Guidance for Industry and FDA Staff:

Application User Fees for Combination Products

DRAFT GUIDANCE—September 2004

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For questions regarding this draft document, contact Mark D. Kramer, Office of Combination Products (OCP) at 301-427-1934.

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

September 2004

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Application User Fees for Combination Products

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I. PURPOSE

This document provides guidance to industry and FDA staff on marketing application user fees for combination products as defined under 21 CFR 3.2(e). The guidance document explains that combination products for which a single marketing application is submitted will be assessed the user fee associated with that particular type of marketing application. The document explains that, in the infrequent situation where FDA requires two marketing applications for a combination product, two application fees would ordinarily be assessed. The guidance also describes how the "barrier to innovation" waiver provision[2] under the prescription drug user fee provisions of the Federal Food, Drug, and Cosmetic Act (the Act) may be applied to innovative combination products for which FDA requires the submission of two applications. Such a waiver would provide a reduction in application user fees equivalent to the additional fee burden associated with the submission of two marketing applications.

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.

[1] This guidance has been prepared by the Office of Combination Products in the Office of the Commissioner in cooperation with the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health at the Food and Drug Administration.
[2] Section 736(d)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(d)(1)).

II. BACKGROUND INFORMATION

A. What is a combination product?

A combination product is a product comprised 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 21 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 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.

Drug-drug, device-device, or biologic-biologic products do not meet the definition of a combination product as defined in 21 CFR 3.2 (e), and are outside the scope of this guidance.

B. How are combination products assigned for review and what type of marketing applications are required?

A combination product is assigned to an Agency center[3] that will have primary jurisdiction for its premarket review and 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.[4] For example, if the PMOA of a combination product is that of a biological product, then the combination product would be assigned to the Agency component

[3] Section 503(g) of the Act defines the term "agency center" as a center or alternative organizational component of the Food and Drug Administration.

[4] 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.

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.

For most combination products, a single marketing application is sufficient for the product's approval, clearance or licensure. In some cases, however, a sponsor may choose to submit two marketing applications for a combination product when one application would suffice. For example, a sponsor may choose to submit two applications in order to receive some benefit that accrues only from approval under a particular type of application (e.g., new drug product exclusivity, orphan status, or proprietary data protection when two firms are involved). In other cases, FDA may determine that two marketing applications are necessary. For example, when one of the individual constituent parts of a combination product is already approved for another use, and where the labeling of the already approved product will need to be changed to reflect its new intended use in the combination product, FDA may determine that two applications are necessary if the labeling of the already approved product is subject to legal requirements different from those that will apply to the combination product. A guidance addressing the factors FDA expects to consider in determining whether a single or multiple marketing applications should be submitted for a combination product is in development and will be provided separately for public review and comment.

C. What are user fees?

In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA), P.L. 102-571. The user fee amendments were reauthorized by the Food and Drug Administration Modernization Act of 1997 and again by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. PDUFA authorized FDA to collect fees from companies that produce certain human drug and biological products. When a company requests approval of a new drug or biological product prior to marketing, it must submit an application (e.g., new drug application (NDA) or biologics license application (BLA)) along with a fee to support the review process. In addition, companies pay annual fees for each prescription drug product marketed and the establishment where the prescription drug product is manufactured. More information about PDUFA is available at http://www.fda.gov/oc/pdufa/ and http://www.fda.gov/cder/pdufa/default.htm .

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA), P.L. 107-250, amended the Act to provide for user fees for device reviews. The fees apply to certain premarket reviews of premarket approval applications (PMAs), product development protocols (PDPs), premarket reports (PMRs), biologics license applications (BLAs), certain supplements, and premarket notifications (510(k)s). More information about MDUFMA is available at http://www.fda.gov/oc/mdufma/.

III. USER FEES FOR COMBINATION PRODUCTS

A. How are application user fees determined for combination products?

As explained in the document "Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products; Guidance for Industry and FDA" available at http://www.fda.gov/cdrh/mdufma/guidance/1201.pdf, a combination product with a device component (i.e., a drug-device or biologic-device product) will be subject to the fee associated with the type of application required for the product's premarket approval, clearance, or licensure. For example, a biologic-device or a drug-device combination product for which a PMA is required will be subject to the PMA fee under MDUFMA, while a biologic-device or a drug-device combination product for which a 510(k) is required will be subject to the 510(k) fee under MDUFMA.

