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Frequently Asked Questions About Combination Products

General:

What is a combination product?

combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Under 2 CFR 3.2 (e) a combination product is defined to include:

1. A product comprised of two or more regulated components (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as single entity [often referred to as "single-entity" combination product];

2. Two or more separate products packaged together in single package or as unit and comprised of drug and device products, device and biological products, or biological and drug products [often referred to as a "co-packaged" combination product];

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, upo 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) [often referred to as a "cross-labeled" combination product]; 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 [another type of "cross-labeled" combination product].

What are some examples of combination products?

Example of a single-entity combination products (where the components are physically, chemically or otherwise combined) (2 CFR 3.2(e)(1)):

- Monoclonal antibody combined with a therapeutic drug
- Device coated or impregnated with a drug or biologic
    - Drug-eluting stent, pacing lead with steroid-coated tip, catheter with antimicrobial coating, condom with spermicide, transdermal patch
- Prefilled drug delivery systems (syringes, insulin injector pen, metered dose inhaler)

Examples of co-packaged combination products (the components are packaged together) (2 CFR 3.2(e)(2)):

- Drug or vaccine vial packaged with a delivery device
- Surgical tray with surgical instruments, drapes, and anesthetic or antimicrobial swabs
- First-aid kits containing devices (bandages, gauze), and drugs (antibiotic ointments, pain relievers)

Example of product that may be cross-labeled combination product (components are separately provided but specifically labeled for use together) (2 CFR 3.2(e)(3) or (e)(4)):

- Photosensitizing drug and activating laser/light source

What are the roles of the Office of Combination Products?

The Office of Combination Products was established on December 24, 200 as required by Sec. 20 of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA). Its duties are detailed in section 503(g) of the Federal Food, Drug, and Cosmetic Act (2 USC 353(g))

The roles of the Office of Combination Products (OCP) include:

- To serve as focal point for combination product issues and for medical product classification and assignment issues for agency staff and industry.
- To develop guidance and regulations to clarify the regulation of combination products.
- To classify medical products as drugs, devices, biological products or combination products and assign them to an FDA center for premarket review and regulation, where their classification or assignment is unclear or in dispute.
- To ensure timely and effective premarket review of combination products by overseeing the timeliness, alignment of coordination of reviews involving more than one agency center, including through monitoring and management of the intercenter consult process
- To ensure consistent and appropriate postmarket regulation of combination products.
- To resolve disputes regarding the timeliness of premarket review of combination products.

The Director of OCP is member of the FDA Combination Products Policy Council.

OCP prepares statutorily mandated annual report to Congress regarding regulatory activities for combination products and medical product classification and assignment. OCP's annual reports to Congress for 2002 onward are posted on this webpage.

Who works in the Office of Combination Products?

Office of Combination Products staff members:

Thinh X. Nguyen - Director

Patricia Y. Love, MD., MBA. - Deputy Director

John (Barr) Weiner, J.D. - Associate Director for Policy and Product Classification Officer

Leigh Hayes, J.D. – Lead Product Jurisdiction Officer

Joseph Milone, Ph.D. - Senior Scientific Reviewer

Jose L. Moreno, Ph.D. - Senior Scientific Reviewer

Diana M. Yoon, Ph.D. - Senior Scientific Reviewer

Melissa Burns - Senior Program Manager

Bindi Nikhar, MD. - Associate Clinical Director

Maryam Mokhtarzadeh, MD. – Senior Medical Officer

Bibi K. Jakrali - Management Analyst

Danita M. Dixon - Project Management Officer

How can I contact OCP?

You may e-mail OCP at combination@fda.gov Our mailing address is WO32, Hub/Mail Room #5129, 1090 New Hampshire Avenue, Silver Spring, MD 20993-0002. Our fax number is (301) 847-8619.

Product Jurisdiction/Assignment of Combination and Non-Combination Products

How are combination products assigned for review?

