

Transparency and Communication for NME (New Molecular Entity) NDAs and Original BLAs, and risk evaluation and mitigation strategies.

In addition, the draft guidance has been consolidated to focus on the fundamental values and operational principles that serve as the foundation for the GRMPs. Details of the review process are covered in other documents referenced by this guidance. Fundamental values and operational principles should remain relatively constant over time, while processes must be able to adapt and respond to scientific advances in product development and evolving public health needs.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on GRMPs for NDAs and BLAs. 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. This guidance is not subject to Executive Order 12866.

## II. Electronic Access

Persons with access to the internet may obtain the draft guidance at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>, or <https://www.regulations.gov>.

Dated: September 19, 2018.

**Leslie Kux,**

*Associate Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2018-N-0007]

### Fee for Using a Tropical Disease Priority Review Voucher in Fiscal Year 2019

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA or the Agency) is announcing the fee rates for using a tropical disease priority review voucher for fiscal year (FY) 2019. The Federal Food, Drug, and Cosmetic Act (FD&C

Act), as amended by the Food and Drug Administration Amendments Act of 2007 (FDAAA), authorizes FDA to determine and collect priority review user fees for certain applications for review of drug or biological products when those applications use a tropical disease priority review voucher. These vouchers are awarded to the applicants of certain tropical disease product applications, submitted after September 27, 2007, upon FDA approval of such applications. The amount of the fee submitted to FDA with applications using a tropical disease priority review voucher is determined each fiscal year based on the difference between the average cost incurred by FDA to review a human drug application designated as priority review in the previous fiscal year and the average cost incurred in the review of an application that is not subject to priority review in the previous fiscal year. This notice establishes the tropical disease priority review fee rate for FY 2019.

#### FOR FURTHER INFORMATION CONTACT:

Lola Olajide, Office of Financial Management, Food and Drug Administration, 8455 Colesville Rd., COLE-14541B, Silver Spring, MD 20993-0002, 240-402-4244.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

Section 1102 of FDAAA (Pub. L. 110-85) added section 524 to the FD&C Act (21 U.S.C. 360n). In section 524, Congress encouraged development of new drug and biological products for prevention and treatment of tropical diseases by offering additional incentives for obtaining FDA approval of such products. Under section 524, the applicant of an eligible human drug application submitted after September 27, 2007, for a tropical disease (as defined in section 524(a)(3) of the FD&C Act) shall receive a priority review voucher upon approval of the tropical disease product application (assuming other criteria are met). The recipient of a tropical disease priority review voucher may either use the voucher with a future submission to FDA under section 505(b)(1) of the FD&C Act (21 U.S.C. 355(b)(1)) or section 351(a) of the Public Health Service Act (42 U.S.C. 262), or transfer (including by sale) the voucher to another party. The voucher may be transferred (including by sale) repeatedly until it ultimately is used for a human drug application submitted to FDA under section 505(b)(1) of the FD&C Act or section 351(a) of the Public Health Service Act. A priority review is a review conducted with a Prescription Drug User Fee Act (PDUFA) goal date of

6 months after the receipt or filing date, depending upon the type of application. Information regarding the PDUFA goals is available at: <https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf>.

The applicant that uses a priority review voucher is entitled to a priority review but must pay FDA a priority review user fee in addition to any other fee required by PDUFA. FDA published guidance on its website about how this tropical disease priority review voucher program operates (available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080599.pdf>).

This notice establishes the tropical disease priority review fee rate for FY 2019 as \$2,457,140 and outlines FDA's process for implementing the collection of the priority review user fees. This rate is effective on October 1, 2018, and will remain in effect through September 30, 2019, for applications submitted with a tropical disease priority review voucher. The payment of this priority review user fee is required in addition to the payment of any other fee that would normally apply to such an application under PDUFA before FDA will consider the application complete and acceptable for filing.

##### II. Tropical Disease Priority Review User Fee for FY 2019

FDA interprets section 524(c)(2) of the FD&C Act as requiring that FDA determine the amount of the tropical disease priority review user fee each fiscal year based on the difference between the average cost incurred by FDA in the review of a human drug application subject to priority review in the previous fiscal year and the average cost incurred by FDA in the review of a human drug application that is not subject to priority review in the previous fiscal year.

