not withdrawn from sale for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list metaxalone tablets, 640 mg, in the ''Discontinued Drug Product List'' section of the Orange Book. The ''Discontinued Drug Product List'' delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to metaxalone tablets, 640 mg, may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: July 20, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–16031 Filed 7–26–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2016–N–0007]

Generic Drug User Fee Rates for Fiscal Year 2019

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II), authorizes the Food and Drug Administration (FDA, Agency, or we) to assess and collect fees for abbreviated new drug applications (ANDAs), drug master files (DMFs), generic drug active pharmaceutical ingredient (API) facilities, finished dosage form (FDF) facilities, contract manufacturing organization (CMO) facilities, and generic drug applicant program user fees. In this document, FDA is announcing fiscal year (FY) 2019 rates for GDUFA II fees.

FOR FURTHER INFORMATION CONTACT: Melissa Hurley, Office of Financial Management, Food and Drug Administration, 8455 Colesville Rd., COLE–14202J, Silver Spring, MD 20993–0002, 240–402–4585.

SUPPLEMENTARY INFORMATION:

I. Background

Sections 744A and 744B of the FD&C Act (21 U.S.C. 379j–41 and 379j–42) establish fees associated with human generic drug products. Fees are assessed on: (1) Certain types of applications for human generic drug products; (2) certain facilities where APIs and FDFs are produced; (3) certain DMFs associated with human generic drug products; and (4) generic drug applicants who have approved ANDAs (the program fee) (see section 744B(a)(2)–(5) of the FD&C Act).

GDUFA II stipulates that user fees should total $493,600,000 annually adjusted each year for inflation. For FY 2019, the generic drug fee rates are: ANDA ($178,799), DMF ($55,013), domestic API facility ($44,226), foreign API facility ($59,226), domestic FDF facility ($211,305), foreign FDF facility ($226,305), domestic CMO facility ($70,435), foreign CMO facility ($85,435), large size operation generic drug applicant program ($1,862,167), medium size operation generic drug applicant program ($744,867), and small business generic drug applicant program ($186,217). These fees are effective on October 1, 2018, and will remain in effect through September 30, 2019.

II. Fee Revenue Amount for FY 2019

The base revenue amount for FY 2019 is $493,600,000, as set in the statute (see section 744B(b)(1) of the FD&C Act). GDUFA II directs FDA to use the yearly revenue amount as a starting point to set the fee rates for each fee type. For more information about GDUFA II, please refer to the FDA website (*https://www.fda.gov/gdufa*). The ANDA, DMF, API facility, FDF facility, CMO facility, and generic drug applicant program fee (GDUFA program fee) calculations for FY 2019 are described in this document.

GDUFA II specifies that the $493,600,000 is to be adjusted for inflation increases for FY 2019 using two separate adjustments—one for personnel compensation and benefits (PC&B) and one for non-PC&B costs (see sections 744B(c)(1)(B) and (C) of the FD&C Act).

The component of the inflation adjustment for PC&B costs shall be one plus the average annual percent change in the cost of all PC&B paid per full-time equivalent position (FTE) at FDA for the first 3 of the 4 preceding fiscal years, multiplied by the proportion of PC&B costs to total FDA costs of human generic drug activities for the first 3 of the preceding 4 fiscal years (see section 744B(c)(1)(B) of the FD&C Act).

Table 1 summarizes the actual cost and total FTE for the specified fiscal years, and provides the percent change from the previous fiscal year and the average percent change over the first 3 of the 4 fiscal years preceding FY 2019. The 3-year average is 2.4152 percent.

TABLE 1—FDA PERSONNEL COMPENSATION AND BENEFITS (PC&B) EACH YEAR AND PERCENT CHANGE

Fiscal year	2015	2016	2017	3-Year average
Total PC&B	$2,232,304,000	$2,414,728,159	$2,581,551,000	
Total FTE	15,484	16,381	17,022	
PC&B per FTE	$144,168	$147,408	$151,660	
Percent Change from Previous Year	2.1136	2.2474	2.8845	2.4152

The statute specifies that this 2.4152 percent should be multiplied by the proportion of PC&B expended for human generic drug activities for the first 3 of the preceding 4 fiscal years. Table 2 shows the amount of PC&B and the total amount obligated for human generic drug activities from FY 2015 through FY 2017.

