Application User Fees for Combination Products

Guidance for Industry and FDA Staff

Additional copies are available from:
Office of Combination Products
Food and Drug Administration
WO-32, Hub #5129
10903 New Hampshire Avenue
Silver Spring, MD 20903
(Tel) 301-796-8930, (Fax) 301-847-8619
combination@fda.gov
https://www.fda.gov/combination-products

For questions regarding this document, contact the Office of Combination Products at combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)

July 2024
User Fees
Revision - 1

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

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

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. PURPOSE

This document provides guidance to industry and FDA staff on application user fees for combination products as defined under 21 CFR 3.2(e). Combination products may be reviewed in a single application or in separate applications for the constituent parts (see section II.B).[2] The guidance explains that combination products for which a single application is submitted should be assessed the applicable user fee associated with that particular type of application.[3] The document also addresses how the Agency applies user fees for combination products when separate applications are submitted for the constituent parts. If the applicant chooses to submit two applications for a cross-labeled combination product, each would be assessed the applicable user fee for each application. In the infrequent situation when FDA determines that a single application is not appropriate and separate applications are warranted,[4] the guidance describes how the total application fee amount might be reduced when the applicant qualifies for certain waiver provisions under the Prescription Drug User Fee Act (PDUFA) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act).[5]

This guidance replaces the final guidance for industry with the same title *Application User Fees for Combination Products* issued in April 2005. This replacement provides consistency with current user fee programs and revisions to the combination product provisions in section 503(g) of the FD&C Act (21 U.S.C. 353(g)) and should be used in conjunction with the guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and*

[1] This guidance was prepared by the Office of Combination Products in the Office of the Commissioner, in cooperation with the Division of User Fee Management, Office of Management, Center for Drug Evaluation and Research; the Center for Biologics Evaluation and Research; and the Center for Devices and Radiological Health at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2004-D-0371.

[2] See section II.A. of this guidance for a discussion of *combination product* and *constituent parts*.

[3] For purposes of this guidance the term *application* applies to a biologics license application submitted under section 351(a) of the Public Health Service Act, a new drug application, a premarket approval application, a premarket notification (510(k)) submission, or a De Novo request.

[4] For more information on applications for combination products, see section II.B of this guidance.

[5] See section 736(d) of the FD&C Act (21 U.S.C. 379h(d)).

Biological Products[6] and the appropriate medical device user fee amendments (MDUFA) guidance document(s).[7]

This guidance does not apply to combination products that are the subject of an application submitted under section 505(j) of the FD&C Act or submitted under section 351(k) of the Public Health Service Act (PHS Act). Therefore, application fees under the Generic Drug User Fee Amendments (GDUFA) and Biosimilar User Fee Amendments (BsUFA) are not addressed. This guidance does not apply to PDUFA prescription drug program fees.

In general, FDA's guidance documents 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.

II. BACKGROUND INFORMATION

A. What is a combination product?

Combination products, as described in 21 CFR part 3, are comprised of two or more different types of products (i.e., a combination of a drug, device, and/or biological product with one another).[8] The drugs, devices, and biological products included in combination products are referred to as *constituent parts*[9] of the combination product.

Drug-drug products, device-device products, or products that consist solely of more than one biological product do not meet the definition of a combination product and are outside the scope of this guidance.

B. How are combination products assigned for review?

A combination product is assigned to an Agency center[10] that will have primary jurisdiction for its premarket review and regulation. Under section 503(g)(1) of the FD&C Act (21 U.S.C. 353(g)(1)), the assignment to a *lead center* is based upon a determination of the *primary mode of action* (PMOA) of the combination product.[11] For example, if the PMOA of a combination

---

[6] Published in October 2019. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[7] See MDUFA guidance documents available at https://www.fda.gov/industry/medical-device-user-fee-amendments-mdufa/mdufa-guidance-documents.
[8] See 21 CFR 3.2(e).
[9] See 21 CFR 4.2.
[10] Section 503(g)(9) of the FD&C Act defines the term *agency center* as a center or alternative organizational component of the FDA.
[11] See also 21 CFR 3.2(k) (which defines *mode of action*), 3.2(m) (which defines *primary mode of action*), and 3.4 (which describes the assignment of combination products). For more information on product classification, assignment, and PMOA, see the guidance for industry *How to Write a Request for Designation (RFD)* (April 2011).

product is that of a biological product, then the combination product would be assigned to the Agency center responsible for premarket review of that biological product.