A biologic-device product regulated under section 351 of the PHS Act will be subject to the BLA fee under MDUFMA, if the biological component meets the definition of a device. Other biologic-device combination products (those with biologic components that do not meet the definition of a device) or drug-biologic combination products regulated under section 351 of the PHS Act, or drug-device or drug-biologic combination products regulated under section 505(b) of the Act, that are human drug applications as defined in section 735 of the Act, will be subject to prescription drug user fees. Prescription drug user fees may include application and yearly product and establishment fees. More information about prescription drug user fees is available at http://www.fda.gov/cder/pdufa/default.htm.

Therefore, combination products for which a single marketing application is submitted are subject to the fee associated with that type of application. Sponsors may be eligible for fee waivers or reductions (e.g., for small businesses) under PDUFA and MDUFMA. More information on available waiver options is provided below.

In some circumstances, a sponsor may choose to submit two applications covering the various components of a combination product when one application would suffice. In such cases, two application fees would be assessed, i.e., one fee for each application. For example, a sponsor may choose to submit two applications when one would suffice in order to receive some benefit from having two applications (e.g., new drug product exclusivity, orphan status, or proprietary data protection when two firms are involved). Although sponsors may still be eligible for existing fee waivers or reductions in this circumstance, the sponsor receives benefit by submitting two applications. Review of two applications when one would suffice places extra burden on FDA review resources, and a user fee for each application would ordinarily be assessed.

Likewise, when FDA requires two applications for a combination product, two application fees would be assessed. Sponsors may be eligible for existing waivers or reductions under PDUFA or MDUFMA. In particular, as explained below, the Agency intends to look closely at whether

a PDUFA "barrier to innovation" waiver may be appropriate to reduce the additional fee burden associated with FDA's requirement for two marketing applications.

B. What user fee waivers are available under MDUFMA?[5]

MDUFMA provides more limited user fee waiver options than those provided for under PDUFA. Other than specific situations identified in Table 1 below for which no application fee is required, standard MDUFMA fees are required for all device applications other than those from small businesses. Under MDUFMA, a small business is defined as one whose annual gross sales and revenues (for the firm and its affiliates) is ≤ $30 million. Under MDUFMA, small businesses pay 38% of the standard PMA and BLA fee and 80% of the standard 510(k) fee. MDUFMA also provides a one-time waiver for the first premarket application from a qualified small business.

Table 1: MDUFMA Fee Exemptions and Waivers (No Fee for These)

Category	Exemption or Waiver
Humanitarian Device Exemption (HDE)	Exempt from any fee.
BLA for a product licensed for further manufacturing use only	Exempt from any fee.
First premarket application (PMA, PDP, BLA, or premarket report) from a small business	One-time waiver of the fee that would otherwise apply.
Third-party 510(k)	Exempt from any FDA fee; however, the third-party may charge a fee for its review.
Any application for a device intended solely for pediatric use.	Exempt from any fee. If an applicant obtains an exemption under this provision, and later submits a supplement for adult use, that supplement is subject to the fee then in effect for an original premarket application.
Any application from a State or Federal Government entity.	Exempt from any fee unless the device is to be distributed commercially.

C. What user fee waivers are available under PDUFA?[6]

PDUFA provides for a waiver of the fee for the first human drug application from a small business.[7] The criteria for qualifying as a small business under PDUFA are different than

[5] MDUFMA waivers are described in Section 738 of the Act.
[6] PDUFA waivers are described in Section 736(d) of the Act (21 U.S.C. 379h(d)).
[7] See section 736(d)(1)(D) of the Act (21 U.S.C. 379h(d)(1)(D)).

those under MDUFMA.[8] Under PDUFA, "small business" means an entity that has fewer than 500 employees for the small business and its affiliates.[9]

PDUFA also provides for waivers or reductions of fees where:

- such waiver or reduction is necessary to protect the public health;
- the assessment of the fee would present a significant barrier to innovation because of limited resources available to such person or other circumstances; or
- the fees to be paid by such person will exceed the anticipated present and future costs incurred by the Secretary in conducting the process for the review of human drug applications for such person.