TABLE 2—PC&B AS A PERCENT OF FEE REVENUES SPENT ON THE PROCESS OF HUMAN GENERIC DRUG APPLICATIONS OVER THE LAST 3 YEARS

Fiscal year	2015	2016	2017	3-Year average
PC&B	$201,116,305	$242,963,571	$271,748,229	
Non-PC&B	$251,589,013	$250,987,599	$262,058,852	
Total Costs	$452,705,318	$493,951,170	$533,807,081	

TABLE 2—PC&B AS A PERCENT OF FEE REVENUES SPENT ON THE PROCESS OF HUMAN GENERIC DRUG APPLICATIONS OVER THE LAST 3 YEARS—Continued

Fiscal year	2015	2016	2017	3-Year average
PC&B Percent	44.4254	49.1878	50.9076	48.1736
Non-PC&B Percent	55.5746	50.8122	49.0924	51.8264

The payroll adjustment is 2.4152 percent multiplied by 48.1736 percent (or 1.1635 percent).

The statute specifies that the portion of the inflation adjustment for non-PC&B costs for FY 2019 is the average annual percent change that occurred in the Consumer Price Index (CPI) for urban consumers (Washington-Baltimore, DC-MD-VA-WV; not seasonally adjusted; all items; annual index) for the first 3 of the preceding 4 years of available data multiplied by the proportion of all costs other than PC&B costs to total costs of human generic drug activities (see section 744B(c)(1)(C) of the FD&C Act). Table 3 provides the summary data for the percent change in the specified CPI. The data are published by the Bureau of Labor Statistics and can be found on its website at: *https://data.bls.gov/pdq/SurveyOutputServlet?data_tool=dropmap&series_id=CUURA311SA0,CUUSA311SA0.*

TABLE 3—ANNUAL AND 3-YEAR AVERAGE PERCENT CHANGE IN CPI FOR BALTIMORE-WASHINGTON AREA

Year	2015	2016	2017	3-Year average
Annual CPI	155.353	157.180	159.202	.....
Annual Percent Change	0.3268	1.1760	1.2864	0.9297

To calculate the inflation adjustment for non-pay costs, we multiply the 3-year average percent change in the CPI (0.9297 percent) by the proportion of all costs other than PC&B to total costs of human generic drug activities obligated. Because 48.1736 percent was obligated for PC&B as shown in table 2, 51.8264 percent is the portion of costs other than PC&B. The non-pay adjustment is 0.9297 percent times 51.8264 percent, or 0.4818 percent.

To complete the inflation adjustment for FY 2019, we add the PC&B component (1.1635 percent) to the non-PC&B component (0.4818 percent) for a total inflation adjustment of 1.6453 percent (rounded), making 1.016453. We then multiply the base revenue amount for FY 2019 ($493,600,000) by 1.016453, yielding an inflation-adjusted amount of $501,721,000 (rounded to the nearest thousand dollars).

III. ANDA Filing Fee

Under GDUFA II, the FY 2019 ANDA filing fee is owed by each applicant that submits an ANDA on or after October 1, 2018. This fee is due on the submission date of the ANDA. Section 744B(b)(2)(B) of the FD&C Act specifies that the ANDA fee will make up 33 percent of the $501,721,000, which is $165,567,930.