A priority review is a review conducted with a PDUFA goal date of 6 months after the receipt or filing date, depending on the type of application. Under the PDUFA goals letter, FDA has committed to reviewing and acting on 90 percent of the applications granted priority review status within this expedited timeframe. Normally, an application for a human drug or biological product will qualify for priority review if the product is intended to treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. An application that does not receive a priority designation receives a standard review. Under the

PDUFA goals letter, FDA committed to reviewing and acting on 90 percent of standard applications within 10 months of the receipt or filing date, depending on the type of application. A priority review involves a more intensive level of effort and a higher level of resources than a standard review.

FDA is setting fees for FY 2019, and the previous fiscal year is FY 2018. However, the FY 2018 submission cohort has not been closed out yet, and the cost data for FY 2018 are not complete. The latest year for which FDA has complete cost data is FY 2017. Furthermore, because FDA has never tracked the cost of reviewing applications that get priority review as a separate cost subset, FDA estimated this cost based on other data that the Agency has tracked. FDA uses data that the Agency estimates and publishes on its website each year—standard costs for review. FDA does not publish a standard cost for “the review of a human drug application subject to priority review in the previous fiscal year.” However, we expect all such applications would contain clinical data. The standard cost application categories with clinical data that FDA does publish each year are: (1) New drug applications (NDAs) for a new molecular entity (NME) with clinical data and (2) biologics license applications (BLAs).

The worksheets for standard costs for FY 2017 show a standard cost of \$5,340,560 for an NME NDA and \$4,596,936 for a BLA. Based on these standard costs, the total cost to review the 57 applications in these two categories in FY 2017 (31 NME NDAs with clinical data and 26 BLAs) was \$285,077,688. (Note: These numbers exclude the President’s Emergency Plan for AIDS Relief NDAs; no investigational new drug review costs are included in this amount.) Of these applications 33 (20 NDAs and 13 BLAs) received priority review, which would mean that the remaining 24 received standard reviews. Because a priority review compresses a review that ordinarily takes 10 months into 6 months, FDA estimates that a multiplier of 1.67 (10 months divided by 6 months) should be applied to non-priority review costs in estimating the effort and cost of a priority review as compared to a standard review. This multiplier is consistent with published research on this subject, which supports a priority review multiplier in the range of 1.48 to 2.35 (Ref. 1). Using FY 2017 figures, the costs of a priority and standard review are estimated using the following formula:

$$(33 \alpha \times 1.67) + (24 \alpha) = \$285,077,688$$

where “ $\alpha$ ” is the cost of a standard review and “ $\alpha$  times 1.67” is the cost of a priority review. Using this formula, the cost of a standard review for NME

NDAs and BLAs is calculated to be \$3,603,561 (rounded to the nearest dollar) and the cost of a priority review for NME NDAs and BLAs is 1.67 times that amount, or \$6,017,946 (rounded to the nearest dollar). The difference between these two cost estimates, or \$2,414,386, represents the incremental cost of conducting a priority review rather than a standard review.

For the FY 2019 fee, FDA will need to adjust the FY 2017 incremental cost by the average amount by which FDA’s average costs increased in the 3 years prior to FY 2018, to adjust the FY 2017 amount for cost increases in FY 2018. That adjustment, published in the **Federal Register** on August 1, 2018 (83 FR 37504), setting FY 2019 PDUFA fees, is 1.7708 percent for the most recent year, not compounded. Increasing the FY 2017 incremental priority review cost of \$2,414,386 by 1.7708 percent (or 0.017708) results in an estimated cost of \$2,457,140 (rounded to the nearest dollar). This is the tropical disease priority review user fee amount for FY 2019 that must be submitted with a priority review voucher for a human drug application in FY 2019, in addition to any PDUFA fee that is required for such an application.

**III. Fee Schedule for FY 2019**

The fee rate for FY 2019 is set out in table 1:

TABLE 1—TROPICAL DISEASE PRIORITY REVIEW SCHEDULE FOR FY 2019

Fee category	Fee rate for FY 2019
Application submitted with a tropical disease priority review voucher in addition to the normal PDUFA fee .....	\$2,457,140

**IV. Implementation of Tropical Disease Priority Review User Fee**

Under section 524(c)(4)(A) of the FD&C Act, the priority review user fee is due upon submission of a human drug application for which the priority review voucher is used. Section 524(c)(4)(B) of the FD&C Act specifies that the application will be considered incomplete if the priority review user fee and all other applicable user fees are not paid in accordance with FDA payment procedures. In addition, FDA may not grant a waiver, exemption, reduction, or refund of any fees due and payable under section 524 of the FD&C Act (see section 524(c)(4)(C)), and FDA may not collect priority review voucher fees “except to the extent provided in advance in appropriation Acts.” (Section 524(c)(5)(B) of the FD&C Act.)

