

Guidance for Industry and FDA Staff:

Application User Fees for Combination Products

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

April 2005

2004D-0410

GDL 2

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**U.S. Department of Health and Human Services
Food and Drug Administration
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April 2005**

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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?13

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Guidance for Industry and FDA Staff¹
Application User Fees for Combination Products

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

I. 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 provision² 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)).

40 **II. BACKGROUND INFORMATION**

41
42 **A. What is a combination product?**

43
44 A combination product is a product comprised of any combination of a drug and a device; a
45 biological product and a device; a drug and a biological product; or a drug, device, and a
46 biological product. Under 21 CFR 3.2 (e), a combination product is defined to include:

- 47
48 (1) A product comprised of two or more regulated components; i.e., drug/device,
49 biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically,
50 or otherwise combined or mixed and produced as a single entity;
51
52 (2) Two or more separate products packaged together in a single package or as a unit and
53 comprised of drug and device products, device and biological products, or biological
54 and drug products;
55
56 (3) A drug, device, or biological product packaged separately that according to its
57 investigational plan or proposed labeling is intended for use only with an approved
58 individually specified drug, device, or biological product where both are required to
59 achieve the intended use, indication, or effect and where upon approval of the proposed
60 product the labeling of the approved product would need to be changed; e.g., to reflect
61 a change in intended use, dosage form, strength, route of administration, or significant
62 change in dose; or
63
64 (4) Any investigational drug, device, or biological product packaged separately that
65 according to its proposed labeling is for use only with another individually specified
66 investigational drug, device, or biological product where both are required to achieve
67 the intended use, indication, or effect.
68

69 Drug-drug, device-device, or biologic-biologic products do not meet the definition of a
70 combination product as defined in 21 CFR 3.2 (e), and are outside the scope of this guidance.
71

72
73 **B. How are combination products assigned for review and what type of marketing**
74 **applications should be used?**

75
76 A combination product is assigned to an Agency center³ that will have primary jurisdiction for
77 its premarket review and regulation. Under section 503(g) of the Act, the assignment of a
78 “lead center” is based upon a determination of the “primary mode of action” (PMOA) of the
79 combination product.⁴ For example, if the PMOA of a combination product is that of a
80 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/combinat/default.htm>.

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81 responsible for premarket review of that biological product. A combination product's PMOA
82 does not automatically determine the type of marketing application that will be used for the
83 product's approval, clearance, or licensure. Depending upon the type of combination product,
84 approval, clearance or licensure may be obtained through submission of a single marketing
85 application, or through separate marketing applications for the individual constituent parts of
86 the combination product.

87
88 For most combination products, a single marketing application is sufficient for the product's
89 approval, clearance or licensure. In some cases, however, a sponsor may choose to submit two
90 marketing applications for a combination product when one application would suffice. For
91 example, a sponsor may choose to submit two applications in order to receive some benefit that
92 accrues only from approval under a particular type of application (e.g., new drug product
93 exclusivity, orphan status, or proprietary data protection when two firms are involved). In
94 other cases, FDA may determine that two marketing applications are necessary. For example,
95 when one of the individual constituent parts of a combination product is already approved for
96 another use, and where the labeling of the already approved product will need to be changed to
97 reflect its new intended use in the combination product, FDA may determine that two
98 applications are necessary if the labeling of the already approved product is subject to legal
99 requirements different from those that will apply to the combination product. A guidance
100 addressing the factors FDA expects to consider in determining whether a single or multiple
101 marketing applications should be submitted for a combination product is in development and
102 will be provided separately for public review and comment. FDA encourages applicants who
103 are uncertain as to whether a single or multiple marketing applications should be submitted for
104 a combination product to discuss the issue with the lead reviewing Division and/or the Office
105 of Combination Products.

C. What are user fees?

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107
108
109
110 In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA), P.L. 102-571. The
111 user fee amendments were reauthorized by the Food and Drug Administration Modernization
112 Act of 1997 and again by the Public Health Security and Bioterrorism Preparedness and
113 Response Act of 2002. PDUFA authorized FDA to collect fees from companies that produce
114 certain human drug and biological products. When a company requests approval of a new drug
115 or biological product prior to marketing, it must submit an application (e.g., new drug
116 application (NDA) or biologics license application (BLA)) along with a fee to support the
117 review process. In addition, companies pay annual fees for each prescription drug product
118 marketed and for the establishment where the prescription drug product is manufactured.
119 More information about PDUFA is available at <http://www.fda.gov/oc/pdufa/> and
120 <http://www.fda.gov/cder/pdufa/default.htm> .

