
Guidance for Industry Tropical Disease Priority Review Vouchers

DRAFT GUIDANCE

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For questions regarding this draft document contact David Roeder (CDER), 301-796-0799, or the Office of Communications, Training, and Manufacturers Assistance (CBER), 301-827-1800 or 800-835-4709.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**October 2008
Procedural**

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Guidance for Industry¹

Tropical Disease Priority Review Vouchers

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I. INTRODUCTION

16
17 This guidance provides information on the implementation of section 1102 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which adds new section 524 to the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360n). Section 524 authorizes FDA to award priority review vouchers to sponsors of certain tropical disease product applications that meet the criteria specified by the Act. A priority review voucher may be used by the sponsor who obtains it or another sponsor to obtain a priority review for a different application. A priority review voucher may be transferred from the sponsor who obtains it to another sponsor.

24
25 FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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II. BACKGROUND

33
34 Section 524 is designed to encourage development of new drug and biological products for prevention and treatment of certain tropical diseases affecting millions of people throughout the world. While diseases addressed by this legislation represent an important disease burden for humanity, there has been remarkably little progress over the past 50 years in development of drugs for these diseases. Because these diseases are found primarily in poor and developing countries, existing incentives have been insufficient to encourage development of new and innovative drug therapies. Although these tropical diseases are rare in the United States, intercontinental jet transport, immigration, tourism, and military operations are increasing the direct impact these diseases have on the health of Americans. By enacting section 524, Congress

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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43 is attempting to stimulate new drug development by offering additional incentives for obtaining
44 FDA approval of certain tropical disease drug products. Under section 524, the sponsor of a
45 human drug application for a qualified tropical disease may be eligible for a voucher that can be
46 used to obtain a priority review for any subsequent human drug application under section
47 505(b)(1) of the Act or section 351 of the Public Health Service (PHS) Act.
48

49 III. PROVISIONS OF SECTION 524 – AN OVERVIEW

50
51 A. What applications are eligible to receive a tropical disease priority review voucher?
52

- 53 • The application must be for a listed tropical disease (see section IV, Question 2 of
54 this guidance).
- 55 • The application must be submitted under section 505(b)(1) of the Act or section 351
56 of the PHS Act.
- 57 • The drug that is the subject of the application must contain no active ingredient
58 (including any ester or salt of the active ingredient) that has been approved in any
59 other application under section 505(b)(1) the Act or section 351 of the PHS Act.
- 60 • The application must be submitted after the enactment of FDAAA (September 27,
61 2007).
- 62 • The application must qualify for a priority review.
63

64 B. What are the parameters for use of a tropical disease priority review voucher?
65

- 66 • The voucher cannot be issued until at least 1 year after September 27, 2007, the date
67 of FDAAA enactment.
- 68 • The application using the priority review voucher must also be a 505(b)(1) or section
69 351 PHS Act application, and is not limited to products for tropical diseases.
- 70 • At least 1 year in advance, the sponsor planning to use the voucher must notify FDA
71 of intent to use the voucher and the date on which the sponsor intends to submit the
72 application.
- 73 • A sponsor using the voucher must pay an extra user fee to support the review of the
74 application based on the average cost of a priority NDA/BLA review in the previous
75 fiscal year. Payment of this extra fee, to which the sponsor is legally committed as a
76 result of the notification of its intent to use the voucher, is not subject to waivers,
77 exemptions, reductions, or refunds.
- 78 • The sponsor of a tropical disease product receiving a priority review voucher may
79 transfer the voucher to another sponsor (see section IV, Question 8)
80

81 IV. POLICIES AND PROCEDURES – QUESTIONS AND ANSWERS

82
83 Since the enactment of FDAAA, the Agency has received numerous inquiries about the scope of
84 section 524 and how various aspects of section 524 should be interpreted. The purpose of this
85 guidance is to provide a response to these questions.
86
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89 **Q1. What is a tropical disease product application?**

90

91 The term *tropical disease product application* is defined in section 524(a)(4) of the Act. The
92 term refers to an application that —

93

94 • is a human drug application as defined in section 735(1) of the Act²—

95 ○ for prevention or treatment of a tropical disease; and

96 ○ the FDA deems eligible for priority review;

97 • is approved after the date of the enactment of FDAAA by the FDA for use in the
98 prevention or treatment of a tropical disease; and

99 • is for a human drug, no active ingredient (including any ester or salt of the active
100 ingredient) of which has been approved in any other application under section 505(b)(1)
101 of the Act or section 351 of the PHS Act.