Sections 503(g)(1)(B) and 503(g)(6) of the FD&C Act provide that FDA "shall conduct the premarket review of any combination product under a single application, whenever appropriate" and that a sponsor may choose to submit separate applications for the different constituent parts of a combination product unless FDA "determines that a single application is necessary." As described further in guidance,[12] FDA's current thinking is that a single application is generally appropriate for a combination product to streamline regulatory interactions with the Agency and to avoid unnecessary duplication that may occur with multiple applications. However, as described further in the aforementioned guidance, it is generally permissible for the applicant to choose to submit two applications (of different types) for a cross-labeled combination product. In limited situations FDA may determine that a single application is not appropriate and thus an application for each constituent part is warranted.

C. What are PDUFA and MDUFA user fees?

As explained in section I, this document provides guidance on PDUFA and MDUFA application user fees for combination products. The Prescription Drug User Fee Act of 1992 (PDUFA) added sections 735 and 736 to the FD&C Act and authorized FDA to collect user fees from persons that submit applications for certain human drug and biological products. Since 1992, Congress has reauthorized PDUFA every 5 years. Under this legislation, FDA assesses application fees for certain applications submitted under section 505(b) of the FD&C Act or section 351(a) of the PHS Act.[13] FDA also assesses annual prescription drug program fees for certain actively marketed prescription drugs.[14] More information about the current PDUFA reauthorization is available at the FDA Prescription Drug User Fee Amendments website.[15]

Device user fees were first established by the Medical Device User Fee and Modernization Act of 2002 (Pub. L. 107-250) which added sections 737 and 738 to the FD&C Act (21 U.S.C. 379i and 379j). Since 2002, Congress has reauthorized the device user fee provisions through amendments (referred to as the medical device user fee amendments or MDUFA) every 5 years. Under the device user fee provisions, medical device companies pay fees to the FDA when they register their establishments with the Agency (initially or annually), when they submit an application under section 515 of the FD&C Act (21 U.S.C. 360e) or a notification under section 510(k) of the FD&C Act (21 U.S.C. 360(k)) to market a device in the United States, and for certain other types of submissions. More information about the current MDUFA reauthorization is available at the FDA's MDUFA website.[16]

---

[12] See the guidance for industry and FDA staff *Principles of Premarket Pathways for Combination Products* (January 2022).
[13] See section 736(a)(1) of the FD&C Act.
[14] See section 736(a)(2) of the FD&C Act.
[15] Available at https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments.
[16] Available at https://www.fda.gov/industry/fda-user-fee-programs/medical-device-user-fee-amendments-mdufa.

D. What application user fee waivers, reductions, exceptions, or exemptions are available under PDUFA?

PDUFA includes provisions for application fee waivers, reductions, exceptions, and exemptions. Table 1 provides information about certain provisions for application fee waivers and reductions in section 736(d), and an exception in section 736(a)(1)(F) which may be particularly relevant to combination products. Additional information on these and other user fee waivers, reductions, exceptions, and exemptions under PDUFA, and factors that the Agency generally considers when evaluating such requests, is provided in the guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products.*

Table 1: PDUFA Application Fee Selected Waivers, Reductions, and Exceptions

Category	Eligibility
Public Health Waiver	FDA finds that the waiver or reduction is necessary to protect the public health.[17]
Barrier to Innovation Waiver	FDA finds that the assessment of fees presents a significant barrier to innovation because of limited resources available to the applicant or other circumstances.[18, 19]
Small Business Waiver	FDA finds that the applicant is a small business submitting its first human drug application to the Agency.[20]
Exception for Orphan Designated Products	A human drug application for a product designated by FDA as a drug for a rare disease or condition pursuant to section 526 is not subject to an application fee unless the application includes an indication for other than a rare disease or condition.[21]
State or Federal Government Entity Exemption	An application submitted by a State or Federal government entity for a product that is not distributed commercially, is not considered a human drug application, and therefore, an application fee is not assessed.[22]

[17] See section 736(d)(1)(A) of the FD&C Act.
[18] See section 736(d)(1)(B) of the FD&C Act.
[19] For more information on the barrier to innovation waiver, including the "other circumstances" provision related to combination products, see sections III.C, D, E, and F.
[20] See sections 736(d)(1)(C) and (d)(3) of the FD&C Act.
[21] See section 736(a)(1)(F) of the FD&C Act.
[22] See section 735(1) of the FD&C Act.

