Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product

Guidance for Industry and FDA Staff

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For questions regarding this document, contact Suzanne O'Shea at 301-827-1934 or by email at: **combination@fda.gov (mailto:combination@fda.gov)** **Address Update (/CombinationProducts/JurisdictionalInformation/ucm148279.htm)**

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) was enacted on October 26, 2002. Among other things, this act created the Office of Combination Products (OCP) within the Office of the Commissioner of Food and Drugs. One of OCP's functions is to develop and implement policies and processes to streamline the review and regulation of drug-device, drug-biologic and device-biologic combination products as defined in 21 CFR 3.2(e). For example, OCP is responsible for overseeing the timeliness of, and coordinating reviews of combination products when more than one agency Center is involved. In addition, OCP is available as a resource to sponsors and agency reviewers at any time throughout the development of a combination product.[1] ,[2]

This guidance document provides information affecting a relatively narrow range of inquiries to OCP, i.e., for applicants wishing to present a formal dispute about the timeliness of review of a premarket application for a combination product.

OCP does not have the authority to direct a reviewing division to take any particular action, but it is responsible for resolving disputes about the timeliness of premarket reviews of combination products:

> Any dispute regarding the timeliness of the premarket review of a combination product may be presented to the Office for resolution, unless the timeliness of the dispute is clearly premature.
> 21 U.S.C. § 353(g)(4)(E)(i).

A combination product is assigned to an Agency center that will have primary jurisdiction for its regulation. Under section 503(g) of the Act, the assignment of a "lead center" is based upon a determination of the "primary mode of action" (PMOA) of the combination product.[3] ,[4] For example, i f the PMOA of a combination product is that of a biological product, then the combination product would be assigned to the Agency component responsible for premarket review of that biological product. Depending upon the type of combination product, approval, clearance or licensure may be obtained through submission of a single marketing application, or through separate marketing applications for the individual constituent parts of the combination product.

A center assigned primary jurisdiction for the regulation of a combination product frequently accomplishes its review in consultation or collaboration with another center. Good communication between the lead and consulting centers, clear articulation of questions that arise throughout the review process, good review practices, appropriate supervisory review, effective pre-submission meetings and consultations, specified internal points of contact, and consultation milestones are all critical to ensuring a timely and effective premarket review process.

FDA recognizes that timely premarket reviews also depend on timely and effective review consultations and collaborations between and among centers. For this reason, the Agency has established a Standard Operating Procedure for the Intercenter Consultative/Collaborative Review Process to help ensure the timeliness and consistency of intercenter reviews. For example, consultation time frames are established taking into account the time frame for Agency response to the regulatory submission. Furthermore, OCP actively monitors the progress of consultative reviews to ensure their timely and effective completion.[5]

Issues arising from the timeliness of internal consultations and collaborations are outside the scope of this guidance document. This guidance document covers only disputes arising from the timeliness of the overall premarket review process for the marketing application.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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II. What is a premarket review timeliness dispute?

For the purpose of this guidance document, a timeliness dispute arises when FDA does not review and act on an applicant's premarket submission within the applicable time frame, and the applicant presents the issue to OCP for resolution. For example, if an applicable time frame states that a particular action is to be taken within 90 days, and the action is not taken by that time, the sponsor or applicant may present the issue to OCP for resolution.

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III. What are the applicable time frames?

The Prescription Drug User Fee Act (PDUFA) and MDUFMA set performance goals for many types of drug, device, and biological product premarket applications. (Goals pertaining to biologic license applications are contained in both PDUFA and MDUFMA.) These goals reflect current expectations about the portion of premarket applications that will be reviewed within a specified time frame. Performance goals apply to only a portion of all applications of a certain type; [6] they do not require that every application be reviewed in accordance with the applicable time frame. Nevertheless, because PDUFA and MDUFMA goals reflect current expected review time frames, OCP believes it is appropriate to use them as measures to evaluate whether timeliness dispute resolution requests are premature.

Current PDUFA performance goals can be found at www.fda.gov/FDAgov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm118925.htm. Current MDUFMA performance goals can be found at www.fda.gov/cdrh/mdufma/presentations/mdufma.html (Part III).

