure safety and efficacy (e.g., device postmarketing reporting for the combination product, with drug current good manufacturing practices (CGMPs) applicable to the drug component only). Should the need to apply a mixed regulatory approach influence whether one application or two are more appropriate?

### *C. Other Issues*

Issues:

Combination products sometime raise concerns about safety and effectiveness, or risks to the public health, arising specifically from the combination nature of the product. The agency may draw from the statutory and regulatory authorities applicable to all components of the combination product in order to ensure adequate review of the safety and effectiveness of a product. For example, a drug-coated device may be subject to the device Quality Systems Regulation for the device component, to drug good manufacturing practices (GMPs) for the drug coating, and to a mix of requirements, as appropriate, for the combined product.

While this flexibility is appropriate to enable FDA to best promote and protect public health and address unique issues arising from the combination of two products that would otherwise be separately regulated, stakeholders

have complained that there is a lack of consistency, predictability, and transparency in the application of postmarket requirements for such products. Since manufacturers must design their manufacturing and quality systems for the types of products they produce, an applicant that primarily manufactures devices, for example, may not have the systems in place to manufacture a drug-coated device that will be subject to drug GMPs. Similarly, applicants report confusion in deciding which adverse event monitoring regulations to follow for a combination product. Applicants report that reporting to multiple centers has been required in some cases, and is duplicative and unnecessary.

Questions:

5. What scientific and policy principles should be followed in determining the appropriate manufacturing and quality system regulatory authorities (e.g., Current Good Manufacturing Practices versus Quality System Regulation) applicable to combination products?

6. What scientific and policy principles should be followed in determining the appropriate adverse event reporting requirements (e.g., the drugs and biologics adverse event reporting system, Medical Device Reporting) to be applied to a combination product?

7. What other comments do you have concerning other issues related to FDA regulation of combination products? (Examples may include cross labeling of products intended to be used together, though manufactured by different companies; and application of promotion and advertising policies to combination products.)

#### IV. Notice of Hearing Under Part 15

The Commissioner of Food and Drugs (the Commissioner) is announcing that the public hearing will be held in accordance with part 15. The hearing will have a presiding officer, who will be accompanied by senior management from CBER, CDER, CDRH, and the agency's Combination Products Program.

Persons who wish to participate in the part 15 hearing must file a written or electronic notice of participation with the Dockets Management Branch (see **ADDRESSES**). To ensure timely handling, any outer envelope should be clearly marked with the docket number listed at the head of this notice along with the statement "Combination Products Hearing." Groups should submit two written copies. The notice of participation should contain the person's name; address; telephone number; affiliation, if any; the sponsor of the presentation (e.g., the organization paying travel expenses or fees), if any; a brief summary of the presentation (including the specific discussion questions that will be addressed); and approximate amount of time requested for the presentation. The agency requests that interested persons and groups having similar interests consolidate their comments and present them through a single representative. After reviewing the notices of participation and accompanying information, FDA will schedule each appearance and notify each participant by telephone of the time allotted to the person and the approximate time the person's oral presentation is scheduled to begin. If time permits, FDA may allow interested persons attending the hearing who did not submit a written or electronic notice of participation in advance to make an oral presentation at the conclusion of the hearing. The hearing schedule will be available at the hearing. After the hearing, the hearing schedule will be placed on file in the Dockets Management Branch under the docket number listed at the head of this notice.

Under § 15.30(f), the hearing is informal, and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members may question any person during or at the conclusion of each presentation.

Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (part 10, subpart C (21 CFR part 10, subpart C)). Under § 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. The hearing will be transcribed as stipulated in § 15.30(b). The transcript of the hearing will be available on the Internet at <http://www.fda.gov/ohrms/dockets>, and orders for copies of the transcript can be placed at the meeting or through the Freedom of Information Staff (HFI-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Any handicapped persons requiring special accommodations to attend the hearing should direct those needs to the contact person (see **FOR FURTHER INFORMATION CONTACT**).

To the extent that the conditions for the hearing, as described in this notice, conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h).

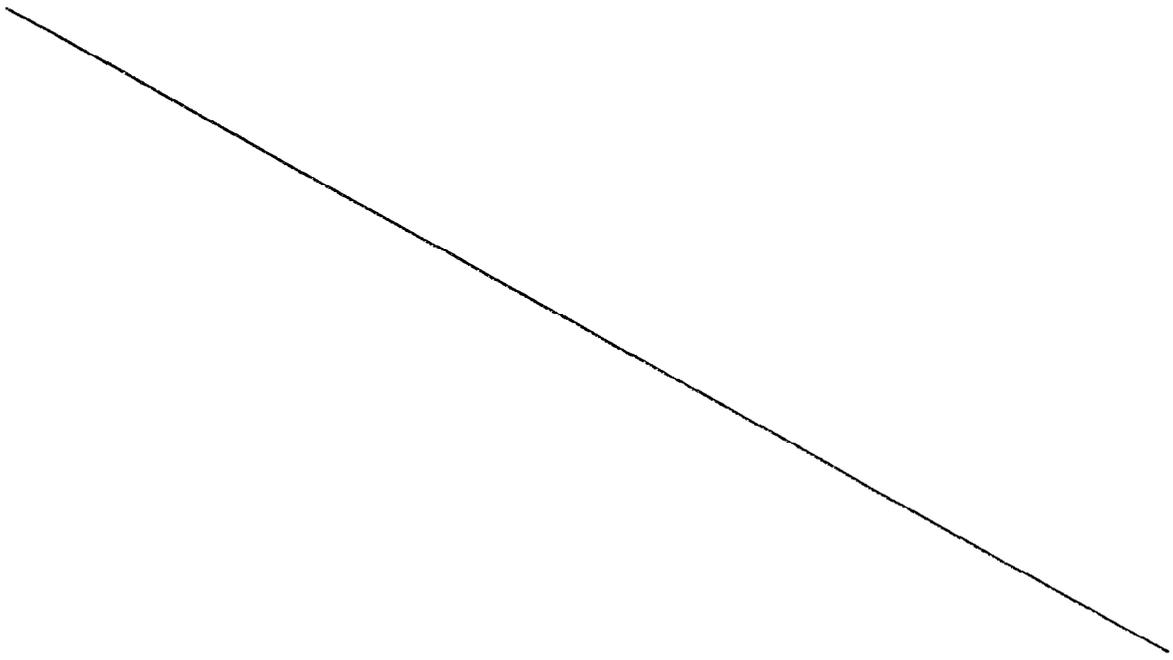
## **V. Request for Comments**

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written or electronic notices of participation and comments for consideration at the hearing. To permit time for all interested persons to submit data, information, or views on this subject, the administrative record of the

hearing will remain open following the hearing. Persons who wish to provide additional materials for consideration should file these materials with the Dockets Management Branch (see **ADDRESSES**). You should annotate and organize your comments to identify the specific questions to which they refer (see section III of this document). Two copies of any mailed comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number at the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Transcripts of the hearing also will be available for review at the Dockets Management Branch.

## **VI. Electronic Access**

Persons with access to the Internet may obtain more information about this hearing or combination products in general at <http://www.fda.gov/oc/ombudsman/combination.html>.



Dated: 10/18/02  
October 18, 2002.



Margaret M. Dotzel,  
Associate Commissioner for Policy.

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*Dawn P. Hawkins*