To calculate the ANDA fee, FDA estimated the number of full application equivalents (FAEs) that will be submitted in FY 2019. The submissions are broken down into three categories: New originals (submissions that have not been received by FDA previously); submissions that have been refused to receive (RTR) for reasons other than failure to pay fees; and applications that are resubmitted after having been RTR for reasons other than failure to pay fees. An ANDA counts as one FAE; however, 75 percent of the fee paid for an ANDA that has been RTR shall be refunded according to GDUFA II if (1) the ANDA is refused for a cause other than failure to pay fees, or (2) the ANDA has been withdrawn prior to receipt (section 744B(a)(2)(D)(i) of the FD&C Act). Therefore, an ANDA that is considered not to have been received by FDA due to reasons other than failure to pay fees or withdrawn prior to receipt counts as one-fourth of an FAE. After an ANDA has been RTR, the applicant has the option of resubmitting. For user fee purposes, these resubmissions are equivalent to new original submissions—ANDA resubmissions are charged the full amount for an application (one FAE).

FDA utilized data from ANDAs submitted from October 1, 2013, to April 30, 2018, to estimate the number of new original ANDAs that will incur filing fees in FY 2019. For FY 2019, the Agency estimates that approximately 918 new original ANDAs will be submitted and incur filing fees. Not all of the new original ANDAs will be received by the Agency and some of those not received will be resubmitted in the same fiscal year. Therefore, the Agency expects that the FAE count for ANDAs will be 926 for FY 2019.

The FY 2019 application fee is estimated by dividing the number of FAEs that will pay the fee in FY 2019 (926) into the fee revenue amount to be derived from ANDA application fees in FY 2019 ($165,567,930). The result, rounded to the nearest dollar, is a fee of $178,799 per ANDA.

The statute provides that those ANDAs that include information about the production of active pharmaceutical ingredients other than by reference to a DMF will pay an additional fee that is based on the number of such active pharmaceutical ingredients and the number of facilities proposed to produce those ingredients (see section 744B(a)(3)(F) of the FD&C Act). FDA considers that this additional fee is unlikely to be assessed often; therefore, FDA has not included projections concerning the amount of this fee in calculating the fees for ANDAs.

IV. DMF Fee

Under GDUFA II, the DMF fee is owed by each person that owns a type II active pharmaceutical ingredient DMF that is referenced, on or after October 1, 2012, in a generic drug submission by an initial letter of authorization. This is a one-time fee for each DMF. This fee is due on the earlier of the date on which the first generic drug submission is submitted that references the associated DMF or the date on which the drug master file holder requests the initial completeness assessment. Under section 744B(a)(2)(D)(iii) of the FD&C Act, if a DMF has successfully undergone an initial completeness assessment and the fee is paid, the DMF will be placed on a publicly available list documenting DMFs available for reference.

To calculate the DMF fee, FDA assessed the volume of DMF

submissions over time. The Agency assessed DMFs from October 1, 2016, to April 30, 2018, and concluded that averaging the number of fee-paying DMFs provided the most accurate model for predicting fee-paying DMFs for FY 2019. The monthly average of paid DMF submissions the Agency received in FY 2017 and FY 2018 is 38. To determine the FY 2019 projected number of fee-paying DMFs, the average of 38 DMF submissions is multiplied by 12 months, which results in 456 estimated FY 2019 fee-paying DMFs. FDA is estimating 456 fee-paying DMFs for FY 2019.

The FY 2019 DMF fee is determined by dividing the DMF target revenue by the estimated number of fee-paying DMFs in FY 2019. Section 744B(b)(2)(A) of the FD&C Act specifies that the DMF fees will make up 5 percent of the $501,721,000, which is $25,086,050. Dividing the DMF revenue amount ($25,086,050) by the estimated fee-paying DMFs (456), and rounding to the nearest dollar, yields a DMF fee of $55,013 for FY 2019.

V. Foreign Facility Fee Differential

Under GDUFA II, the fee for a facility located outside the United States and its territories and possessions shall be $15,000 higher than the amount of the fee for a facility located in the United States and its territories and possessions. The basis for this differential is the extra cost incurred by conducting an inspection outside the United States and its territories and possessions.