The tropical disease priority review fee established in the new fee schedule must be paid for any application that is received on or after October 1, 2018, and submitted with a priority review voucher. This fee must be paid in addition to any other fee due under PDUFA. Payment should be made in U.S. currency by electronic check, check, bank draft, wire transfer, credit card, or U.S. postal money order payable to the order of the Food and Drug Administration. The preferred payment method is online using electronic check (Automated Clearing House (ACH) also known as eCheck). Secure electronic payments can be submitted using the User Fees Payment Portal at <https://userfees.fda.gov/pay>. (Note: only full payments are accepted. No partial payments can be made online). Once you search for your invoice, select “Pay Now” to be

redirected to *Pay.gov*. Note that electronic payment options are based on the balance due. Payment by credit card is available for balances that are less than \$25,000. If the balance exceeds this amount, only the ACH option is available. Payments should be made using U.S bank accounts as well as U.S. credit cards.

FDA has partnered with the U.S. Department of the Treasury to use *Pay.gov*, a web-based payment application, for online electronic payment. The *Pay.gov* feature is available on the FDA website after the user fee identification (ID) number is generated.

If paying with a paper check, the user fee ID number should be included on the check, followed by the words “Tropical Disease Priority Review.” All paper checks should be in U.S. currency from a U.S. bank made payable and

mailed to: Food and Drug Administration, P.O. Box 979107, St. Louis, MO 63197–9000.

If checks are sent by a courier that requests a street address, the courier can deliver the checks to: U.S. Bank, Attention: Government Lockbox 979107, 1005 Convention Plaza, St. Louis, MO 63101. (Note: This U.S. Bank address is for courier delivery only.) If you have any questions concerning courier delivery, contact the U.S. Bank at 314–418–4013. (This telephone number is only for questions about courier delivery.) The FDA post office box number (P.O. Box 979107) must be written on the check. If needed, FDA's tax identification number is 53–0196965.

If paying by wire transfer, please reference your unique user fee ID number when completing your transfer. The originating financial institution may charge a wire transfer fee. If the financial institution charges a wire transfer fee, it is required to add that amount to the payment to ensure that the invoice is paid in full. The account information is as follows: U.S. Dept. of Treasury, TREAS NYC, 33 Liberty St., New York, NY 10045, Account Number: 75060099, Routing Number: 021030004, SWIFT: FRNYUS33.

## V. Reference

The following reference is on display with the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is not available electronically at <https://www.regulations.gov> as this reference is copyright protected. FDA has verified the website address, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

- Ridley, D.B., H.G. Grabowski, and J.L. Moe, "Developing Drugs for Developing Countries," *Health Affairs*, vol. 25, no. 2, pp. 313–324, 2006, available at: [https://faculty.fuqua.duke.edu/~willm/HSM\\_RA/Documents/HA2006\\_Ridley\\_Vouchers.pdf](https://faculty.fuqua.duke.edu/~willm/HSM_RA/Documents/HA2006_Ridley_Vouchers.pdf).

Dated: September 19, 2018.

**Leslie Kux,**

*Associate Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA–2014–D–0900]

#### **Benefit-Risk Factors To Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) With Different Technological Characteristics; Guidance for Industry and Food and Drug Administration Staff; Availability**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice of availability.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing the availability of the final guidance entitled "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics." This guidance document describes factors FDA considers when evaluating the benefit-risk profile of a device in comparison to a predicate device in a 510(k) when the device has the same intended use as the predicate device, and different technological characteristics that do not raise different questions of safety and effectiveness. This guidance can be helpful in situations when there is an increase in risk and increase or equivalent benefit, or a decrease in benefit and a decrease or equivalent risk when comparing a new device to a predicate device. FDA developed this guidance to improve the predictability, consistency, and transparency of the 510(k) premarket review process.

**DATES:** The announcement of the guidance is published in the **Federal Register** on September 25, 2018.

**ADDRESSES:** You may submit either electronic or written comments on Agency guidances at any time as follows:

#### *Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal:** <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or

anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

#### *Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand Delivery/Courier (for written/paper submissions):** Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

**Instructions:** All submissions received must include the Docket No. FDA–2014–D–0900 for "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—**To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this