121
122 The Medical Device User Fee and Modernization Act of 2002 (MDUFMA), P.L. 107-250,
123 amended the Act to provide for user fees for device reviews. The fees apply to certain
124 premarket reviews of premarket approval applications (PMAs), product development protocols
125 (PDPs), premarket reports (PMRs), biologics license applications (BLAs), certain supplements,

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126 and premarket notifications (510(k)s). More information about MDUFMA is available at
127 <http://www.fda.gov/oc/mdufma/>.

128
129

130 **III. USER FEES FOR COMBINATION PRODUCTS**

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

133

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

144

145 A biologic-device product regulated under section 351 of the PHS Act will be subject to the
146 BLA fee under MDUFMA, if the biological component meets the definition of a device. Other
147 biologic-device combination products (those with biologic components that do not meet the
148 definition of a device) or drug-biologic combination products regulated under section 351 of
149 the PHS Act, or drug-device or drug-biologic combination products regulated under section
150 505(b) of the Act, that are human drug applications as defined in section 735 of the Act, will be
151 subject to prescription drug user fees. Prescription drug user fees may include application and
152 yearly product and establishment fees. More information about prescription drug user fees is
153 available at <http://www.fda.gov/cder/pdufa/default.htm>.

154

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

159

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

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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.

| 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.

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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.

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233 **D. How might the PDUFA barrier to innovation waiver apply to innovative combination**
234 **products for which two applications may be appropriate?**
235

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

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

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

251
252

253 **E. What factors may be considered in determining whether a product is eligible for an**
254 **“Innovative Combination Product” waiver?**
255

256 To be eligible for the “Innovative Combination Product” waiver under PDUFA’s “barrier to
257 innovation because of...other circumstances” provision, FDA expects to consider the following
258 factors:

259

- 260 ▪ The combination product (as defined in 21 CFR 3.2(e)) as a whole is innovative (see
261 Section F below for factors FDA expects to consider in determining whether a
262 combination product is innovative);
- 263 ▪ FDA is requiring two fee-eligible¹² marketing applications¹³ for the combination
264 product;
- 265 ▪ The applications only request approval of the two components of the combination
266 product for use together. Applications that include independent uses of one or both
267 components outside the combination product generally would not be eligible for this
268 waiver. However, applications for combinations of already approved, independent
269
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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).

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271 products generally would be eligible if two applications are required for approval of the
272 new combined use.

- 273
274
- 275 ■ The applicant does not qualify for a PDUFA small business waiver or have limited
276 resources. Applicants who qualify for a PDUFA small business waiver receive a full
277 waiver of their first PDUFA application fee. In addition, applicants with an innovative
278 combination product who do not qualify for a PDUFA small business waiver, but who
279 have limited resources, may be eligible for a standard PDUFA barrier to innovation
280 waiver, which may provide a full waiver of the PDUFA application fee because of the
281 applicant's financial need. More information about the standard barrier to innovation
282 waiver is available at <http://www.fda.gov/cder/pdufa/default.htm>. Applicants who
283 believe they qualify are encouraged to explore their eligibility for the PDUFA small
284 business or barrier to innovation waivers first.
285

F. When would a combination product be considered innovative for the purposes of the 286 "Innovative Combination Product" waiver? 287

288
289 FDA expects to consider the following factors¹⁴ in determining whether a combination product
290 is innovative for the purposes of this waiver:
291

- 292 ■ The product addresses an unmet medical need in the treatment, diagnosis or prevention
293 of disease, as demonstrated by one of the following:
294
 - 295 ● No approved alternative treatment or means of diagnosis exists; or
 - 296
 - 297 ● The combination product offers significant, meaningful advantages over
298 existing approved alternative treatments. The combination product
299 should provide for clinically important earlier or more accurate
300 diagnosis or offer important therapeutic advantages in safety and/or
301 effectiveness or patient compliance over existing alternatives. Such
302 advantages may include demonstrated superiority over current
303 treatments for effects on serious outcomes (e.g., morbidity), ability to
304 provide clinical benefit for those patients unable to tolerate current
305 treatments, or ability to provide clinical benefit without the serious side
306 effects associated with current treatments. Innovative combination
307 products may also provide these types of significant, meaningful
308 advantages over existing approved alternative treatments by providing
309 greater convenience or ease of use for patients and/or healthcare
310 providers. For example, an innovative combination product
311 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.

