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DRAFT GUIDANCE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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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. INTRODUCTION

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.

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.

II. BACKGROUND

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.

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

III. PROVISIONS OF SECTION 524 – AN OVERVIEW

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

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

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

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

IV. POLICIES AND PROCEDURES – QUESTIONS AND ANSWERS

Since the enactment of FDAAA, the Agency has received numerous inquiries about the scope of section 524 and how various aspects of section 524 should be interpreted. The purpose of this guidance is to provide a response to these questions.

Q1. What is a tropical disease product application?

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

- is a human drug application as defined in section 735(1) of the Act[2]—
  - for prevention or treatment of a tropical disease; and
  - the FDA deems eligible for priority review;
- is approved after the date of the enactment of FDAAA by the FDA for use in the prevention or treatment of a tropical disease; and
- is for a human drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under section 505(b)(1) of the Act or section 351 of the PHS Act.

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

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

- Tuberculosis
- Malaria
- Blinding trachoma
- Buruli Ulcer
- Cholera
- Dengue/Dengue haemorrhagic fever
- Dracunculiasis (guinea-worm disease)
- Fascioliasis
- Human African trypanosomiasis
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Onchocerciasis
- Schistosomiasis
- Soil transmitted helminthiasis
- Yaws
- Any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulation by the Secretary (section 524(a)(3))

[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.

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

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

Q4. What is a priority review?

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

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

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

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

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[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.

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

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

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

Q7. What form will the voucher take?

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

Q8. Will these vouchers be transferable?

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

Q9. What is the procedure for voucher transfer?

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

Q10. When can a voucher be used?

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

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.

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

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

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

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

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

Q18. Would a new pediatric formulation for a drug already approved for adults be eligible?

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

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

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

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

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

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

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

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

<u>CDER and CBER</u>

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

<u>Office of Orphan Products Development</u>

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

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

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

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

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

Sponsors with questions not addressed in this guidance should contact the appropriate review 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.

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