submit payments. The draft guidance also explains how respondents can request discontinuation from the BPD program as well as how respondents can request to move products to the discontinued section of the biosimilar list. Finally, the draft guidance provides information on the consequences of failing to pay BsUFA II fees, as well as processes for submitting reconsideration and appeal requests. The draft guidance is available on our website at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM584984.pdf.

We estimate the burden of this collection of information as follows:

<table>
<thead>
<tr>
<th>Information collection title</th>
<th>Number of respondents</th>
<th>Number of responses per respondent</th>
<th>Total annual responses</th>
<th>Average burden per response (hours)</th>
<th>Total hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosimilar User Fee Cover Sheet; Form FDA 3792</td>
<td>35</td>
<td>1</td>
<td>35</td>
<td>0.5 (30 minutes)</td>
<td>17.5</td>
</tr>
<tr>
<td>Annual Survey</td>
<td>35</td>
<td>1</td>
<td>35</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Request for discontinuation from BPD program</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Request to move products to discontinued section of the biosimilar list.</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>0.5 (30 minutes)</td>
<td>2.5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>57</td>
</tr>
</tbody>
</table>

1 There are no capital costs or operating and maintenance costs associated with this collection of information.

We have increased our estimate by an additional 15 respondents since last OMB approval of the information collection. This estimated increase is based on our expectation that participation in the BPD program will continue to grow, consistent with our experience since establishment of the information collection in 2012.

Dated: June 26, 2018.
Leslie Kux,
Associate Commissioner for Policy.

[FR Doc. 2018–14057 Filed 6–28–18; 8:45 am]
BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
[Docket No. FDA–2018–N–1903]

Modernizing Pharmaceutical Quality Systems; Studying Quality Metrics and Quality Culture; Quality Metrics Feedback Program

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) Center for Drug Evaluation and Research (CDER) is announcing two new efforts to gather feedback on the use of quality metrics to modernize pharmaceutical quality systems and advance innovation based on stakeholder feedback. These efforts include Type C formal meeting requests and pre-abbreviated new drug application (pre-ANDA) meeting requests, and a pilot study to gain feedback from those establishments for which Type C formal meetings or pre-ANDA meetings do not apply (e.g., active pharmaceutical ingredients (API) establishments, contract manufacturing organizations, over-the-counter (OTC) monograph products establishments, or marketed unapproved finished drug products establishments). Participation in either of these efforts is voluntary and the programs are intended to foster the joint efforts of FDA and stakeholders to further develop an FDA Quality Metrics Program. The FDA Quality Metrics Program aims to evaluate a new approach for regulatory oversight of pharmaceutical products through the collection of certain quality information developed and maintained in the course of manufacturing drugs under current good manufacturing practices. FDA intends to use quality metrics data to further develop the Agency’s risk-based inspection scheduling (e.g., decreased surveillance inspection frequency for certain establishments) to improve the efficiency and effectiveness of establishment inspections, improve FDA’s evaluation of drug manufacturing and control operations, and identify situations in which there may be a risk for drug supply disruption.

DATES: Submit a written request to participate in the program by July 29, 2019. See sections II and III.B of this notice for information to include in such requests. FDA will start accepting requests beginning July 30, 2018.

FOR FURTHER INFORMATION CONTACT: Tara Gooen Bizjak, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 2109, Silver Spring, MD 20993, 301–796–3257, Tara.Gooen@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

More than a decade ago, FDA launched an initiative to encourage the implementation of a modern, risk-based pharmaceutical quality assessment system. As part of this initiative, and in recognition of the increasing complexity of pharmaceutical manufacturing, FDA developed a 21st century vision for manufacturing and quality with input from academia and industry. The desired state was described as follows: “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.” ¹

There has been significant progress toward this vision in the intervening years, as evidenced by programs and guidance from FDA around major initiatives such as pharmaceutical development and quality by design, quality risk management and pharmaceutical quality systems, process validation, and process analytical technology, among other initiatives. These programs and guidelines are intended to promote effective use of the most current pharmaceutical science and engineering principles and knowledge throughout the life cycle of a product.

While much progress has been made, we have not fully realized our 21st century vision for manufacturing and quality. Rather than focusing on use of science- and risk-based principles as described in current good manufacturing practices, many establishments continue to focus on minimum requirements (e.g., check-box approach). Recalls and drug shortages, which are often indications of serious product quality defects caused by drug

manufacturing issues, continue to occur.\(^2\) The Agency has found that most drug shortages stem from quality issues (e.g., substandard manufacturing facilities or processes, or significant quality defects are identified in the finished product). These situations necessitate remediation efforts to fix the issue, which in turn may interrupt production and cause a shortage of drugs. Taking action to reduce drug shortages remains a top priority for FDA.

FDA sought input from industry on the establishment of an FDA Quality Metrics Program as another mechanism to promote continual improvement in manufacturing quality. FDA has also consulted with other stakeholders to identify mutually useful and objective quality metrics. The Agency learned that it should perform further studies of the FDA Quality Metrics Program through a pilot program and additional discussions with stakeholders. Based on this input, FDA is initiating this Quality Metrics Feedback Program to assist the Agency in the development of a Quality Metrics Program. Stakeholders are encouraged to participate in these efforts by using the two feedback procedures described below. Additional references may be found at the FDA web page, Quality Metrics for Drug Manufacturing. [https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm526869.htm](https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm526869.htm).