Combination products are assigned to FDA center that will have primary jurisdiction for its premarket review and regulation. Consistent with section 503(g)(1) of the Act, assignment to a center with primary jurisdiction for premarket review and post-market regulation, or a lead center, is based on a determination of the "primary mode of action" (PMOA) of the combination product. For example, if the PMOA of device-biological combination product is attributable to the biological product, the Agency component responsible for premarket review of that biological product would have primary jurisdiction for the combination product.

Section 503(g) defines primary mode of action as "the single mode of action of combination product that provides the most important therapeutic action of the combination product" (see also definitions at

2 CFR 3.2. In some cases, the most important therapeutic action cannot be determined. For example, combination product may have two independent modes of action, neither of which is subordinate to the other. To resolve these types of questions, FDA's regulations at 2 CFR Part 3 include an algorithm for determining center assignment. The algorithm directs center assignment based on which center regulates combination products raising similar types of safety and effectiveness questions, or, if there is n such center, based o which center has the most expertise to evaluate the most significant safety and effectiveness questions raised by the combination product.

What is the process for obtaining an Agency decision regarding the classification or center assignment for my medical product?

Sponsors may request formal assignment through the Request for Designation (RFD) process or alternatively obtain informal non-binding feedback regarding their combination product or product through submission of a Pre-Request for Designation (Pre-RFD).

How do I submit a Pre-Request for Designation (Pre-RFD)?

The Pre-RFD process is available to provide informal, non-binding feedback o whether a medical product is a drug, device, biological product, or combination product and/or the Center to which it would be assigned. Sponsors may contact OCP (i.e. at combination@fda.gov for information about how to submit a Pre-RFD. Additionally, OCP recently published a draft guidance about Pre-RFDs that may be helpful.

How do I submit a Request for Designation?

The Request for Designation (RFD) process is outlined in 2 CFR Part 3 and the specific information to be included in the RFD is described in detail in 2 CFR 3.7. FDA also has issued a guidance document "How to Write a Request for Designation to provide guidance to sponsors on the kind of information FDA needs in an RFD in order to make product classification and assignment determinations.

Premarket Review and Postmarket Regulation of Combination Products

What investigational application should I use for a combination product?

a. How many applications?

One investigational application is generally sufficient for a combination product. That application should include all information on the entire combination product. For example, if the investigation is for a drug-device combination product, the application should include the details o the drug and device that typically would be submitted in an IND and IDE, respectively.

b. Is an IND/IDE needed?

You should consider the regulatory requirements for when an investigational new drug application (IND) or an investigational device exemption application (IDE) is required in determining whether an investigational application is needed for a combination product, and take into account each constituent part as well as the combination product in making these determinations. Typically, an IND is submitted if the combination product has a drug or biologic PMOA and an IDE if the combination product has a device PMOA. OCP is available to assist you if you have questions regarding investigational applications and the investigational application requirements at 2 CFR 312 and 812 with respect to your investigational combination product.

c. Which center has the lead?

The lead center for the investigation of combination product is determined by the primary mode of action (PMOA). In most cases, the investigational application is determined by the lead center. For example, if the drug constituent part provides the PMOA, the lead center would typically be the Center for Drug Evaluation and Research, and the investigation would be under an IND.

What types of marketing applications are required for a combination product?

Combination products are typically marketed under a marketing authorization type associated with the constituent part that provides the primary mode of action (PMOA) for the combination product (i.e., a new drug application (NDA) or abbreviated new drug application (ANDA) if it has a drug PMOA, a biologic license application (BLA) if it has a biologic PMOA, or a premarket approval application (PMA), de novo classification, or premarket notification ("510(k)") if it has a device PMOA). A single marketing application is generally sufficient for combination product. In some cases, however, a sponsor may wish to submit separate marketing applications for different constituent parts of a combination product, and FDA may consider this permissible.

Does OCP review marketing applications for combination products?

No, OCP does not review marketing applications for combination products. As needed, OCP assigns the lead Center (CBER, CDER or CDRH) that will have primary jurisdiction for the premarket review and regulation of a combination. In addition, OCP is available as a resource to industry and agency reviewers to help facilitate the review process.