102

103 **Q2. What tropical disease product applications may qualify for a priority review** 104 **voucher?**

105

106 Product applications for the prevention or treatment of the following tropical diseases may
107 qualify:

108

109 • Tuberculosis

110 • Malaria

111 • Blinding trachoma

112 • Buruli Ulcer

113 • Cholera

114 • Dengue/Dengue haemorrhagic fever

115 • Dracunculiasis (guinea-worm disease)

116 • Fascioliasis

117 • Human African trypanosomiasis

118 • Leishmaniasis

119 • Leprosy

120 • Lymphatic filariasis

121 • Onchocerciasis

122 • Schistosomiasis

123 • Soil transmitted helminthiasis

124 • Yaws

125 • Any other infectious disease for which there is no significant market in developed nations
126 and that disproportionately affects poor and marginalized populations, designated by
127 regulation by the Secretary (section 524(a)(3))

128

129

² This definition includes drugs and most biological drugs, excluding blood components and certain other biological drug products. For details, refer to section 735(1) of the Act (21 U.S.C. 379g(1)). The definition does not cover medical devices.

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130 **Q3. What user fees apply to a tropical disease application?**

131
132 User fees for human drug applications are described in sections 735 and 736 of the Act.³ In
133 general, a tropical disease application would be subject to these statutory requirements like any
134 other application. However, we anticipate that many tropical disease applications may qualify
135 for designation as orphan drug products. Under section 736(a)(1)(F) of the Act, if a human drug
136 application for a prescription drug product that has been designated as a drug for a rare disease or
137 condition under section 526 of the Act, the application is not subject to an application user fee,
138 unless the application includes an indication for other than a rare disease or condition. In
139 addition, section 736(k) of the Act provides for an exemption from annual product and
140 establishment fees for certain orphan designated drugs.

141 142 **Q4. What is a priority review?**

143
144 A priority review is a review conducted with a PDUFA goal date of 6 months. Normally, an
145 application for a CDER product will qualify for a priority review if FDA determines that the
146 product, if approved, would provide safe and effective therapy where no satisfactory alternative
147 therapy exists or would be a significant improvement compared to marketed products, including
148 non-drug products and/or therapies, in the treatment, diagnosis, or prevention of a disease. See
149 CDER's Manual of Policies and Procedures (MAPP) 6020.3, "Review Classification Policy:
150 Priority and Standard."⁴ A CBER product will qualify for a priority review if FDA determines
151 that the product, if approved, would be a significant improvement in the safety or effectiveness
152 of the treatment, diagnosis, or prevention of a serious or life-threatening disease.

153
154 FDA has committed to a goal to review and act on 90 percent of the applications that have been
155 granted priority review status no later than 6 months after receipt, as described in the CDER
156 MAPP and goals identified in the letters described in section 101(c) of the FDAAA.⁵ An
157 application that does not receive a priority designation will receive a "standard" review. Under
158 the goals referenced in FDAAA section 101(c), FDA commits to a goal to review and act on 90
159 percent of "standard" applications within 10 months of the date of receipt. Please note that an
160 FDA review within a specific time frame does not mean an application will be approved within
161 that time frame. The term "review and act on" is understood to mean the issuance of an approval
162 or complete response letter after the review of a filed application. The action letter, if it is not an
163 approval, will set forth in detail the specific deficiencies that need to be addressed before the
164 application can be approved.

165 166 **Q5. What is a priority review voucher and when is it awarded?**

167
168 The term *priority review voucher* is defined in section 524(a)(2) of the Act. It refers to a voucher
169 issued by the Secretary to the sponsor of a tropical disease product application at the time of

³ 21 U.S.C. 379g and 379h.

⁴ Available on the Internet at <http://www.fda.gov/cder/mapp.htm>.

⁵ See letters from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives, as set forth in the Congressional Record, available on the Internet at <http://www.fda.gov/oc/pdufa4/pdufa4ltr.pdf>.

