Guidance for Industry and FDA Staff:

Application User Fees for Combination Products

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

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

April 2005

Guidance for Industry and FDA Staff:

Application User Fees for Combination Products

Additional copies are available from:

Office of Combination Products, HFG-3
Office of the Commissioner
Food and Drug Administration
15800 Crabbs Branch Way, Suite 200
Rockville, MD 20855
(Tel) 301-427-1934
(Fax) 301-427-1935
http://www.fda.gov/oc/combination

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
Office of Combination Products
April 2005

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Guidance for Industry and FDA Staff[1]
Application User Fees for Combination Products

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. 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 should 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 was 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)(1)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(d)(1)(B)).

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 should be used?

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. A combination product's PMOA does not automatically determine the type of marketing application that will be used for the product's approval, clearance, or licensure. 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. FDA encourages applicants who are uncertain as to whether a single or multiple marketing applications should be submitted for a combination product to discuss the issue with the lead reviewing Division and/or the Office of Combination Products.

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 for 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 (e.g., a drug-device or biologic-device product) should 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 should 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 should 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 should be 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 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 are 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.

[5] MDUFMA waivers are described in Section 738 of the Act.

197
198 **C. What user fee waivers are available under PDUFA?[6]**
199
200 PDUFA provides for a waiver of the fee for the first human drug application from a small
201 business.[7] The criteria for qualifying as a small business under PDUFA are different than
202 those under MDUFMA.[8] Under PDUFA, "small business" means an entity that has fewer than
203 500 employees for the small business and its affiliates.[9]
204
205 PDUFA also provides for waivers or reductions of fees where:
206
207 - such waiver or reduction is necessary to protect the public health;
208
209 - the assessment of the fee would present a significant barrier to innovation because of
210 limited resources available to such person or other circumstances; or
211
212 - the fees to be paid by such person will exceed the anticipated present and future costs
213 incurred by the Secretary in conducting the process for the review of human drug
214 applications for such person.
215
216 The document "Interim Guidance Document for Waivers of and Reductions in User Fees,"
217 available at http://www.fda.gov/cder/pdufa/default.htm, provides information for requesting,
218 and the criteria for evaluating, a waiver of PDUFA application, establishment, or product
219 fees.[10] In addition, the document "Fees-Exceed-The-Costs Waivers Under the Prescription
220 Drug User Fee Act," available at http://www.fda.gov/cder/pdufa/default.htm, provides further
221 explanation of the waiver option described in the third bullet above.
222
223 It should be noted that PDUFA applications (NDA or BLA) not requiring clinical data for
224 approval are assessed half the fee that is assessed for applications that do require clinical data
225 for approval.[11] NDA or BLA supplements that require clinical data for approval are assessed
226 half the full application fee; however NDA or BLA supplements that do not require clinical
227 data for approval are not assessed a fee.
228
229
230
231
232

---

[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)).
[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.

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 or both 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.

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 applications only request approval of the two components of the combination product 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

[12] Orphan product applications exempt from fees under 736(a)(1)(E) of the Act, BLAs for further manufacturing use only, HDEs, pediatric device applications, and 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).

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 their first 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 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, 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. Innovative combination products may also provide these types of significant, meaningful advantages over existing approved alternative treatments by providing greater convenience or ease of use for patients and/or healthcare providers. For example, an innovative combination product distinguished by its ease of use or convenience may significantly

[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. FDA notes that a product need not be "life-saving" or for use in critical conditions to satisfy these factors, although the benefits of such innovation are sometimes more evident in these circumstances.

improve safety by resulting in fewer adverse events, or may significantly improve effectiveness by providing better patient compliance or more effective dosing.[15]

- Factors such as whether one of the two applications includes a new molecular entity, has been designated as a priority drug[16] or eligible for expedited device review, or has been granted fast track status,[17] 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.

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.

[15] Innovative Combination Product Waiver Requests that are based on convenience or ease of use should describe how the convenience or ease of use results in significant, meaningful advantages as described here.

[16] Further information on FDA's policies in determining priority status of drugs can be found in CDER's Manual of Policies and Procedures (MAPP) 6020.3, *Priority Review Policy*, available on the Internet at www.fda.gov/cder, or CBER's Manual of Standard Operating Procedures and Policies (SOPP) 8405, *Complete Review and Issuance of Actions Letters*, available on the Internet at www.fda.gov/cber/regsopp/regsopp.htm.

[17] Further information on FDA's policies regarding designation of fast track status can be found in FDA's guidance for industry on *Fast Track Drug Development Programs — Designation, Development, and Application Review*, available on the Internet at www.fda.gov/cder/guidance.