The document "Interim Guidance Document for Waivers of and Reductions in User Fees," available at http://www.fda.gov/cder/pdufa/default.htm, provides information for requesting, and the criteria for evaluating, a waiver of PDUFA application, establishment or product fees.[10] In addition, the document "Fees-Exceed-The-Costs Waivers Under the Prescription Drug User Fee Act," available at http://www.fda.gov/cder/pdufa/default.htm, provides further explanation of the waiver option described in the third bullet above.

It should be noted that PDUFA applications (NDA or BLA) not requiring clinical data for approval are assessed half the fee that is assessed for applications that do require clinical data for approval.[11] Supplemental applications to NDAs or BLAs that do not require clinical data for approval are not assessed a fee.

D. How might the PDUFA barrier to innovation waiver apply to innovative combination products for which two applications may be appropriate?

Combination products may incorporate cutting edge, innovative technologies that hold great promise for advancing patient care. For example, by combining two different types of regulated components, treatment may be made safer or more effective than it would be using either of the components independently.

FDA believes that the assessment of two marketing application fees for an innovative combination product could represent a significant barrier to its development.

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[8] Qualifying sponsors could receive a waiver from one or both application fees for their first PDUFA and MDUFMA premarket applications. Given the different criteria for small businesses, however, some companies may qualify for one waiver but not the other.

[9] See section 736(d)(3) of the Act (21 U.S.C. 379h(d)(3)).

[10] The current mailing addresses for submitting PDUFA waiver requests can be found on the Internet at http://www.fda.gov/cder/pdufa/addresses.htm.

[11] For FY 2005, the full NDA or BLA fee is $672,000, and the fee for an NDA or BLA that does not require clinical data for approval is $336,000.

After reviewing the various waiver options available under PDUFA and MDUFMA, FDA believes that the PDUFA barrier to innovation waiver allows the Agency to reduce the additional fee burden associated with the requirement for two marketing applications for an innovative combination product. In particular, PDUFA provides for a fee waiver or reduction when the assessment of the fee would present a significant barrier to innovation because of limited resources available to such person or other circumstances. FDA believes such "other circumstances" may exist in the infrequent case where two marketing applications are required. FDA expects to consider the factors discussed below in determining whether a particular innovative combination product is eligible for this fee reduction.

E. What factors may be considered in determining whether a product is eligible for an "Innovative Combination Product" waiver?

To be eligible for the "Innovative Combination Product" waiver under PDUFA's "barrier to innovation because of...other circumstances" provision, FDA expects to consider the following factors:

- The combination product (as defined in 21 CFR 3.2(e)) as a whole is innovative (see Section F below for factors FDA expects to consider in determining whether a combination product is innovative).

- FDA is requiring two fee-eligible[12] marketing applications[13] for the combination product.

- The two components of the product are specifically intended and labeled only for use together. Applications that include independent uses of one or both components outside the combination product generally would not be eligible for this waiver. However, applications for combinations of already approved, independent products generally would be eligible if two applications are required for approval of the new combined use.

- The applicant does not qualify for a PDUFA small business waiver or have limited resources. Applicants who qualify for a PDUFA small business waiver receive a full waiver of the PDUFA application fee. In addition, applicants with an innovative combination product who do not qualify for a PDUFA small business waiver, but who have limited resources, may be eligible for a standard PDUFA barrier to innovation

[12] Orphan product applications, BLAs for further manufacturing use only, HDEs, pediatric device applications or other applications where a fee is not assessed would not qualify. This waiver is specifically intended to reduce the additional fee burden associated with the requirement of two fee-paying applications. In these cases, only one application would be assessed a fee.

[13] The two applications could be any combination of fee-eligible original or supplemental applications (e.g., two original applications, an original application and a supplemental application, or two supplemental applications).

waiver, which may provide a full waiver of the PDUFA application fee because of the applicant's financial need. More information about the standard barrier to innovation waiver is available at http://www.fda.gov/cder/pdufa/default.htm. Applicants who believe they qualify are encouraged to explore their eligibility for the PDUFA small business or barrier to innovation waivers first.

F. When would a combination product be considered innovative for the purposes of the "Innovative Combination Product" waiver?