VI. FDF and CMO Facility Fees

Under GDUFA II, the annual FDF facility fee is owed by each person who owns an FDF facility that is identified in at least one approved generic drug submission owned by that person or his affiliates. The CMO facility fee is owed by each person who owns an FDF facility that is identified in at least one approved ANDA but is not identified in an approved ANDA held by the owner of that facility or its affiliates. These fees are due no later than the first business day on or after October 1 of each such year. Section 744B(b)(2)(C) of the FD&C Act specifies that the FDF and CMO facility fee revenue will make up 20 percent of the $501,721,000, which is $100,344,200.

To calculate the fees, data from FDA's Integrity Services (IS) were utilized as the primary source of facility information for determining the denominators of each facility fee type. IS is the master data steward for all facility information provided in generic drug submissions received by FDA. A facility's reference status in an approved generic drug submission is extracted directly from submission data rather than relying on data from self-identification. This information provided the number of facilities referenced as FDF manufacturers in at least one approved generic drug submission. Based on FDA's IS data, the FDF and CMO facility denominators are 180 FDF domestic, 216 FDF foreign, 73 CMO domestic, and 97 CMO foreign facilities for FY 2019.

GDUFA II specifies that the CMO facility fee is to be equal to one-third the amount of the FDF facility fee. Therefore, to generate the target collection revenue amount from FDF and CMO facility fees ($100,344,200), FDA must weight a CMO facility as one-third of an FDF facility. FDA set fees based on the estimate of 180 FDF domestic, 216 FDF foreign, 24.33 CMO domestic (73 multiplied by one-third), and 32.33 CMO foreign facilities (97 multiplied by one-third), which equals 452.66 total weighted FDF and CMO facilities for FY 2019.

To calculate the fee for domestic facilities, FDA first determines the total fee revenue that will result from the foreign facility differential by subtracting the fee revenue resulting from the foreign facility fee differential from the target collection revenue amount ($100,344,200) as follows. The foreign facility fee differential revenue equals the foreign facility fee differential ($15,000) multiplied by the number of FDF foreign facilities (216) plus the foreign facility fee differential ($15,000) multiplied by the number of CMO foreign facilities (97), totaling $4,695,000. This results in foreign fee differential revenue of $4,695,000 from the total FDF and CMO facility fee target collection revenue. Subtracting the foreign facility differential fee revenue ($4,695,000) from the total FDF and CMO facility target collection revenue ($100,344,200) results in a remaining facility fee revenue balance of $95,649,200. To determine the domestic FDF facility fee, FDA divides the $95,649,200 by the total weighted number of FDF and CMO facilities (452.66), which results in a domestic FDF facility fee of $211,305. The foreign FDF facility fee is $15,000 more than the domestic FDF facility fee, or $226,305.

According to GDUFA II, the domestic CMO fee is calculated as one-third the amount of the domestic FDF facility fee. Therefore, the domestic CMO fee is $70,435, rounded to the nearest dollar. The foreign CMO fee is calculated as the domestic CMO fee plus the foreign fee differential of $15,000. Therefore, the foreign CMO fee is $85,435.

VII. API Facility Fee

Under GDUFA II, the annual API facility fee is owed by each person who owns a facility that is identified in (1) at least one approved generic drug submission or (2) in a Type II API DMF referenced in at least one approved generic drug submission. These fees are due no later than the first business day on or after October 1 of each such year. Section 744B(b)(2)(D) of the FD&C Act specifies the API facility fee will make up 7 percent of $501,721,000 in fee revenue, which is $35,120,470.

To calculate the API facility fee, data from FDA's IS were utilized as the primary source of facility information for determining the denominator. As stated above, IS is the master data steward for all facility information provided in generic drug submissions received by FDA. A facility's reference status in an approved generic drug submission is extracted directly from submission data rather than relying on data from self-identification. This information provided the number of facilities referenced as API manufacturers in at least one approved generic drug submission.