Table 2 below illustrates how, in a variety of scenarios, 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 Product 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
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[18] 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

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

Table 2: Examples of Fees Under Innovative Combination Product 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)
Small Business[19] 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	$672,000	$689,225	$672,000: $17,225 MDUFMA $654,775 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
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

355

[19] Assumes sponsor qualifies as a small business under MDUFMA but not 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 would only provide 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.[20]

I. I am submitting two marketing applications for my innovative combination product, but FDA has determined that only a single marketing application is necessary. By submitting two applications, do I forfeit my eligibility for the PDUFA barrier to innovation waiver?

No. As described in Section III.A above, sponsors may still be eligible for existing fee waivers or reductions under both PDUFA and MDUFMA when submitting two applications covering the various components of a combination product, even when one application would suffice. For example, sponsors may qualify for small business waivers or fee reductions under PDUFA and/or MDUFMA, or other waivers provided under PDUFA, such as the barrier to innovation waiver.

In the particular case of the PDUFA barrier to innovation waiver, as described in the document "Interim Guidance Document for Waivers of and Reductions in User Fees," available at http://www.fda.gov/cder/pdufa/default.htm, FDA ordinarily considers a variety of factors, including the applicant's financial status, to determine whether the submission of an application presents a barrier to innovation because of limited resources available to the applicant. FDA believes it is also appropriate to use these criteria in the case where an applicant chooses to submit two applications when one would suffice because the sponsor receives some benefit by submitting two applications (e.g., new drug product exclusivity, orphan designation, or proprietary data protection when two firms are involved).

In contrast, for the Innovative Combination Product Waiver, when FDA *requires* the submission of two marketing applications for an innovative combination product meeting the criteria outlined in this document, FDA expects to reduce the total application fee burden (i.e., grant a partial waiver) as described in this document, *regardless of the applicant's financial status*. FDA believes this approach is reasonable because of the "other circumstances" associated with FDA's requirement for two marketing applications.

[20] It should be noted that only PDUFA NDA and BLA holders are assessed product and establishment fees under PDUFA. In general, NDA products without generic competition are assessed product fees. If you are assessed a product fee, then you would likely be assessed an establishment fee. Please note that if multiple applicants share the same establishment, under PDUFA, the establishment fee is shared equally among the user fee paying applicants.

Applicants with an innovative combination product who qualify for a standard PDUFA barrier to innovation waiver (because the applicant has limited resources) may qualify for a full waiver of the PDUFA application fee as compared to the partial fee reduction provided by the Innovative Combination Product Waiver.

J. A MDUFMA application is required for the approval of a new use for my combination product (e.g., a drug delivery device), but the vast majority of the review is covered by the PDUFA application for the drug product. Whether my combination product is innovative or not, do I have to pay a full MDUFMA fee?

Under MDUFMA, the user fee assessed for a particular type of marketing application is related to the resources required for the review of that specific type of application. FDA believes that under appropriate circumstances, as described below, changes to approved devices, such as use of an existing drug delivery device with a new drug product where in-depth review of such use is being evaluated under a PDUFA application, should be handled under a device application appropriate to the level of review required.

For example, while most new indications for PMA products require panel-track PMA supplements or original PMA applications, submission of a real-time or 180-day PMA supplement may be appropriate when only a minor change is being made to the device and the review of the new use is being conducted as part of the PDUFA application. Such an approach would also provide for lower device application user fees, since real-time and 180-day PMA supplements have lower fees than those for panel-track supplements or original PMAs. FDA encourages applicants to discuss the appropriate type of device application in such circumstances.

K. 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 would appropriately address 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?

Each fiscal year, FDA publishes a document titled "Guidance for Industry and FDA: MDUFMA Small Business Qualification Worksheet and Certification" (see http://www.fda.gov/cdrh/mdufma/guidance), which 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.

If you submit an application before FDA has determined you qualify as a small business, you must pay the standard (full) amount of any fee that applies. FDA will not refund the difference between the standard (full) fee and the small business fee if you later qualify as a small business.[21] If you want to pay the small business fee for an application, do not submit it until you obtain your Small Business Decision number from FDA. FDA expects to make its decision about whether you qualify as a small business within 60 days of receiving your Certification and supporting materials. Therefore, applicants are encouraged to submit MDUFMA small business waiver requests/certifications at least 60 days before the required fees are expected to be paid.

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.[22]

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

Persons are encouraged to submit requests for fee waivers or reductions at least 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.

[21] See Sections 738(d)(2)(D) and 738(e)(2)(D) of the Act.

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

485 **C. Where can I get more information about combination products?**
486
487 The Office of Combination Products is available as a resource to sponsors and review staff
488 throughout the development of a combination product. The Office may be reached at (301)
489 427-1934 or by email at combination@fda.gov. In addition, the Office maintains an updated
490 website with information on the regulation of combination products at
491 http://www.fda.gov/oc/combination.