Tropical Disease Priority Review Vouchers

Guidance for Industry

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 2016
Procedural

OMB Control No. 0910-0822
Expiration Date 08/31/2019
See additional PRA statement in section V of this guidance.

Tropical Disease Priority Review Vouchers

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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 2016
Procedural

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 1

III. PROVISIONS OF SECTION 524 — AN OVERVIEW 2

A. For Which Human Drug Application Is a Sponsor Eligible to Receive a Tropical Disease Priority Review Voucher? 2

B. What Are the Parameters for Use of a Tropical Disease Priority Review Voucher? 3

IV. POLICIES AND PROCEDURES — QUESTIONS AND ANSWERS 3

A. Definitions: Tropical Disease Product Application and Tropical Disease 3

B. Priority Review Vouchers: General Information 5

C. Priority Review Vouchers: Eligibility 7

D. Priority Review Vouchers: Transferability 8

E. Priority Review Voucher Fees and Use 8

F. Relationship Among the Priority Review Voucher Program and Other Programs 10

V. PAPERWORK REDUCTION ACT OF 1995 11

Contains Nonbinding Recommendations

Tropical Disease Priority Review Vouchers Guidance for Industry[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. INTRODUCTION

This guidance provides information on the implementation of section 1102 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which added section 524 to the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360n).[2] Section 524 authorizes the FDA to award priority review vouchers to sponsors of certain tropical disease product applications that meet the criteria specified in that section. Since the enactment of FDAAA, we have 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 those questions.

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

Section 524 was 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. Although the diseases addressed by this legislation represent a significant disease burden for humanity, there has been remarkably little progress over the past 50 years in development of drugs and vaccines for these diseases. Because these diseases are found primarily in poor and developing countries, existing incentives have been insufficient to encourage development of

[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.

[2] Section 524 of the FD&C Act subsequently was amended December 16, 2014 (Public Law 113-233).

new and innovative drug therapies. Although these tropical diseases generally are rare in the United States, intercontinental jet transport, immigration, tourism, and military operations are increasing the direct effect these diseases have on the health of Americans. By enacting section 524, Congress intended 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 (as defined in section 735(1) of the FD&C Act) for a tropical disease drug product may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug application submitted under section 505(b)(1)[3] of the FD&C Act or section 351 of the Public Health Service (PHS) Act after the date of approval of the tropical disease drug product.

III. PROVISIONS OF SECTION 524 — AN OVERVIEW

A. For Which Human Drug Application Is a Sponsor Eligible to Receive a Tropical Disease Priority Review Voucher?

- The application must be for the prevention or treatment of a *tropical disease* as defined in section 524(a)(3) of the FD&C Act (see section IV, Question 2, of this guidance)

- The application must be submitted under section 505(b)(1) of the FD&C Act or section 351 of the PHS Act

- The human drug that is the subject of the application must not contain any active ingredient (including any ester or salt of the active ingredient) that has been approved in any other application under section 505(b)(1) of the FD&C Act or section 351 of the PHS Act

- The application must be "for prevention or treatment of a tropical disease," and must be approved "for use in the prevention, detection, or treatment of a tropical disease"[4]

- The application must have been submitted after the enactment of FDAAA (September 27, 2007)

- The application must otherwise be eligible for a priority review

[3] Section 505(b)(2) new drug applications (NDAs) are submitted under section 505(b)(1), so all references to NDAs submitted under section 505(b)(1) include 505(b)(2) applications.

[4] The statute uses two different but overlapping qualifications for meeting the definition of "tropical disease product application." Under section 524(a)(4)(A)(i), the "tropical disease product application" must be a "human drug application . . . for prevention or treatment of a tropical disease[.]" Under section 524(a)(4)(B), the "tropical disease product application" must be "approved after September 27, 2007, by the Secretary for use in the prevention, detection, or treatment of a tropical disease[.]"

B. What Are the Parameters for Use of a Tropical Disease Priority Review Voucher?

- The application using the priority review voucher must also be submitted under section 505(b)(1) of the FD&C Act or section 351 of the PHS Act, and is not limited to drug products for tropical diseases.

- At least 90 days before submission of the human drug application for which the priority review voucher will be used, the sponsor planning to use the voucher must notify the FDA of an intent to use the voucher and the date on which the sponsor intends to submit the application.

- When using the voucher, a sponsor must pay an extra user fee (i.e., a separate priority review user fee) to support the review of the application based on the average cost of a priority new drug application/biologics license application (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. For further explanation, see the response to Question 21 in section IV.