The total number of API facilities identified was 613; of that number, 79 were domestic and 534 were foreign facilities. The foreign facility differential is $15,000. To calculate the fee for domestic facilities, FDA must first subtract the fee revenue that will result from the foreign facility fee differential. FDA takes the foreign facility differential ($15,000) and multiplies it by the number of foreign facilities (534) to determine the total fee revenue that will result from the foreign facility differential. As a result of that calculation, the foreign fee differential revenue will make up $8,010,000 of the total API fee revenue. Subtracting the foreign facility differential fee revenue ($8,010,000) from the total API facility target revenue ($35,120,470) results in a remaining balance of $27,110,470. To determine the domestic API facility fee, we divide the $27,110,470 by the total number of facilities (613), which gives us a domestic API facility fee of $44,226. The foreign API facility fee is $15,000 more than the domestic API facility fee, or $59,226.

VIII. Generic Drug Applicant Program Fee

Under GDUFA II, if a person and its affiliates own at least one but not more than five approved ANDAs on October 1, 2018, the person and its affiliates shall owe a small business GDUFA program fee. If a person and its affiliates own at least 6 but not more than 19

approved ANDAs, the person and its affiliates shall owe a medium size operation GDUFA program fee. If a person and its affiliates own at least 20 approved ANDAs, the person and its affiliates shall owe a large size operation GDUFA program fee. These fees are due no later than the first business day on or after October 1 of each such year. Section 744B(b)(2)(E) of the FD&C Act specifies the GDUFA program fee will make up 35 percent of $501,721,000 in fee revenue, which is $175,602,350.

To determine the appropriate number of applicants for each tier, the Agency has posted lists of approved ANDAs on the FDA website (*https://www.fda.gov/gdufa*) and asked applicants on the list to claim which ANDAs and affiliates belong to the parent company. The original list of approved ANDAs came from the Agency's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), which included all ANDAs with the status of ''approved'' as of April 30, 2018.

In determining the appropriate number of approved ANDAs, the Agency has factored in a number of variables that could affect the collection of the target revenue: (1) Inactive ANDAs—applicants who have not submitted an annual report for one or more of their approved applications within the past 2 years; (2) FY 2018 Program Fee Arrears List—applicants who failed to satisfy the FY 2018 program fee and were unresponsive to attempts to collect; and (3) Prediction of Approvals Due to Goal Dates and Office of Generic Drugs Approval Rate—Due to the low percentage of additional approved ANDAs for a specified time period and the difficulties in determining how this population would affect the program fee tier of each company, this variable was not included in the determination of the FY 2019 GDUFA program fee. The list of original approved ANDAs from the DARRTS database as of April 30, 2018, shows 259 applicants in the small business tier, 62 applicants in the medium size tier, and 58 applicants in the large size tier. This list also takes into account all the withdrawals, consolidations, and transfer of ownerships from industry as of April 30, 2018. Factoring in all the variables for the second year of GDUFA II, the Agency estimates there will be 177 applicants in the small business tier, 49 applicants in the medium size tier, and 57 applicants in the large size tier for FY 2019.

To calculate the GDUFA program fee, GDUFA II provides that large size operation generic drug applicants pay the full fee, medium size operation applicants pay two-fifths of the full fee, and small business applicants pay one-tenth of the full fee. To generate the target collection revenue amount from GDUFA program fees ($175,602,350), we must weigh medium and small tiered applicants as a subset of a large size operation generic drug applicant. FDA will set fees based on the weighted estimate of 17.70 applicants in the small business tier (177 multiplied by 10 percent), 19.60 applicants in the medium size tier (49 multiplied by 40 percent), and 57 applicants in the large size tier, arriving at 94.30 total weighted applicants for FY 2019.

To generate the large size operation GDUFA program fee, FDA divides the target revenue amount of $175,602,350 by 94.30, which equals $1,862,167. The medium size operation GDUFA program fee is 40 percent of the full fee ($744,867), and the small business operation GDUFA program fee is 10 percent of the full fee ($186,217).

IX. Fee Schedule for FY 2019

The fee rates for FY 2019 are set out in table 4.