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

315
316 ■ Factors such as whether one of the two applications includes a new molecular
317 entity, has been designated as a priority drug¹⁶ or eligible for expedited device
318 review, or has been granted fast track status,¹⁷ may also be considered in
319 determining whether a product is considered innovative for the purposes of this
320 waiver.

321
322 ■ The existence of treatment alternatives would weigh against deciding that a
323 product is innovative.

324
325

326 **G. How does FDA expect to reduce application fees under the “Innovative Combination**
327 **Product” waiver for innovative combination products for which two applications are**
328 **required?**

329

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

336

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

342

343

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

347

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.

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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.

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| 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 |

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¹⁹ Assumes sponsor qualifies as a small business under MDUFMA but not PDUFA.

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

360 The Innovative Combination Product waiver would only provide for a reduction of *application*
361 fees equivalent to the additional fee burden associated with the requirement for two marketing
362 applications. This use of the PDUFA barrier to innovation waiver is not applicable to the
363 yearly product and establishment fees. FDA intends to review requests for waivers of PDUFA
364 product and/or establishment fees for combination products, including innovative combination
365 products, under existing criteria established for the review of such waivers, which are
366 applicable to both combination and non-combination products.²⁰

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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?

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

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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).

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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.

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

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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?

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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.

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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.

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

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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.

442 **IV. PROCEDURES FOR REQUESTING WAIVERS FOR USER FEES FOR**
443 **COMBINATION PRODUCTS**

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446 **A. How do I request a small business waiver under MDUFMA?**
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448 Each fiscal year, FDA publishes a document titled “Guidance for Industry and FDA:
449 MDUFMA Small Business Qualification Worksheet and Certification” (see
450 <http://www.fda.gov/cdrh/mdufma/guidance>), which provides instructions for obtaining an FDA
451 decision that a business qualifies as a small business and is eligible for reduced or waived
452 MDUFMA application fees.
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454 If you submit an application before FDA has determined you qualify as a small business, you
455 must pay the standard (full) amount of any fee that applies. FDA will not refund the difference
456 between the standard (full) fee and the small business fee if you later qualify as a small
457 business.²¹ If you want to pay the small business fee for an application, do not submit it until
458 you obtain your Small Business Decision number from FDA. FDA expects to make its
459 decision about whether you qualify as a small business within 60 days of receiving your
460 Certification and supporting materials. Therefore, applicants are encouraged to submit
461 MDUFMA small business waiver requests/certifications at least 60 days before the required
462 fees are expected to be paid.
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465 **B. How do I request a waiver for a PDUFA application, establishment, or product fee?**
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467 The document “Interim Guidance Document for Waivers of and Reductions in User Fees,”
468 available at <http://www.fda.gov/cder/pdufa/default.htm> provides instructions for requesting a
469 waiver of application, establishment, or product fees under PDUFA.²²
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471 The same instructions should be followed for requesting the Innovative Combination Product
472 waiver described above. The request should be clearly identified as an Innovative
473 Combination Product Waiver Request, and be accompanied by a statement of reasons the
474 applicant believes the Innovative Combination Product Waiver should be applied. To facilitate
475 FDA’s consideration of the request, FDA encourages sponsors to fully address and substantiate
476 each of the criteria outlined in Section III above. Current mailing addresses for submitting
477 PDUFA waiver requests, including an Innovative Combination Product waiver, are provided at
478 <http://www.fda.gov/cder/pdufa/addresses.htm>.
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480 Persons are encouraged to submit requests for fee waivers or reductions at least 90 days before
481 the required fees are expected to be paid. In addition, under section 736(i) of the Act, to
482 qualify for a refund of any fee collected under the user fee provisions of the Act, you must
483 submit a written request for a refund within 180 days after such fee is due.
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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.

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

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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>.