- The sponsor of a tropical disease drug product receiving a priority review voucher may transfer the voucher to another sponsor (see section IV, Question 17).

IV. POLICIES AND PROCEDURES — QUESTIONS AND ANSWERS

This section provides answers to frequently asked questions regarding the scope of section 524.

A. Definitions: Tropical Disease Product Application and Tropical Disease

Q1. What is a tropical disease product application?

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

- A human drug application as defined in section 735(1) of the FD&C Act:[5]
  - For prevention or treatment of a tropical disease (see Question 2); and
  - That the FDA deems eligible for priority review

- Approved by the FDA after the date of the enactment of FDAAA for use in the prevention or treatment of a tropical disease

[5] This definition includes applications for drugs submitted under section 505(b) of the FD&C Act and applications for most biological drugs, including vaccines, submitted under section 351(a) of the PHS Act, but excludes applications for blood components and certain other biological drug products. For details, refer to section 735(1) of the FD&C Act (21 U.S.C. 379g(1)). The definition does not cover applications for medical devices.

- 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 FD&C Act or section 351 of the PHS Act

Q2. What diseases are considered tropical diseases for priority review voucher purposes?

A tropical disease is any of the following diseases (see section 524(a)(3) of the FD&C Act):

- 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
- Filovirus Diseases
- Zika Virus Disease
- Any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by order of the Secretary.

Q3. Does the FDA plan to add other infectious diseases to the list? If so, when can we expect that to occur?

Section 524 allows the FDA to designate by order any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations. On August 20, 2015, the FDA issued the final order "Designating Additions to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act" in the *Federal Register* (80 FR 50559). The order sets forth the criteria for adding a disease to the list, added Chagas disease and neurocysticercosis to the list, and opened a docket to receive recommendations from the public for future additions to the list (FDA-2008-N-0567). We will review these recommendations and make future additions to the list, as appropriate.

Q4. Can a tropical disease listed in the statute be removed from the list by the FDA?

No. The statute does not contain a provision for removing a tropical disease from the statutory list.

Q5. What user fees apply to a tropical disease product application?

User fees for human drug applications are described in section 736 of the FD&C Act. In general, a tropical disease product application would be subject to these statutory requirements like any other application. However, we anticipate that some tropical disease products may qualify for designation as orphan drugs because the tropical diseases these drugs are intended to prevent or treat may affect fewer than 200,000 persons in the United States (see section 526 of the FD&C Act) (see also the response to Question 24). Under section 736(a)(1)(F) of the FD&C Act, if a human drug application for a prescription drug product has been designated as a drug product for a rare disease or condition under section 526 of the FD&C Act, the application is not subject to an application user fee, unless the application includes an indication other than for a rare disease or condition. In addition, section 736(k) of the FD&C Act provides for an exemption from annual drug product and establishment fees for certain orphan-designated drug products.

B. Priority Review Vouchers: General Information

Q6. 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 FD&C Act. It refers to a voucher issued by the FDA to the sponsor of a tropical disease product application at the time of approval of the application that entitles the holder of such voucher to designate a single human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the PHS Act (see section 524(a)(2) of the FD&C Act) as qualifying for a priority review. Such a subsequent application would not have to meet the usual requirements for a priority review. (See Question 13.)

Q7. What is a priority review?

A priority review is a review conducted within a time frame prescribed in FDA commitments made in connection with the Prescription Drug User Fee Act (PDUFA). Normally, an application for a drug product will qualify for a priority review if we determine that the drug product, if approved, would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition.[6]

For the fiscal years 2013 through 2017, we have committed to a goal to review and act on 90 percent of priority new molecular entity (NME) NDA and original BLA submissions within 6 months of the 60-day filing date, and 90 percent of priority non-NME original NDA submissions

[6] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

within 6 months of receipt, as described in the goals identified in the letters described in section 101(c) of FDAAA.[7] An application that does not receive a priority designation will receive a *standard* review. The FDA commits to a goal to review and act on 90 percent of standard applications for NME and original BLA submissions within 10 months of the 60-day filing date, and 90 percent of priority non-NME original NDA submissions within 10 months of receipt. 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.

Q8. What form will the voucher take?

We will include information related to the priority review voucher in the approval letter for the tropical disease product application. This letter will include a priority review voucher identification number, which should be referred to when redeeming the voucher.

Q9. When can a voucher be used?