TABLE 4—FEE SCHEDULE FOR FY 2019

Fee category	Fees rates for FY 2019
Applications:	.....
Abbreviated New Drug Application (ANDA)	$178,799
Drug Master File (DMF)	55,013
Facilities:	.....
Active Pharmaceutical Ingredient (API) Domestic	44,226
API—Foreign	59,226
Finished Dosage Form (FDF)—Domestic	211,305
FDF—Foreign	226,305
Contract Manufacturing Organization (CMO)—Domestic	70,435
CMO—Foreign	85,435
GDUFA Program:	.....
Large size operation generic drug applicant	1,862,167
Medium size operation generic drug applicant	744,867
Small business operation generic drug applicant	186,217

X. Fee Payment Options and Procedures

The new fee rates are effective October 1, 2018. To pay the ANDA, DMF, API facility, FDF facility, CMO facility, and GDUFA program fees, a Generic Drug User Fee Cover Sheet must be completed, available at *https://www.fda.gov/gdufa* and *https://userfees.fda.gov/OA_HTML/gdufaCAcdLogin.jsp*, and a user fee identification (ID) number must be generated. Payment must be made in U.S. currency drawn on a U.S. bank by electronic check, check, bank draft, U.S. postal money order, credit card, or wire transfer. The preferred payment method is online using electronic check (Automated Clearing House (ACH), also known as eCheck) or credit card (Discover, VISA, MasterCard, American Express). Secure electronic payments can be submitted using the User Fees Payment Portal at *https://userfees.fda.gov/pay.* (Note: IOnly full payments are accepted; no partial payments can be made online.) Once an invoice is located, ''Pay Now'' should be selected to be redirected to *https://www.pay.gov/public/home* (*Pay.gov*). Electronic payment options are based on the balance due. Payment by credit card is available for balances less than $25,000. If the balance exceeds this amount, only the ACH option is available. Payments must 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 utilize Pay.gov, a web-based payment application, for online electronic payment. The Pay.gov feature is available on the FDA website after completing the Generic Drug User Fee

Cover Sheet and generating the user fee ID number.

The user fee ID number must be included on the check, bank draft, or postal money order and must be made payable to the order of the Food and Drug Administration. Payments can be mailed to: Food and Drug Administration, P.O. Box 979108, St. Louis, MO 63197–9000. If checks are to be sent by a courier that requests a street address, the courier can deliver checks to: U.S. Bank, Attention: Government Lockbox 979108, 1005 Convention Plaza, St. Louis, MO 63101. (Note: This U.S. Bank address is for courier delivery only. For questions concerning courier delivery, U.S. Bank can be contacted at 314–418–4013. This telephone number is only for questions about courier delivery.) The FDA post office box number (P.O. Box 979108) must be written on the check, bank draft, or postal money order.

For payments made by wire transfer, the unique user fee ID number must be referenced. Without the unique user fee ID number, the payment may not be applied. If the payment amount is not applied, the invoice amount will be referred to collections. The originating financial institution may charge a wire transfer fee. Applicable wire transfer fees must be included with payment to ensure fees are fully paid. Questions about wire transfer fees should be addressed to the financial institution. The following account information should be used to send payments by wire transfer: U.S. Department of Treasury, TREAS NYC, 33 Liberty St., New York, NY 10045, account number: 75060099, routing number: 021030004, SWIFT: FRNYUS33. FDA's tax identification number is 53–0196965.

Dated: July 24, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–D–2456]

Slowly Progressive, Low-Prevalence Rare Diseases With Substrate Deposition That Results From Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies; Draft Guidance for Industry; 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 a draft guidance for industry entitled ''Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies.'' This document is intended to provide guidance to sponsors on the evidence necessary to demonstrate the effectiveness of new drugs, including biological drugs, or new drug uses intended for slowly progressive, low-prevalence rare diseases that are associated with substrate deposition and are caused by single enzyme defects. This guidance applies only to those low-prevalence rare diseases with a well-characterized pathophysiology and in which changes in substrate deposition can be readily measured in relevant tissue(s).

DATES: Submit either electronic or written comments on the draft guidance by September 25, 2018 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance 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–2018–D–2456 for ''Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies; Draft Guidance for Industry; Availability.'' 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 information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*