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170 approval of the application that entitles the holder of such voucher to designate a single human
171 drug application submitted under section 505(b)(1) or section 351 of the PHS Act (see section
172 524(a)(2) of the Act) as qualifying for a priority review. Such a subsequent application would
173 not have to meet the usual requirements for a priority review. (See Q13.)
174

175 **Q6. Would eligibility to receive a priority review voucher be affected in any way by**
176 **whether the sponsor intends to market or distribute the qualifying tropical disease**
177 **product after approval?**

178 No, it does not matter if the sponsor decides not to market the product. Eligibility will be based
179 on the criteria outlined in the statute.
180

181 **Q7. What form will the voucher take?**
182

183 The FDA will include information related to the priority review voucher in the approval letter for
184 the tropical disease drug application.
185

186 **Q8. Will these vouchers be transferable?**
187

188 Yes, by the sponsor receiving the voucher. As the statute states (section 524(b)(2)), the tropical
189 disease product sponsor receiving a tropical disease priority review voucher may transfer the
190 entitlement to such voucher (including by sale) to another sponsor of a human drug application.
191 The language of the statute allows for one transfer from the original recipient of the voucher to
192 another sponsor of a human drug for which an application under section 505(b)(1) of the Act or
193 section 351 of the PHS Act will be submitted after the date of the approval of the tropical disease
194 product application. Although the statute's language imposes a limitation of one actual transfer
195 of the voucher, FDA believes that contractual arrangements such as the use of an option or
196 transfer of the right to designate the voucher's recipient could comply with the terms of the
197 statute.
198

199 **Q9. What is the procedure for voucher transfer?**
200

201 The transfer should be documented with a letter of transfer from the tropical disease application
202 holder granted the voucher and a letter from the new voucher owner acknowledging the transfer.
203 These letters should be included in the application for which the sponsor wishes to redeem the
204 priority review voucher. A voucher cannot be redeemed unless a complete record of transfer is
205 available to the Agency.
206

207 **Q10. When can a voucher be used?**
208

209 After the voucher is issued, the sponsor redeeming the voucher must notify FDA of their intent
210 to submit a human drug application with a priority review voucher at least 365 days prior to
211 submission of the human drug application for which a priority review voucher will be used to
212 obtain a priority review. The notification must include the date the sponsor intends to submit the
213 application. In accordance with the language of the statute, FDA will consider this notification
214 as a legally binding commitment to pay the priority review user fee for the fiscal year in which
215 the application is submitted.

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Q11. What fees apply when using a priority review voucher?

The sponsor of a human drug application that is the subject of a priority review voucher must pay FDA a priority review user fee in addition to any other fee required under the prescription drug user fee program. As the statute requires, the amount of the priority review user fee will be determined each fiscal year and based on the average cost incurred by FDA in the review of a human drug application subject to priority review in the previous fiscal year.

FDA will establish the fee amount before the beginning of each fiscal year and will publish the fee schedule in the *Federal Register*.

Q12. When do I pay the priority review voucher fee?

According to the terms of the statute, the priority review user fee is due upon submission of the application for which the priority review voucher is used. The statute specifies that the application will be considered incomplete if the priority fee and all other applicable user fees are not paid in accordance with FDA payment procedures. In addition, FDA cannot collect these fees in any fiscal year until Congress has passed a law appropriating funds for these fees. Because FDA may not grant a waiver, exemption, reduction, or refund of any fees due and payable under this section of the Act and FDA may not collect priority review voucher fees prior to a relevant appropriation for that fiscal year, FDA cannot accept any application using a priority review voucher if the necessary appropriation has not become law for that fiscal year.

Q13. If I present a voucher to FDA for priority review, am I guaranteed a 6-month review on my new drug application?

No. The definition of priority review in section 524(a)(1) refers to the CDER MAPP and the PDUFA goals letter.⁶ We believe the intent of this section is that drugs for which priority review vouchers are used should be treated as if they were any other priority review drug. Therefore, these applications would be placed in the priority review group. The Agency has committed to a goal of completing 90 percent of priority reviews within 6 months.

Q14. Can FDA determine whether an application will be eligible to receive a voucher before an application is approved or licensed (i.e., prior to NDA/BLA submission or during review of the application)?

No. It is important to note that a product that meets the criteria at the time of submission may not meet those same criteria at the time of the approval action and would thus not be eligible to receive a priority review voucher. This could occur if another application containing the same active ingredient is approved first. For this reason, the Agency will not make voucher determinations until the time of application approval.

Q15. Are combination products eligible for priority review vouchers?

⁶ The PDUFA goals can be found on the Internet at <http://www.fda.gov/oc/pdufa4/pdufa4goals.html>.

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261
262 It depends. A combination product is eligible if the product, including all active ingredients,
263 meets the criteria established in FDAAA. However, if the product contains any active ingredient
264 that has been previously approved, the application is not eligible for a priority voucher (see
265 section 524(a)(4)(C) of the Act).

266
267 **Q16. Are products eligible that have been approved and used in other countries but have**
268 **not previously been submitted for review by the FDA?**

269
270 Yes, as long as they meet all the elements for a tropical disease product application described in
271 section 524(a)(4).