In disputes related to combination product reviews, OCP expects to consider the time frames contained in PDUFA and MDUFMA performance goals in the following ways:

1. When a combination product is to be reviewed under one premarket application, OCP intends to consider the time frames associated with that type of premarket application. For example, if a combination product consisting of drug and device constituent parts is to be reviewed only under a new drug application, then OCP would consider the performance goals associated with new drug applications.[7]
2. When a combination product is reviewed under two premarket applications, OCP intends to consider the time frames associated with each type of premarket application. For example, if a combination product consisting of drug and device constituent parts is to be reviewed under both a device application and a new drug application, then OCP would consider the time frames associated with device applications to that portion of the review covered by the device application. Similarly, OCP would consider the time frames associated with new drug applications to that portion of the review covered by the new drug application.[8]

3. OCP intends to consider time frames to be applicable to combination products even if the applicant does not pay a user fee; for example, when the sponsor is granted a waiver of an applicable user fee.

Some types of submissions are not covered by user fee time frames. For example, there are no user fee time frames for applications covering allergenic extracts, blood and blood components for transfusion, Investigational New Drug applications (21 CFR Part 312) or Investigational Device Exemption applications (21 CFR Part 812); nor is there a user fee time frame covering the review of humanitarian use devices (21 CFR Part 814, Subpart H). In a situation where there is no applicable user fee time frame, OCP intends to consider any relevant time frame identified in an applicable statute or regulation to determine whether a timeliness dispute resolution request is premature. In situations where there is no applicable statute or regulation, sponsors are encouraged to contact OCP to discuss the issue and determine the best way to proceed.

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IV. When should a timeliness dispute resolution request be presented?

The purpose of a timeliness dispute resolution request is to ensure timely completion of the relevant review, rather than to impose any sanction on the reviewing Center. In keeping with this perspective, OCP recommends that dispute resolution requests be presented after the relevant deadline has been missed, and before the reviewing Center has completed its premarket review. For example, if a relevant performance goal states that a particular action is to be taken within 90 days, and the Center completes the review on day 93, a timeliness dispute resolution request presented on day 95 would do nothing to further the goal of obtaining a timely review.

As noted above, when a combination product is reviewed under two marketing applications, OCP would consider the time frames associated with each type of application. Applicants with combination products reviewed under two types of applications may submit dispute resolution requests for one of the applications, even if the time frame for the second application has not yet passed. For example, if a combination product is being reviewed by both CDER and CDRH under drug and device applications respectively, and CDRH fails to meet the relevant MDUFMA time frame, but the PDUFA time frame for action on the drug application has not yet occurred, a timeliness dispute resolution request covering the device application would not be premature once the MDUFMA time frame has not been met. A request related to the device application would be timely even though the PDUFA time frame had not passed for the drug application.

On occasion, a reviewing division may inform an applicant in advance that an applicable time frame will not be met. In that case, a request for a timeliness dispute resolution presented before the time stated in the relevant performance goal has passed would further the goal of obtaining a timely review. OCP recommends that applicants base such a timeliness dispute resolution request on a letter, facsimile, FDA meeting minutes, or some other statement from FDA that a time frame will not be met.

This guidance document does not cover planning discussions or, in the absence of clear notification from the reviewing division, prospective concerns about a reviewing division's ability to meet a time frame in the future. OCP recommends that resolution of such issues be facilitated through informal procedures outside the scope of this guidance.

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V. What is the process for presenting a timeliness dispute resolution request to OCP?

We recommend that sponsors and applicants try to resolve disputes with the lead division, office and center before contacting OCP. If an applicant believes that a date for action on an application has passed without action, or if the reviewing division in the lead center informs the applicant that an applicable time frame will not be met, OCP recommends that the applicant first discuss the status of the review with the reviewing division and/or the Office to which the reviewing division reports within the lead Center.[9] The Center ombudsmen identified below are also available to assist you: **Address Update (/CombinationProducts/JurisdictionalInformation/ucm148279.htm)**

CBER :

Sheryl Lard-Whiteford, Ph.D.
Ombudsman
Center for Biologics Evaluation and Research
1401 Rockville Pike (HFM – 4)
Rockville, MD 20857
301-827-5413

CDRH :

Les Weinstein, Esq.
Ombudsman
Center for Devices and Radiological Health
9200 Corporate Blvd. (HFZ-5)
Rockville, MD 20850
301-827-7991

CDER :

Warren Rumble
Ombudsman
5515 Security Lane (HFD-006)

Suite 500
Rockville, MD 20852
301-594-5480

If the reviewing division or appropriate Office within the lead center does not provide the applicant with a satisfactory response, it would be appropriate to direct the timeliness dispute to OCP.

OCP encourages timeliness disputes to be presented by letter, fax or e-mail.

OCP's contact information is:

Office of Combination Products
15800 Crabbs Branch Way, Suite 200
HFG – 3
Rockville, MD 20855
Telephone: (301) 427-1934
Fax: (301) 427-1935
Email: **combination@fda.gov (mailto:combination@fda.gov)**

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VI. What information should be included in a timeliness dispute resolution request?