After the voucher is issued, the sponsor redeeming the voucher must notify the FDA of its intent to submit a human drug application with a priority review voucher at least 90 days before submission of the human drug application for which the priority review voucher will be used. This timeline is mandated by section 524(b)(4) of the FD&C Act. The notification must include the date the sponsor intends to submit the application (hereinafter referred to as the *intended submission date*). The application for which the voucher is being used should not be submitted before that date. If a sponsor does not submit the application on the intended submission date, the sponsor should inform the FDA as soon as possible of the new intended submission date. The priority review user fee for the fiscal year in which the application is submitted is due upon the submission of the human drug application for which the priority review voucher is used.

If the sponsor decides not to use the voucher for the application described in the notification, the sponsor should notify the FDA and withdraw the notification. The sponsor should submit a new notification informing the FDA that the sponsor intends to submit a different human drug application with a priority review voucher at least 90 days before submission, as noted above, and include the date by which the application will be submitted.[8]

---

[7] This section refers to the commitments made by the FDA in 2007. 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/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm. The goals identified in the 2007 letter thus apply here. We note that the user fee goals identified in the successor 2012 commitment letter differ slightly (in the case of applications covering NMEs, the 6-month goals start with the 60-day filing date for those applications, rather than the date of receipt).

[8] Before Public Law 113-233 was enacted on December 16, 2014, section 524 of the FD&C Act required at least 365 days' notice before a voucher could be redeemed. The requirement for 90 days' notice applies to those vouchers that were awarded before December 16, 2014, as well as those awarded after that date.

C. Priority Review Vouchers: Eligibility

Q10. Can the FDA determine whether an application will be eligible to receive a voucher before an application is approved or licensed (i.e., before NDA/BLA submission or during review of the application)?

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

Although we will not make a determination that an application is eligible to receive a tropical disease priority review voucher before the application is approved, we may render a preliminary, nonbinding opinion, before approval, that a given application appears to meet the criteria for voucher eligibility.

Q11. Are drug-drug combinations eligible for priority review vouchers?

A drug-drug combination is eligible if the product meets the criteria established in section 524. In general, an application for a fixed-combination drug product submitted under section 505(b) of the FD&C Act will be eligible for a voucher if the product contains at least one active moiety that has not been approved in any other application under section 505(b).[9]

Q12. Are drug products that have been approved and used in other countries but have not previously been submitted for review by the FDA eligible for priority review vouchers?

Yes, as long as they meet all the criteria for a tropical disease product application described in section 524(a)(4) of the FD&C Act.

Q13. Is a drug that is already approved for another indication eligible for a priority review voucher for a tropical disease product 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 FD&C Act or section 351 of the PHS Act.

[9] See section 524(a)(4)(C) of the FD&C Act. Because section 524(a)(4)(C) of the FD&C Act contains the same phrase ("no active ingredient (including any ester or salt of the active ingredient) of which has been approved") as is used in sections 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act, the FDA will follow, for drug products approved under the FD&C Act, its guidance on exclusivity for combination drugs under those provisions. See the guidance for industry *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products*. For drug products approved under the PHS Act, the FDA will make decisions on eligibility under section 524(a)(4)(C) on a case-by-case basis.

Q14. Would a new pediatric formulation for a drug already approved for adults be eligible?

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

Q15. Would an application for a tropical disease drug product submitted to the FDA before enactment of the statute but not yet approved qualify for a voucher?

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

Q16. Would eligibility to receive a priority review voucher be affected in any way by whether the sponsor intends to market or distribute the tropical disease drug product after approval?

No, section 524 does not describe marketing or distribution of a drug product as a prerequisite to receiving a priority review voucher. Eligibility will be based on the criteria outlined in the statute.

D. Priority Review Vouchers: Transferability

Q17. Will these vouchers be transferable?

Yes. As section 524(b)(2) of the FD&C Act states, the tropical disease drug 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 statute does not limit the number of times a priority review voucher may be transferred before the voucher is used.

Q18. What is the procedure for voucher transfer?

The transfer should be documented with a letter of transfer from the tropical disease product application holder awarded the voucher and a letter from the new voucher owner acknowledging the transfer. These letters should be included in the application submitted by the sponsor redeeming the priority review voucher. A voucher cannot be redeemed unless a complete record of transfer is made available to the FDA.

E. Priority Review Voucher Fees and Use

Q19. Through what mechanism should a sponsor notify the FDA that it intends to submit an application eligible to receive a voucher?