E. What user fee waivers or exceptions are available under MDUFA? [23]

Other than specific situations identified in Table 2 for which no user fee is required, standard MDUFA fees are required for all applicable device submissions other than those from small businesses.[24] For additional information please refer to the following guidance documents:

- Guidance for industry and FDA staff *User Fees and Refunds for Premarket Approval Applications and Device Biologics License Applications* (October 2022)
- Guidance for industry and FDA staff *User Fees and Refunds for Premarket Notification Submissions (510(k)s)* (October 2022)
- Guidance for industry and FDA staff *User Fees and Refunds for De Novo Classification Requests* (October 2022)
- Guidance for industry, FDA staff, and foreign governments *Medical Device User Fee Small Business Qualification and Certification* (August 2018)

(Continued on the next page)

[23] MDUFA exceptions and waivers are described in section 738 of the FD&C Act.
[24] Small businesses may qualify for reduced fees. See sections 738(d) and (e) of the FD&C Act.

Table 2: MDUFA Fee Exceptions[25] and Waivers	
Category	**Description**
Humanitarian Device Exemption (HDE)	An application under section 520(m) of the FD&C Act is not subject to any fee.[26]
Further Manufacturing Use	No fee shall be required for a biologics license application for a product licensed for further manufacturing use only.[27]
State or Federal Government Sponsors[28]	No fee shall be required for a premarket application, premarket report, supplement, or premarket notification submitted by a State or Federal government entity unless the device involved is to be distributed commercially.[29]
Premarket Notification Reviewed by Third Parties	No fee shall be required for a premarket notification submission reviewed by an accredited person pursuant to section 523 of the FD&C Act.[30]
Pediatric Conditions of Use	No fee shall be required if the proposed conditions of use are solely for a pediatric population. Any supplement that proposes conditions of use for any adult population is subject to the fee then in effect for a premarket application.[31]
First Premarket Application or Premarket Report from a Small Business	The Secretary shall grant a waiver of the fee for one premarket application, or one premarket report, where the Secretary finds that the applicant involved is a small business submitting its first premarket application, or its first premarket report, respectively, for review.[32]

III. USER FEES FOR COMBINATION PRODUCTS

As described in section II.B, most combination products are reviewed under one application. However, separate applications for each constituent part could be submitted in one of two instances: 1) at the choice of the applicant or 2) as determined appropriate by FDA.

A. Single application: How are application fees determined for combination products?

[25] Section 738(a)(2)(B) of the FD&C Act.
[26] See section 738(a)(2)(B)(i) of the FD&C Act.
[27] See section 738(a)(2)(B)(ii) of the FD&C Act.
[28] For purposes of this document, the terms sponsor and applicant are synonymous.
[29] See section 738(a)(2)(B)(iii) of the FD&C Act.
[30] See section 738(a)(2)(B)(iv) of the FD&C Act.
[31] See section 738(a)(2)(B)(v) of the FD&C Act.
[32] See section 738(d)(1) of the FD&C Act.

A combination product for which a single application is submitted is subject to the applicable user fee associated with that particular type of application. For example, if a drug-device or device-biological product combination product applicant submits one PDUFA application (e.g., a biologics license application (BLA) or new drug application (NDA)), the application is subject to a PDUFA application fee. If submitted under MDUFA (e.g., a premarket approval application (PMA) or 510(k)), the application is subject to a MDUFA application fee. Under either PDUFA or MDUFA, the single application may be eligible for a user fee waiver, reduction, exception, or exemption, including those identified in sections II.D[33] and II.E, respectively.