What format should I use to submit a marketing application for a combination product?

OCP and the Centers are continuing to work on recommendations for formatting of marketing applications for combination products that will help facilitate review by all appropriate agency components based on the application submission types.

For applicants submitting IND, BLA or NDAs to CBER or CDER using the eCTD format, see information in the combination products section found in the eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry *Providing Regulatory Submissions in Electronic Format*

—Certain Human Pharmaceutical Product Applications an Related Submissions Using the eCTD Specifications September, 2016.

In the interim, for other submission types sponsors are encouraged to discuss this issue during pre-submission meetings with the Agency.

How do I request that OCP or review staff from a consulting Center attend a regulatory meeting, such as a pre-IDE or pre-IND meeting, with agency reviewers?

You can make such a request in your submission to the lead Center, and copy OCP.

What good manufacturing practice regulations apply to combination products?

final rule o CGMP requirements for combination products identifies what CGMP requirements apply to combination products (codified at 2 CFR 4 and options for demonstrating compliance with them. For additional information, please review the final rule and final guidance document o this topic that provide additional information.

How are adverse events reported for combination products?

final rule addresses postmarket safety reporting requirements (PMSR) for combination products.

Where can I find guidance for what kind of information is needed to support marketing authorization for a combination product?

OCP and the Centers have published guidance regarding specific combination product categories and premarket regulatory considerations. These guidance documents can be found on the FDA website. If you have any issues or concerns, please contact the lead Center's review division to discuss.

How can I submit proprietary information to the Agency for use in the review of combination products?

master file can be used by the applicant to submit confidential, trade secret data that is not known to the applicant but is proprietary information for use in the review of investigational or marketing submissions. For reliance on the data, the applicant should provide right of reference letter from the master file holder. The applicant may cross-reference a master file that resides in any medical product center (i.e., CBER, CDER, CDRH). Information in these master files should be updated and organized to expedite FDA review. Se guidance for Drug Master Files and Drug Master File Binders Drug Master Files for CBER-Regulated Products and for Master Files for Devices available on FDA's website.

How can OCP help me resolve a dispute regarding the premarket review of a combination product?

OCP is available to assist FDA regulated entities in resolving issues that may arise between them and Centers or other FDA components, relating to premarket review or other regulatory issues for combination products. Requests for assistance may be submitted to OCP's mailbox at combination@fda.gov. With respect to formal disputes regarding the timeliness of premarket review of combination products, OCP has published a guidance document which describes the procedures for submitting a request for OCP to resolve the dispute. If a regulated entity wishes to appeal an FDA combination product premarket review decision, the entity should use the appropriate appeals mechanism for the lead Center.

What are some examples of medical product types that are commonly mistaken as "combination products"?

Some FDA regulated products are intended to be used together to achieve their therapeutic or diagnostic effect but d not meet the regulatory definition of a combination product. This can be the case for medical products intended to be used together, for example, syringes marketed for general delivery of unspecified drugs or two or more of the same type of medical product (e.g., a drug and drug, or device and device) that are packaged or labeled for use with one another (e.g., fixed dose combination drugs under 2 CFR 300.50). Similarly, combinations of a medical product with a non-medical product, for example a drug with a dietary supplement, cosmetic, or food, are not combination products.

I believe my combination product may qualify for orphan drug or biological product designation or a humanitarian use device exemption. Where can I find information about these designations?

Information about orphan product and humanitarian use device designations may be found on the Developing Products for Rare Diseases & Conditions section of the FDA website. If you are unsure whether your product is a drug, biological product, device or combination product (i.e., its regulatory identity is unclear), you are encouraged to contact OCP (see information above) prior to submitting an orphan product or humanitarian use designation request.

How do I submit a Freedom of Information Act (FOIA) Request to obtain more information about combination product approvals or other information?

Please visit FDA's FOIA request page for additional information.