272
273 **Q17. Is a drug that is already approved for another indication eligible for a priority**
274 **review voucher for a tropical disease application?**

275
276 No. For an application to qualify, it must be for a human drug, no active ingredient (including
277 any ester or salt of the active ingredient) of which has been approved in any other application
278 under section 505(b)(1) of the Act or section 351 of the PHS Act.

279
280 **Q18. Would a new pediatric formulation for a drug already approved for adults be**
281 **eligible?**

282
283 No. As noted above, an application for a product containing a previously approved drug is not
284 eligible to receive a tropical disease priority voucher.

285
286 **Q19. Would an application for a tropical disease product submitted to FDA prior to**
287 **enactment of the statute but not yet approved qualify for a voucher?**

288
289 No. The tropical disease product sponsor may not receive a tropical disease priority voucher if
290 the application was submitted to the FDA before the date of the enactment of section 524
291 (September 27, 2007).

292
293 **Q20. Through what mechanism should a sponsor notify FDA that it intends to submit an**
294 **application eligible to receive a voucher?**

295
296 The original submission of the tropical disease application should include the sponsor's request
297 outlining how they meet the eligibility criteria for a priority review voucher. We encourage early
298 communication with the review division in which these issues could be discussed; however,
299 notification before submission of the tropical disease application is not required.

300
301 **Q21. Could a tropical disease product also qualify as an orphan drug?**

302
303 It is likely that a drug product meeting the requirements of section 524 will also qualify for
304 marketing exclusivity, tax credits, fee exemptions, and orphan product grants provided under the
305 Orphan Drug Act. For information regarding these incentives, potential sponsors should contact
306 the Office of Orphan Products Development (OOPD). These products may also qualify for new

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307 chemical entity marketing exclusivity provided under the Act. For information regarding new
308 chemical entity marketing exclusivity, potential sponsors should contact the appropriate CDER
309 review division.

310

311 **Q22. What are the different roles played by CDER, CBER, and the Office of Orphan**
312 **Products Development?**

313

314 CDER and CBER

315

316 The review divisions within the Center for Drug Evaluation and Research and the Center for
317 Biologics Evaluation and Research have the responsibility for premarket review of the tropical
318 disease product applications and for determining whether an application meets the eligibility
319 criteria for receiving a priority review voucher.

320

321 Office of Orphan Products Development

322

323 The Office of Orphan Products Development is located within the Office of the Commissioner
324 and is responsible for determining whether a drug or biologic qualifies for orphan drug status.
325 For example, to secure orphan status for the treatment of a rare disease, a sponsor demonstrates
326 to OOPD that the disease or condition is rare in the United States (i.e., <200,000 persons in the
327 United States are currently affected) *and* that the drug is expected to be effective (i.e., is
328 promising) in the treatment of the disease. Orphan-drug designation must be granted prior to the
329 submission of a marketing application. This is a separate process from the determination of
330 whether a drug or biologic will qualify as a tropical disease drug or will ultimately be eligible for
331 a voucher under the provisions of section 524. The latter determination will be made by CDER
332 or CBER, as appropriate.

333

334 If the product meets the criteria of the Orphan Drug Act, OOPD will provide orphan designation
335 that qualifies the sponsor of the product for a tax credit and the marketing incentives of the
336 Orphan Drug Act.⁷ Questions concerning orphan drug designations, or the benefits and
337 requirements associated with such designations, should be directed to OODP
338 (<http://www.fda.gov/orphan>).

339

340 **Q23. Does FDA plan to add other infectious diseases to the list? If so, when can we expect**
341 **to see that?**

342

343 Section 524 allows FDA to designate by regulation any other infectious disease for which there
344 is no significant market in developed nations and that disproportionately affects poor and
345 marginalized populations. FDA intends to seek public input regarding the criteria that could be
346 used to designate other diseases as well as specific diseases that might meet those criteria.

347

348 **Q24. What should I do if I have other questions about a tropical disease application?**

349

350 Sponsors with questions not addressed in this guidance should contact the appropriate review
351 division within the Center for Drug Evaluation and Research (CDER) or Center for Biologics

⁷ Information on the Orphan Drug Act is available at <http://www.fda.gov/orphan/progovw.htm>.

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352 Evaluation and Research (CBER). CDER and CBER encourage early interaction with potential
353 sponsors so these types of questions can be discussed. Such interactions could begin as early as
354 the pre-IND phase of drug development.
355