B. Two application types by applicant choice: What fees will be assessed?

As noted in section II.B, for most combination products, one application is appropriate. However, in some circumstances an applicant may choose to submit two applications and FDA did not determine that an application for each constituent part is warranted, even though one application would be appropriate for FDA review.[34] In this situation the applications may fall under the same or different user fee programs.[35] In such cases, FDA would evaluate each application user fee independently under the relevant user fee statute, as if it were a stand-alone application, and two application fees would be assessed (i.e., one fee for each application). Accordingly, PDUFA and MDUFA direct FDA to collect fees for each program application upon submission, reflecting the commitment of program resources (e.g., the review of two applications when one application would be appropriate places extra burden on FDA resources). Where a request for a fee waiver, reduction, exception, or exemption is submitted, the Agency would determine whether each application would qualify under the applicable PDUFA or MDUFA authorities (see sections II.D and II.E). Any user fee waiver, reduction, exception, or exemption is applied to the applicable qualifying application(s).

C. Two application types are warranted (i.e., a single application is not appropriate) as determined by FDA: How does FDA expect to waive or reduce the application fees under the PDUFA user fee program?

When FDA determines that a single application is not appropriate for the combination product and separate applications for each constituent part are warranted (as discussed in section II.B), the PDUFA application fee considerations described in this section apply. Note that already approved/cleared, independent products submitted as a new combination product using two applications that are appropriate for approval of the new innovative combination product (21 CFR 3.2(e)(3)) are within the scope of this section.[36] Also, this section focuses on certain waivers and reductions authorized under the PDUFA program because exceptions under MDUFA are more limited. Generally, any user fee waivers, reductions, exceptions, or exemptions that may otherwise be applicable would be applied to the qualifying application(s) as

[33] See section III.C for information on situations in which FDA may apply the "other circumstances" provision of the barrier to innovation waiver listed in section II.D.
[34] See footnote 12.
[35] For example, one application is under PDUFA (e.g., NDA) and one application is under MDUFA (e.g., PMA) for a drug-device combination product, or two different PDUFA applications (i.e., NDA and BLA) for a drug-biological product combination product.
[36] Under PDUFA, supplements do not incur a user fee. Under MDUFA, supplements are eligible for a user fee.

described in section III.B. In addition any application may be eligible for other user fee waivers, reductions, exceptions, or exemptions not addressed in this policy.

For the two application types that are warranted as determined by FDA, FDA confirms whether each application only requests approval of the constituent parts of the combination product for use together. If so, because FDA determined that separate applications for each constituent part are warranted, FDA considers whether the indication for the combination product as a whole either 1) protects the public health per the PDUFA public health waiver[37] or 2) is innovative per the PDUFA barrier to innovation waiver (as described in section III.D). Based on those determinations, FDA expects to waive or reduce the PDUFA fees as follows:

1. Public Health Waiver

If the combination product protects the public health and the applicant has limited resources, then FDA will reduce the user fees as follows:

- Products requiring a MDUFA application and a PDUFA application - The PDUFA application fee would be waived. The total amount assessed would be equivalent to one MDUFA application fee (in accordance with any applicable MDUFA waivers or exceptions) for both applications.

- Products requiring two PDUFA applications - The PDUFA application fees would be waived. The total amount assessed would be zero for both applications.

2. Barrier to Innovation Waiver

If the combination product is innovative and the applicant has limited resources, then FDA intends to reduce the user fees as described in the preceding section III.C.1.

If the combination product is innovative and the applicant does not have limited resources, FDA generally intends to consider "other circumstances" justifying the waiver to be present if the agency requires two applications, and accordingly, to reduce the user fees as follows:

- Products requiring a MDUFA application and a PDUFA application - An applicant would be assessed the MDUFA application fee[38] associated with the type of MDUFA application, and a PDUFA application fee reduced by the assessed MDUFA application fee [MDUFA + (PDUFA-MDUFA)]. The total amount assessed would be equivalent to one PDUFA application fee.

- Products requiring two PDUFA applications - In the case where two full PDUFA fees would otherwise be assessed, the total amount assessed would be equivalent to one PDUFA application fee.

[37] For information on the public health waiver see section IV of the guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products*.
[38] The MDUFA fee in accordance with any applicable MDUFA waivers or exceptions.

This reduction under the "other circumstances" of the PDUFA barrier to innovation waiver provision would apply to combination products *when the applicant does not have limited resources*. FDA believes this approach is reasonable because of the "other circumstances" associated with FDA's determination that two applications is most appropriate for the combination product.