FDA expects to consider the following factors[14] in determining whether a combination product is innovative for the purposes of this waiver:

- The product addresses an unmet medical need in the treatment, diagnosis or prevention of disease, as demonstrated by one of the following:
  - No approved alternative treatment or means of diagnosis exists; or
  - The combination product offers significant, clinically meaningful advantages over existing approved alternative treatments. The combination product should provide for clinically important earlier or more accurate diagnosis or offer important therapeutic advantages in safety and/or effectiveness or patient compliance over existing alternatives. Such advantages may include demonstrated superiority over current treatments for effects on serious outcomes (e.g., morbidity), ability to provide clinical benefit for those patients unable to tolerate current treatments, or ability to provide clinical benefit without the serious side effects associated with current treatments.
- Factors such as whether one of the two applications includes a new molecular entity, has been designated as a priority drug or eligible for expedited device review, or has been granted fast track status, may also be considered in determining whether a product is considered innovative for the purposes of this waiver. The existence of treatment alternatives would weigh against deciding that a product is innovative.

[14] These factors are largely derived from the Agency's approach to determining the eligibility of a product for expedited or priority review, where such factors are relevant to a determination of a combination product's innovativeness.

G. How does FDA expect to reduce application fees under the "Innovative Combination Product" waiver for innovative combination products for which two applications are required?

In evaluating how the PDUFA barrier to innovation waiver provision may apply to innovative combination products, FDA's goal would be to reduce the additional fee burden associated with the requirement for two marketing applications. As noted above, waiver options under MDUFMA are limited, and the only fee reduction under MDUFMA is for small businesses. Therefore, for innovative combination products requiring two marketing applications, in appropriate situations FDA would expect to reduce PDUFA application fees as follows:

- Products requiring a MDUFMA application and a PDUFA application. FDA would expect to reduce the PDUFA fee by the amount of the MDUFMA fee. Thus, a sponsor would pay the full MDUFMA fee associated with the type of MDUFMA application, and a PDUFA fee reduced by the paid MDUFMA fee. The total amount paid would be equivalent to one PDUFA fee.

- Products requiring two PDUFA applications. FDA would expect to reduce each PDUFA fee by half. In the case where two full PDUFA fees would otherwise be required, the total amount paid under this waiver would be equivalent to one PDUFA fee.

Table 2 below illustrates with a variety of scenarios how FDA would expect to reduce fees for innovative combination products for which two marketing applications are required. The actual fee amounts are based on the FY 2005 fee structure, and are subject to change in subsequent fiscal years.

Table 2: Examples of Fees Under Innovative Combination Products Waiver (FY05 Fees)

Application #1	Standard Fee for Application #1	Application #2	Standard Fee for Application #2	Total Fee for both Applications (Without Waivers)	Proposed Total Fee (With Waiver)
PMA, PMA Panel-Track Supplement or MDUFMA BLA or BLA Efficacy Supplement	$239,237	NDA/BLA	$672,000	$911,237	$672,000: $239,237 MDUFMA, $432,763 PDUFA
180-Day PMA Supplement	$51,436	NDA/BLA	$672,000	$723,436	$672,000: $51,436 MDUFMA, $620,564 PDUFA

Table 2: Examples of Fees Under Innovative Combination Products Waiver (FY05 Fees)					
Application #1	Standard Fee for Application #1	Application #2	Standard Fee for Application #2	Total Fee for both Applications (Without Waivers)	Proposed Total Fee (With Waiver)
PMA, PMA Panel-Track Supplement or MDUFMA BLA or BLA Efficacy Supplement	$239,237	NDA/BLA Efficacy Supplement	$336,000	$575,237	$336,000: $239,237 MDUFMA, $96,763 PDUFA
First Small Business[15] PMA, PMA Panel-Track Supplement or MDUFMA BLA or BLA Efficacy Supplement	$0	NDA/BLA	$672,000	$672,000	$672,000: $0 MDUFMA $672,000 PDUFA
Small Business[16] PMA, PMA Panel-Track Supplement or MDUFMA BLA or BLA Efficacy Supplement	$90,910	NDA/BLA	$672,000	$762,910	$672,000: $90,910 MDUFMA $581,090 PDUFA
Real-Time PMA Supplement	$17,225	NDA/BLA Efficacy Supplement	$336,000	$353,225	$336,000: $17,225 MDUFMA, $318,775 PDUFA
510(k)	$3,502	NDA/BLA	$672,000	$675,502	$672,000: $3,502 MDUFMA, $668,498 PDUFA
510(k)	$3,502	NDA/BLA Efficacy Supplement	$336,000	$339,502	$336,000: $3,502 MDUFMA, $332,498 PDUFA

[15] Assumes sponsor qualifies as a small business under MDUFMA but not PDUFA.
[16] Assumes sponsor qualifies as a small business under MDUFMA but not PDUFA.