The original submission of the tropical disease product application should include the sponsor's request describing how the application meets 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 product application is not required.

Q20. If I present a voucher to the FDA for priority review, am I guaranteed a 6-month review (or 6-month review from the 60-day filing date in the case of an NME NDA or original BLA) on my drug application?

No. The definition of *priority review* in section 524(a)(1) refers to the 2007 PDUFA goals letter.[10] We believe the intent of this section is that a human drug application for which priority review vouchers are used should be treated as if it were any other priority review human drug application under the 2007 goals. The 2007 goals letter committed the FDA to a goal of completing 90 percent of priority reviews within the prescribed time frames.

Q21. 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 the FDA a priority review user fee in addition to any other fee required under PDUFA. As the statute requires, the amount of the priority review user fee will be determined each fiscal year and is based on the average cost incurred by the FDA in the review of a human drug application subject to priority review in the previous fiscal year.

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

Q22. When do I pay the priority review voucher user fee?

According to the terms of the statute, the priority review voucher 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 review voucher user fee and all other applicable user fees are not paid in accordance with FDA payment procedures.

Q23. If I pay the priority review user fee and submit an application with the intent of using the priority review voucher and during the filing review the FDA determines that the application meets the criteria for a priority review on its own merit, can I get a refund for the priority review user fee so that I can use the voucher for another application instead of this one?

No. Once the priority review user fee is paid, it cannot be refunded. As the statute states (section 524(c)(4)(C) of the FD&C Act), "[T]he Secretary may not grant a waiver, exemption, reduction, or refund of any fees due and payable under this section."

[10] See note 8, supra.

F. Relationship Among the Priority Review Voucher Program and Other Programs

Q24. Could a tropical disease drug product also qualify as an orphan drug?

It is possible that a drug product meeting the requirements of section 524 also may qualify for designation as an orphan drug under section 526 of the FD&C Act. If designated as an orphan drug, such a drug product may be eligible for orphan drug marketing exclusivity and tax credits for qualified clinical testing as well as fee exemptions under section 736 of the FD&C Act. For information regarding these orphan drug incentives, potential sponsors should contact the Office of Orphan Products Development (OOPD). For information regarding user fee exemptions, potential sponsors should contact the User Fee staff in the Center for Drug Evaluation and Research's (CDER's) Office of Management. Drug products meeting the requirements of section 524 may also qualify for new chemical entity marketing exclusivity provided under the FD&C Act. For information regarding new chemical entity marketing exclusivity, potential sponsors should contact the appropriate CDER review division.

Q25. What are the different roles played by CDER, CBER, and the OOPD?

CDER and CBER

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

OOPD

The OOPD is distinct from CDER and CBER and is responsible for determining whether a drug (including biologics) qualifies for orphan drug status. For a drug to be eligible for orphan status, a sponsor generally must demonstrate to OOPD that, among other things, the disease or condition for which the drug is to be used is rare in the United States (i.e., the disease or condition affects fewer than 200,000 persons in the United States) and must provide an adequate scientific rationale for using that drug for that rare disease or condition.[11] A request for orphan drug designation must be submitted before the submission of a marketing application.[12] This process is separate from the determination of whether a drug or biologic will qualify as a tropical disease drug or biologic, or the determination of whether the drug or biologic ultimately will be eligible for a voucher under the provisions of section 524 of the FD&C Act. The latter determination will be made by CDER or CBER, as appropriate.

If the drug meets the criteria established under section 526 of the FD&C Act and 21 CFR part 316, OOPD will grant the drug orphan designation, which then makes the drug eligible for orphan drug marketing exclusivity and tax credits for qualified clinical testing as well as fee

[11] See 21 CFR 316.20(b).

[12] See 21 CFR 316.23(a).

exemptions under section 736 of the FD&C Act. Questions concerning orphan drug designations, or the benefits and requirements associated with such designations, should be directed to OOPD.[13]

Q26. What should I do if I have other questions about a tropical disease product application?

Sponsors with questions not addressed in this guidance should contact the appropriate review division within CDER or 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-investigational new drug application phase of drug development.

V. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average 8 hours to prepare a priority review voucher request, 8 hours to prepare notifications of intent to use a voucher, and 8 hours to prepare the necessary letters indicating the transfer of a voucher and acknowledging the receipt of a transferred voucher. These estimates include the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection.

Send comments regarding this burden estimate or suggestions for reducing this burden to: Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0822 (expires 08/31/2019).

[13] See http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm.