

recommending a BE study with clinical endpoints for demonstration of BE of generic mesalamine rectal suppositories.

In July 2007, Axcan Scandipharm (Axcan), manufacturer of CANASA, submitted a citizen petition requesting that FDA withhold approval of any ANDA application for a generic version of CANASA (mesalamine rectal suppositories) unless certain studies that demonstrated BE were conducted (Docket No. FDA-2007-P-0010, formerly 2007P-0302/CP1). FDA is reviewing the issues raised in the petition and is also reviewing the supplemental information submitted to the docket for this petition. FDA will consider any comments on the Draft Mesalamine Rectal Suppository BE Recommendations of 2013 before responding to Axcan's citizen petition.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on the design of BE studies to support ANDAs for mesalamine rectal suppositories. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

## II. Comments

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

## III. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <http://www.regulations.gov>.

Dated: July 29, 2013.

**Leslie Kux,**

*Assistant Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2013-N-0007]

### Food Safety Modernization Act Domestic and Foreign Facility Reinspection, Recall, and Importer Reinspection Fee Rates for Fiscal Year 2014

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

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the fiscal year (FY) 2014 fee rates for certain domestic and foreign facility reinspections, failures to comply with a recall order, and importer reinspections that are authorized by the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the FDA Food Safety Modernization Act (FSMA). These fees are effective on October 1, 2013, and will remain in effect through September 30, 2014.

**FOR FURTHER INFORMATION CONTACT:** Hunter Herrman, Office of Resource Management, Office of Regulatory Affairs, Food and Drug Administration, 12420 Parklawn Dr., rm. 2049, Rockville, MD 20857, 240-402-3102, email: [Hunter.Herrman@fda.hhs.gov](mailto:Hunter.Herrman@fda.hhs.gov).

### SUPPLEMENTARY INFORMATION:

#### I. Background

Section 107 of FSMA (Pub. L. 111-353) added section 743 to the FD&C Act (21 U.S.C. 379j-31) to provide FDA with the authority to assess and collect fees from, in part: (1) The responsible party for each domestic facility and the U.S. agent for each foreign facility subject to a reinspection, to cover reinspection-related costs; (2) the responsible party for a domestic facility and an importer who does not comply with a recall order, to cover food<sup>1</sup> recall activities associated with such order; and (3) each importer subject to a reinspection to cover reinspection-related costs (sections 743(a)(1)(A), (B), and (D) of the FD&C Act). Section 743 of the FD&C Act directs FDA to establish fees for each of these activities based on an estimate of 100 percent of the costs of each activity for each year (section 743(b)(2)(A), (B), and (D)), and these fees must be made available solely to pay for the costs of each activity for which the fee was incurred (section 743(b)(3)). These fees are effective on October 1, 2013, and

will remain in effect through September 30, 2014. Section 743(b)(2)(B)(iii) of the FD&C Act directs FDA to develop a proposed set of guidelines in consideration of the burden of fee amounts on small businesses. As a first step in developing these guidelines, FDA invited public comment on the potential impact of the fees authorized by section 743 of the FD&C Act on small businesses (76 FR 45818, August 1, 2011). The comment period for this request ended November 30, 2011. As stated in FDA's September 2011 "Guidance for Industry: Implementation of the Fee Provisions of Section 107 of the FDA Food Safety Modernization Act," (<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/FoodDefense/ucm274176.htm>), because FDA recognizes that for small businesses the full cost recovery of FDA reinspection or recall oversight could impose severe economic hardship, FDA intends to consider reducing certain fees for those firms. FDA is currently developing a guidance document to outline the process through which firms may request such a reduction of fees. FDA does not intend to issue invoices for reinspection or recall order fees until this guidance document has been published.

In addition, as stated in the September 2011 Guidance, FDA is in the process of considering various issues associated with the assessment and collection of importer reinspection fees. FDA is currently developing a guidance document that will provide information regarding fees that the Agency may assess and collect from importers to cover reinspection-related costs. The fee rates set forth in this notice will be used to determine any importer reinspection fees assessed in FY 2014.

#### II. Estimating the Average Cost of a Supported Direct FDA Work Hour for FY 2014

FDA is required to estimate 100 percent of its costs for each activity in order to establish fee rates for FY 2014. In each year, the costs of salary (or personnel compensation) and benefits for FDA employees account for between 50 and 60 percent of the funds available to, and used by, FDA. Almost all of the remaining funds (or the operating funds) available to FDA are used to support FDA employees for paying rent, travel, utility, information technology, and other operating costs.

<sup>1</sup> The term "food" for purposes of this document has the same meaning as such term in section 201(f) of the FD&C Act (21 U.S.C. 321(f)).

### A. Estimating the Full Cost per Direct Work Hour in FY 2012

In general, the starting point for estimating the full cost per direct work hour is to estimate the cost of a full-time-equivalent (FTE) or paid staff year for the relevant activity. This is most reasonably done by dividing the total funds allocated to the elements of FDA primarily responsible for carrying out the activities for which fees are being collected by the total FTEs allocated to those activities, using information from the most recent FY for which data are available. For the purposes of the reinspection and recall order fees authorized by section 743 of the FD&C Act (the fees that are the subject of this notice), primary responsibility for the activities for which fees will be collected rests with FDA's Office of Regulatory Affairs (ORA), which carries out inspections and other field-based activities on behalf of FDA's product centers, including the Center for Food Safety and Applied Nutrition (CFSAN) and the Center for Veterinary Medicine (CVM). Thus, as the starting point for estimating the full cost per direct work hour, FDA will use the total funds allocated to ORA for CFSAN and CVM related field activities. The most recent FY with available data is FY 2012. In that year, FDA obligated a total of \$697,628,866 for ORA in carrying out the CFSAN and CVM related field activities work, excluding the cost of inspection travel. In that same year, the number of ORA staff primarily conducting the CFSAN and CVM related field activities was 2,944 FTEs or paid staff years. Dividing \$697,628,866 by 2,944 FTEs, results in an average cost of \$236,966 per paid staff year, excluding travel costs.

Not all of the FTEs required to support the activities for which fees will be collected are conducting direct work such as inspecting or reinspecting facilities, examining imports, or monitoring recalls. Data collected over a number of years and used consistently in other FDA user fee programs (e.g., under the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee and Modernization Act (MDUFA)) show that every seven FTEs who perform direct FDA work require three indirect and supporting FTEs. These indirect and supporting FTEs function in budget, facility, human resource, information technology, planning, security, administrative support, legislative liaison, legal counsel, program management, and other essential program areas. On average, two of these indirect and supporting FTEs are located in ORA or

the FDA center where the direct work is being conducted, and one of them is located in the Office of the Commissioner. To get the fully supported cost of an FTE, FDA needs to multiply the average cost of an FTE by 1.43, to take into account the indirect and supporting functions. The 1.43 factor is derived by dividing the 10 fully supported FTEs by 7 direct FTEs. In FY 2012, the average cost of an FTE was \$236,966. Multiplying this amount by 1.43 results in an average fully supported cost of \$338,861 per FTE, excluding the cost of inspection travel.

To calculate an hourly rate, FDA must divide the average fully supported cost of \$338,861 per FTE by the average number of supported direct FDA work hours. See Table 1.

TABLE 1—SUPPORTED DIRECT FDA WORK HOURS IN A PAID STAFF YEAR

|                                                                     |       |
|---------------------------------------------------------------------|-------|
| Total number of hours in a paid staff year .....                    | 2,080 |
| Less:                                                               |       |
| 10 paid holidays .....                                              | 80    |
| 20 days of annual leave .....                                       | 160   |
| 10 days of sick leave .....                                         | 80    |
| 10 days of training .....                                           | 80    |
| 2 hours of meetings per week .....                                  | 80    |
| Net Supported Direct FDA Work Hours Available for Assignments ..... | 1,600 |

Dividing the average fully supported cost of an FTE in FY 2012 (\$338,861) by the total number of supported direct work hours available for assignment (1,600) results in an average fully supported cost of \$212 (rounded to the nearest dollar), excluding inspection travel costs, per supported direct work hour in FY 2012—the last FY for which data are available.

### B. Adjusting FY 2012 Costs for Inflation To Estimate FY 2014 Costs

To adjust the hourly rate for FY 2014, FDA must estimate the cost of inflation in each year for FY 2013 and FY 2014. FDA uses the method prescribed for estimating inflationary costs under the PDUFA provisions of the FD&C Act (section 736(c)(1) (21 U.S.C. 379h(c)(1))), the statutory method for inflation adjustment in the FD&C Act that we have used consistently. FDA previously determined the FY 2013 inflation rate to be 2.01 percent; this rate was published in the FY 2013 PDUFA user fee rates notice in the **Federal Register** of August 1, 2012 (77 FR 45639). Utilizing the method set forth in section 736(c)(1) of the FD&C Act, FDA has calculated an inflation rate of 2.20 percent for FY 2014 and FDA intends to use this inflation rate to make inflation

adjustments for FY 2014 for several of its user fee programs; the derivation of this rate is published elsewhere in this issue of the **Federal Register** in the FY 2014 notice for the PDUFA user fee rates. The compounded inflation rate for FYs 2013 and 2014, therefore, is 4.25 percent (one plus 2.01 percent times one plus 2.20 percent).

Increasing the FY 2012 average fully supported cost per supported direct FDA work hour of \$212 (excluding inspection travel costs) by 4.25 percent yields an inflationary adjusted estimated cost of \$221 per a supported direct work hour in FY 2014, excluding inspection travel costs. This is the base unit fee that FDA will use in determining the hourly fee rate for reinspection and recall order fees for FY 2014, prior to including domestic or foreign travel costs as applicable for the activity.

In FY 2012, ORA spent a total of \$5,399,442 for domestic regulatory inspection travel costs and General Services Administration Vehicle costs related to FDA's CFSAN and CVM field activities programs. The total ORA domestic travel costs spent is then divided by the total of 12,302 CFSAN and CVM domestic inspections, which averages a total of \$439 per inspection. These inspections average 29.19 hours per inspection. Dividing \$439 per inspection by 29.19 hours per inspection results in a total and an additional cost of \$15 per hour spent for domestic inspection travel costs in FY 2012. To adjust \$15 for inflationary increases in FY 2013 and FY 2014, FDA must multiply it by the same inflation factor mentioned previously in this document (1.0425) which results in an estimated cost of \$16 dollars per paid hour in addition to \$221 for a total of \$237 per paid hour (\$221 plus \$16) for each direct hour of work requiring domestic inspection travel. These are the rates that FDA will use in charging fees in FY 2014 when domestic travel is required.

In FY 2012, ORA spent a total of \$2,831,056 on a total of 301 foreign inspection trips related to FDA's CFSAN and CVM field activities programs, which averaged a total of \$9,406 per foreign inspection trip. These trips averaged 3 weeks (or 120 paid hours) per trip. Dividing \$9,406 per trip by 120 hours per trip results in a total and an additional cost of \$78 per paid hour spent for foreign inspection travel costs in FY 2012. To adjust \$78 for inflationary increases in FY 2013 and FY 2014, FDA must multiply it by the same inflation factor mentioned previously in this document (1.0425) which results in an estimated cost of

\$81 dollars per paid hour in addition to \$221 for a total of \$302 per paid hour (\$221 plus \$81) for each direct hour of work requiring foreign inspection travel. These are the rates that FDA will use in charging fees in FY 2014 when foreign travel is required.

**TABLE 2—FSMA FEE SCHEDULE FOR FY 2014**

| Fee category                                     | Fee rates for FY 2014 |
|--------------------------------------------------|-----------------------|
| Hourly rate if domestic travel is required ..... | \$237                 |
| Hourly rate if foreign travel is required .....  | 302                   |

### III. Fees for Reinspections of Domestic or Foreign Facilities Under Section 743(a)(1)(A)

#### A. What will cause this fee to be assessed?

The fee will be assessed for a reinspection conducted under section 704 of the FD&C Act (21 U.S.C. 374) to determine whether corrective actions have been implemented and are effective and compliance has been achieved to the Secretary of Health and Human Services' (the Secretary) (and, by delegation, FDA's) satisfaction at a facility that manufactures, processes, packs or holds food for consumption necessitated as a result of a previous inspection (also conducted under section 704) of this facility which had a final classification of Official Action Indicated (OAI) conducted by or on behalf of FDA, when FDA determined the non-compliance was materially related to food safety requirements of the FD&C Act. FDA considers such non-compliance to include non-compliance with a statutory or regulatory requirement under section 402 of the FD&C Act (21 U.S.C. 342) and section 403(w) of the FD&C Act (21 U.S.C. 343(w)). However, FDA does not consider non-compliance that is materially related to a food safety requirement to include circumstances where the non-compliance is of a technical nature and not food safety related (e.g., failure to comply with a food standard or incorrect font size on a food label). Determining when non-compliance, other than under sections 402 and 403(w) of the FD&C Act, is materially related to a food safety requirement of the FD&C Act may depend on the facts of a particular situation. FDA intends to issue guidance to provide additional information about the circumstances under which FDA would consider non-compliance to be

materially related to a food safety requirement of the FD&C Act.

Under section 743(a)(1)(A) of the FD&C Act, FDA is directed to assess and collect fees from "the responsible party for each domestic facility (as defined in section 415(b) (21 U.S.C. 350d)) and the United States agent for each foreign facility subject to a reinspection" to cover reinspection-related costs.

Section 743(a)(2)(A)(i) of the FD&C Act defines the term "reinspection" with respect to domestic facilities as "1 or more inspections conducted under section 704 subsequent to an inspection conducted under such provision which identified non-compliance materially related to a food safety requirement of th[e] Act, specifically to determine whether compliance has been achieved to the Secretary's satisfaction."

The FD&C Act does not contain a definition of "reinspection" specific to foreign facilities. In order to give meaning to the language in section 743(a)(1)(A) of the FD&C Act to collect fees from the U.S. agent of a foreign facility subject to a reinspection, the Agency is using the following definition of "reinspection" for purposes of assessing and collecting fees under section 743(a)(1)(A), with respect to a foreign facility: "1 or more inspections conducted by officers or employees duly designated by the Secretary subsequent to such an inspection which identified non-compliance materially related to a food safety requirement of the FD&C Act, specifically to determine whether compliance has been achieved to the Secretary's (and, by delegation, FDA's) satisfaction."

This definition allows FDA to fulfill the mandate to assess and collect fees from the U.S. agent of a foreign facility in the event that an inspection reveals non-compliance materially related to a food safety requirement of the FD&C Act, causing one or more subsequent inspections to determine whether compliance has been achieved to the Secretary's (and, by delegation, FDA's) satisfaction. By requiring the initial inspection to be conducted by officers or employees duly designated by the Secretary, the definition ensures that a foreign facility would be subject to fees only in the event that FDA, or an entity designated to act on its behalf, has made the requisite identification at an initial inspection of non-compliance materially related to a food safety requirement of the FD&C Act. The definition of "reinspection-related costs" in section 743(a)(2)(B) of the FD&C Act relates to both a domestic facility reinspection and a foreign facility reinspection, as described in section 743(a)(1)(A).

#### B. Who will be responsible for paying this fee?

The FD&C Act states that this fee is to be paid by the responsible party for each domestic facility (as defined in section 415(b) of the FD&C Act) and by the U.S. agent for each foreign facility (section 743(a)(1)(A) of the FD&C Act). This is the party to whom FDA will send the invoice for any fees that are assessed under this section.

#### C. How much will this fee be?

The fee is based on the number of direct hours spent on such reinspections, including time spent conducting the physical surveillance and/or compliance reinspection at the facility, or whatever components of such an inspection are deemed necessary, making preparations and arrangements for the reinspection, traveling to and from the facility, preparing any reports, analyzing any samples or examining any labels if required, and performing other activities as part of the OAI reinspection until the facility is again determined to be in compliance. The direct hours spent on each such reinspection will be billed at the appropriate hourly rate shown in table 2 of this document.

### IV. Fees for Non-Compliance With a Recall Order Under Section 743(a)(1)(B)

#### A. What will cause this fee to be assessed?

The fee will be assessed for not complying with a recall order under section 423(d) (21 U.S.C. 350l(d)) or section 412(f) of the FD&C Act (21 U.S.C. 350a(f)) to cover food recall activities associated with such order performed by the Secretary (and by delegation, FDA) (section 743(a)(1)(B) of the FD&C Act). Non-compliance may include the following: (1) Not initiating a recall as ordered by FDA; (2) not conducting the recall in the manner specified by FDA in the recall order; or (3) not providing FDA with requested information regarding the recall, as ordered by FDA.

#### B. Who will be responsible for paying this fee?

Section 743(a)(1)(B) of the FD&C Act states that the fee is to be paid by the responsible party for a domestic facility (as defined in section 415(b) of the FD&C Act) and an importer who does not comply with a recall order under section 423 or under section 412(f) of the FD&C Act. In other words, the party paying the fee would be the party that received the recall order.

*C. How much will this fee be?*

The fee is based on the number of direct hours spent on taking action in response to the firm's failure to comply with a recall order. Types of activities could include conducting recall audit checks, reviewing periodic status reports, analyzing the status reports and the results of the audit checks, conducting inspections, traveling to and from locations, and monitoring product disposition. The direct hours spent on each such recall will be billed at the appropriate hourly rate shown in table 2 of this document.

**V. How must the fees be paid?**

An invoice will be sent to the responsible party for paying the fee after FDA completes the work on which the invoice is based. Payment must be made within 90 days of the invoice date in U.S. currency by check, bank draft, or U.S. postal money order payable to the order of the Food and Drug Administration. Detailed payment information will be included with the invoice when it is issued.

**VI. What are the consequences of not paying these fees?**

Under section 743(e)(2) of the FD&C Act, any fee that is not paid within 30 days after it is due shall be treated as a claim of the U.S. Government subject to provisions of subchapter II of chapter 37 of title 31, United States Code.

Dated: July 29, 2013.

**Leslie Kux,**

*Assistant Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2013-N-0473]

#### Human Immunodeficiency Virus Patient-Focused Drug Development and Human Immunodeficiency Virus Cure Research; Reopening of Comment Period

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

**ACTION:** Notice; reopening of comment period.

**SUMMARY:** The Food and Drug Administration (FDA) is reopening the comment period for the notice of public meeting entitled "Human Immunodeficiency Virus (HIV) Patient-Focused Drug Development and HIV Cure Research," published in the

**Federal Register** of May 21, 2013 (78 FR 29755). In that notice, FDA requested public comment regarding patients' perspective on current approaches to managing HIV, symptoms experienced because of HIV or its treatment, and issues related to HIV cure research. FDA is reopening the comment period to allow interested persons additional time to submit comments.

**DATES:** Submit either electronic or written comments to the docket by September 3, 2013.

**ADDRESSES:** Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

**FOR FURTHER INFORMATION CONTACT:**

Pujita Vaidya, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 1170, Silver Spring, MD 20993-0002, 301-796-0684, FAX: 301-847-8443, email: [Pujita.Vaidya@fda.hhs.gov](mailto:Pujita.Vaidya@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:****I. Background**

In the **Federal Register** of May 21, 2013 (78 FR 29755), FDA announced the notice of public meeting entitled "HIV Patient-Focused Drug Development and HIV Cure Research." In that notice, FDA requested public comment on specific questions regarding patients' perspective on current approaches to managing HIV, symptoms experienced because of HIV or its treatment, and issues related to HIV cure research. Interested persons were given until July 14, 2013, to comment on the questions. The Agency is reopening the comment period until September 3, 2013 to allow interested persons additional time to submit comments.

**II. Specific Questions for Public Comment**

As part of Patient-Focused Drug Development, FDA is gathering input from HIV patients and patient advocates on current approaches to managing HIV, symptoms experienced because of HIV or its treatment, and issues related to HIV cure research. FDA is interested in receiving patient input that addresses the following questions.

#### *Topic 1: Patients' Perspective on Current Approaches to Managing HIV and on Symptoms Experienced Because of HIV or Its Treatment*

1. What are you currently doing to help manage your HIV and any symptoms you experience because of your condition or other therapies? (Examples may include prescription medicines, over-the-counter products, and nondrug therapies such as diet modification.)

a. What specific symptoms do your therapies or treatments address?

b. How long have you been on treatment and how has your treatment regimen changed over time?

2. How well does your current treatment regimen treat any significant symptoms of your condition?

a. How well have these treatments worked for you as your condition has changed over time?

b. Are there symptoms that your current regimen does not address at all or does not treat as well as you would like?

3. What are the most significant downsides to your current therapies or treatments, and how do they affect your daily life? (Examples of downsides could include bothersome side effects, physical change to your body because of treatment, going to the hospital for treatment.)

4. Of all the symptoms that you experience because of your condition or because of your therapy or treatment, which one to three symptoms have the most significant impact on your life? (Examples could include diarrhea, insomnia, difficulty concentrating, etc.)

• Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition? (Examples of activities may include sleeping through the night, daily hygiene, driving, etc.)

5. Assuming there is currently no complete cure for your condition, what specific things would you look for in an ideal therapy or treatment to manage your condition?

#### *Topic 2: Patients' Perspectives on HIV Cure Research*

1. What do you believe are the benefits of participating in an HIV cure research study?

2. What would motivate you to participate or to not participate in an HIV cure research study?

3. What risks would you find unacceptable for participating in an HIV cure research study and why? (Examples of risks that may be associated with participation in an HIV cure research study include common