D. What factors does FDA consider in determining whether a combination product is considered innovative under the PDUFA barrier to innovation waiver provision?

In making this determination for a combination product, FDA considers the factors listed in the guidance *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products*[39] and how those might apply to a combination product. Examples of frequent considerations related to these factors may include whether:

- The combination product demonstrates new, progressive methods and forward-thinking in the treatment or diagnosis of disease or is at the forefront of new medical technology.

- There are no comparable alternatives for treatment, prevention, or diagnosis available in the U.S. market. The existence of comparable alternatives to the combination product would weigh against a determination that the combination product is innovative.

- The combination product introduces a unique or superior method for diagnosing, curing, mitigating, treating, or preventing disease. For example, the combination product demonstrates the potential for earlier or more accurate diagnosis or the potential to offer superior clinical benefit in the treatment of a disease. Such clinical advantages may include, but are not limited to, potential superiority over current treatments for serious diseases with high and predictable mortality or progressive morbidity, or potential clinical benefit in eliminating or substantially reducing treatment-limiting drug reactions.

- The combination product includes a new molecular entity or biological product, receives priority review designation, breakthrough therapy designation (as a drug/biological product), fast track designation, regenerative medicine advanced therapy designation, or breakthrough device designation.[40]

For a single PDUFA application, these factors apply to the combination product as submitted in the application. When two applications are submitted by applicant choice (see section III.B), each application user fee is considered independently. When FDA determines that separate

[39] See section IV.B.1 of the referenced guidance.

[40] For additional information see the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014). Also see FDA Webpage *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review,* available at https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review. See the guidance for industry *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* (February 2019). See the guidance for industry and FDA staff *Breakthrough Devices Program* (September 2023).

applications for each constituent part are warranted, FDA considers both applications in assessing these user fee factors.[41]

IV. PROCEDURES FOR REQUESTING WAIVERS OR REDUCTIONS OF USER FEES FOR COMBINATION PRODUCTS

A. How can I request a waiver or reduction of an application fee under the PDUFA user fee waiver provisions?

All waiver or reduction requests should follow the procedures in the guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products*. The guidance provides instructions for requesting a waiver or reduction of application fees under PDUFA. The request should be clearly identified as a "Combination Product Waiver Request" specifying the type of PDUFA waiver being requested and providing a statement of reasons the applicant believes the waiver should be granted. To facilitate FDA's consideration of the requests, FDA encourages applicants to fully address and substantiate each of the criteria outlined in sections III.C and III.D, where applicable.

Applicants are encouraged to submit requests for PDUFA fee waivers or reductions at least 3 to 4 months before the required fees are due. In addition, under section 736(i) of the FD&C Act, to qualify for a refund of an application fee paid under the user fee provisions of the FD&C Act, an applicant must submit a written request for a refund within 180 calendar days after such fee is due. Please note that under section 736(i), such request must include any legal authorities under which the request is made.

B. How can I request a small business user fee waiver or reduction under MDUFA?

For information on requesting a small business user fee waiver or reduction under MDUFA, see the guidance for industry, FDA staff, and foreign governments *Medical Device User Fee Small Business Qualification and Certification* and the most recent Federal Register notice announcing the medical device user fee rates (e.g., for fiscal year 2024, see 88 Federal Register 48870, July 28, 2023).

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

The Office of Combination Products is available as a resource to applicants and review staff throughout the development of a combination product. The Office may be reached at (301) 796-8930 or by email at combination@fda.gov. In addition, the Office maintains a *Combination Products* website[42] with related regulatory and guidance information.

---

[41] For other considerations see the guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drugs and Biological Products*.

[42] Available at https://www.fda.gov/combination-products.

For information regarding PDUFA user fees, contact the Division of User Fee Management within CDER at (301) 796-7900 or by email at CDERCollections@fda.hhs.gov. For CBER products, contact the Office of Regulatory Operations by email at CBERUserFeeStaff@fda.hhs.gov.

For information regarding MDUFA user fees for products regulated by CDRH, contact CDRH Division of Industry and Consumer Education at 800-638-2041 or by email at DICE@fda.hhs.gov. For information regarding MDUFA user fees for products regulated by CBER, contact the Office of Regulatory Operations by email at CBERUserFeeStaff@fda.hhs.gov.