Table 2: Examples of Fees Under Innovative Combination Products Waiver (FY05 Fees)					
Application #1	Standard Fee for Application #1	Application #2	Standard Fee for Application #2	Total Fee for both Applications (Without Waivers)	Proposed Total Fee (With Waiver)
Original PDUFA Application (NDA)	$672,000	Original PDUFA Application (BLA)	$672,000	$1,344,000	$672,000: $672,000 PDUFA
Original PDUFA Application (NDA)	$672,000	PDUFA Efficacy Supplement (BLA)	$336,000	$1,008,000	$672,000: $672,000 PDUFA
PDUFA Efficacy Supplement (NDA)	$336,000	PDUFA Efficacy Supplement (BLA)	$336,000	$672,000	$336,000: $336,000 PDUFA

H. My product qualifies for an Innovative Combination Product waiver. How does this affect product and establishment fees payable under PDUFA?

The Innovative Combination Product waiver only provides for a reduction of application fees equivalent to the additional fee burden associated with the requirement for two marketing applications. This use of the PDUFA barrier to innovation waiver is not applicable to the yearly product and establishment fees. FDA intends to review requests for waivers of PDUFA product and/or establishment fees for combination products, including innovative combination products, under existing criteria established for the review of such waivers, which are applicable to both combination and non-combination products.

I. Will other waivers be available for combination products for which two applications are required?

FDA has considered the various options available under PDUFA and MDUFMA, and believes the Innovative Combination Product waiver appropriately addresses the additional fee burden associated with any FDA requirement for the submission of two marketing applications for an innovative combination product. FDA will evaluate its experience in working with this guidance document, and the impact of the Innovative Combination Product waiver on the user fee program as a whole.

IV. PROCEDURES FOR REQUESTING WAIVERS FOR USER FEES FOR COMBINATION PRODUCTS

A. How do I request a small business waiver under MDUFMA?

The document "Guidance for Industry and FDA: FY 2004 MDUFMA Small Business Qualification Worksheet and Certification," available at http://www.fda.gov/cdrh/mdufma/guidance/1225.pdf provides instructions for obtaining an FDA decision that a business qualifies as a small business and is eligible for reduced or waived MDUFMA application fees.

B. How do I request a waiver for a PDUFA application, establishment, or product fee?

The document "Interim Guidance Document for Waivers of and Reductions in User Fees," available at http://www.fda.gov/cder/pdufa/default.htm provides instructions for requesting a waiver of application, establishment or product fees under PDUFA.[17]

The same instructions should be followed for requesting the Innovative Combination Products waiver described above. The request should be clearly identified as an Innovative Combination Products Waiver Request, and be accompanied by a statement of reasons the applicant believes the Innovative Combination Products Waiver should be applied. To facilitate FDA's consideration of the request, FDA encourages sponsors to address and substantiate each of the criteria outlined in Section III above. Current mailing addresses for submitting PDUFA waiver requests, including an Innovative Combination Products waiver, are provided at http://www.fda.gov/cder/pdufa/addresses.htm.

Persons are encouraged to submit requests for fee waivers or reductions 90 days before the required fees are expected to be paid. In addition, under section 736(i) of the Act, to qualify for a refund of any fee collected under the user fee provisions of the Act, you must submit a written request for a refund within 180 days after such fee is due.

C. Where can I get more information about combination products?

The Office of Combination Products is available as a resource to sponsors and review staff throughout the development of a combination product. The Office may be reached at (301) 427-1934 or by email at combination@fda.gov. In addition, the Office maintains an updated website with information on the regulation of combination products at http://www.fda.gov/oc/combination.

[17] See particularly pages 23-24 of that interim guidance document.