A timeliness dispute resolution request should include the following information:

1. Contact information for the applicant;
2. The name of the product, and information about why the product is a combination product;
3. The Request for Designation number if the product went through the Request for Designation process;
4. The FDA Center and reviewing division that is responsible for the premarket review;
5. The application number assigned by the reviewing Center or division;
6. The type of application;
7. Any relevant user fee performance goal;
8. The date the applicant believes the action was due;
9. The name and telephone number of the FDA contact person for the application;
10. A summary of the information provided by the reviewing division in the lead center regarding the timeliness of the review; and

11. A summary of the applicant's perspective on issues or barriers to progress affecting the timeliness of the premarket review process.

VII. How will OCP respond to a request for resolution of a timeliness dispute?

Upon receipt and review of a timeliness dispute resolution request, OCP expects to place a telephone call to the Director of the reviewing division in the lead center, and to the appropriate Center Ombudsman. When appropriate, OCP will convene a meeting with the reviewing division, the Center Ombudsman, and/or with the applicant. The purpose of the telephone call and/or meeting will be to determine:

1. whether the Division Director and the Center Ombudsman agree that the relevant user fee time frame has not been met;
2. the current status of the review;
3. issues that need to be resolved before the review can be completed; and
4. what OCP can do to facilitate the completion of a timely review, and if necessary and feasible, a plan for the completion of the review, including a target date for completion of the review.

OCP will next place a telephone call to the applicant to discuss the current status of the review, and when appropriate and feasible, the review division's plan for completing the review. OCP intends to provide this information to the applicant within 10 working days after the timeliness dispute is presented to OCP.

If the reviewing division fails to meet the new target date for completion of the review, the applicant should advise OCP if further follow-up is requested. OCP will then follow up with the reviewing division on behalf of the applicant.

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Footnotes

1 More information about OCP's functions and responsibilities is available at http://www.fda.gov/oc/combination/default.htm. Examples of ways OCP serves as a resource to sponsors and agency review staff are provided in the Office's Report to Congress, posted at http://www.fda.gov/oc/combination/default.htm.

2 OCP's contact information is provided later in this document.

3 A proposed rule defining the primary mode of action of a combination product was published in the May 7, 2004, Federal Register (69 FR 25527), and is available at http://www.fda.gov/oc/combination/default.htm.

4 The lead Center has responsibility for the premarket review and regulation of a combination product and will ordinarily be the sponsor's primary contact point for issues surrounding the product's review and regulation.

5 See http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126016.pdf for more information about how intercenter consultative reviews are requested, processed, and monitored.

6 For example, under current PDUFA performance goals, FDA is to r eview and act on 90 percent of priority original NDA and BLA submissions within 6 months. Similarly, under MDUFMA performance goals, in 2005, FDA is to issue 75 percent of its “major deficiency” letters on PMA's within 150 days.

7 Similarly, if a combination product consisting of drug and device constituent parts were to be reviewed by CDRH solely under a device application with a consult by CDER, then the performance goals associated with that type of device application would apply. Furthermore, CDER would provide its review of the drug constituent part to CDRH within the device application time frames. See the agency's **Standard Operating Procedure on the Intercenter Consultative/Collaborative Review Process (/downloads/RegulatoryInformation/Guidances/UCM126016.pdf)**, which provides that consultative review deadlines take into account the time frame for agency response to the regulatory application.

8 FDA believes it is not feasible to apply the shorter time frame to both types of marketing applications when two types of applications are submitted. PDUFA and MDUFMA provide time frames for all applications reviewed by a Center, whether the applications cover combination products or non-combination products. Compliance with these time frames requires the Center to carefully observe queuing regimens, and to closely manage reviewers' time. When two applications are submitted for the review of a combination product, OCP will consider the time frames associated with each type of application because to apply only the shorter time frame (e.g. to apply 510(k) time frames to an NDA) would disrupt the queuing of all other applications and possibly prevent reviewers from meeting the time frames for other applications covering non-combination products.

9 Please also see **Guidance for Industry "Formal Dispute Resolution: Appeals above the Division Level" (/downloads/RegulatoryInformation/Guidances/UCM126015.pdf)**. This guidance document sets forth procedures adopted by CBER and CDER to resolve scientific and procedural disputes above the division level. Information about Dispute Resolution guidance issued by CDRH is available at **http://www.fda.gov/FDAgov/RegulatoryInformation/Guidances/ucm113713.htm (/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOmbudsman/ucm113713.htm)**.

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