Based on stakeholder feedback, FDA is presenting two new methods for engaging industry. The approaches announced in this notice provide industry with an opportunity to provide information to further the development of the Quality Metrics Program. CDER will also continue to engage with trade associations to gather feedback for industry subsectors.

FDA does not intend to publicly disclose information submitted to the Agency as part of this Quality Metrics Feedback Program that is exempt from disclosure under disclosure laws and regulations. The following types of information may be exempt from public disclosure if not made public by the owner: (1) Commercial relationships; (2) production and sales volume; (3) business plans; and (4) unapproved applications.

### II. Type C Formal Meetings and Pre-ANDA Meetings

Applicants who have an interest in participating in this method of the FDA Quality Metrics Feedback Program should submit a written request. New drug application (NDA) applicants or sponsors should follow the procedures for submitting Type C meeting requests as described in the draft guidance for industry entitled “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (December 2017).” The requests should be labeled as “Type C Meeting—Request to Participate in the Quality Metrics Feedback Program.” Pre-ANDA applicants or sponsors planning to submit an original or supplemental pre-ANDA should submit a pre-ANDA meeting request to OPQ-OS-QualityMetrics@fda.hhs.gov and label it as “Pre-ANDA Meeting—Request to Participate in the Quality Metrics Feedback Program.”

In addition to the procedures and items outlined in the referenced guidelines, a request for a meeting should include the following items:

1. A description of the quality metrics currently used for the product and processes in the facility(ies) that are specific to the risks of the facility(ies), products, manufacturing processes, supply chain, and current business decisions (e.g., amount of product held in inventory or days on hand). That is, the metrics which have been determined by the applicant to be most meaningful to product quality and for patient impact.

2. A statement on whether the following quality metrics are measured using consistent definitions: Lot acceptance rate per product or rejection rate, invalidation out-of-specification rate per product, product quality complaint rate, process performance and process capability per product, corrective action and preventive action effectiveness, quality system timeliness, and on-time-in-full fulfillment of orders (product specific); and (3) to discuss details of their quality metrics program, including quality metrics data definitions and methods of analyzing available data.

We intend to accept as many meeting requests as Agency resources allow and to focus on establishments that show an interest in engaging in robust discussions regarding their quality metrics programs. FDA expects to notify companies in writing of its decision regarding meeting acceptance within 60 days of receipt of their requests. Although incomplete and/or unclear requests will generally be denied, FDA may contact the applicant to request additional information. Once a meeting is granted, the participant can engage with the Quality Metrics Program team in accordance with existing meeting procedures and guidance(s). FDA anticipates that discussions with stakeholders will help to further develop the Quality Metrics Program and will provide the Agency with information on existing industry practices using modern pharmaceutical quality systems.

### III. Pilot Program

#### A. Participation

Establishments eligible to participate in this voluntary Quality Metrics Pilot...
Program are limited to nine or fewer firms that follow the procedures set forth in section III.B and meet the following selection criteria:

1. The company must be a covered establishment. A covered establishment is an owner or operator of an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a covered drug product, or an API used in the manufacture of a covered drug product. A covered drug product is: (1) Subject to an approved application under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or under section 351 of the Public Health Service Act (42 U.S.C. 262); (2) marketed pursuant to an OTC monograph; or (3) a marketed unapproved finished drug product. A covered establishment does not need to be involved in the physical manipulation of a drug.

2. The company must have a quality metrics program that has been developed and implemented by the quality unit and that is used to support product and process quality improvement. The established quality metrics program must include product-specific measurements and include at a minimum: (1) Lot acceptance rate or rejection rate; (2) validated out-of-specification rate; and (3) product quality complaint rate. If a product is manufactured at more than one location, these product specific metrics could be limited to operations at the participating covered establishment. To provide feedback on recommended changes in the metrics definitions, send an email to OPQ-OS-QualityMetrics@fda.hhs.gov.

The ideal participant in the Quality Metrics Pilot Program will have the following elements in their quality metrics program:

1. Quantitative measurement of quality metrics for the products and processes in the facility(ies) that are specific to the risks of the facility(ies), products, manufacturing processes, supply chain, and current business decisions (e.g., amount of product held in inventory or days on hand);

2. Certain quality metrics measured, such as lot acceptance rate or rejection rate per product, validated out-of-specification rate per product, product quality complaint rate, process performance and process capability per product, CAPA effectiveness, quality system timeliness, and on-time-in-full fulfillment of orders;

3. Suitably detailed technical definitions for the quality metrics data elements to enable consistent measurement and comparison;

4. Routine assessment and management oversight of quality culture at multiple levels of staff, such as senior management to base level employees, to assess and shape the behaviors, beliefs, values, morals, conventions, goals, and practices that characterize or are associated with manufacturing at the facility(ies); and

5. Ongoing site management and senior management review of the quality metrics with identification of areas for continual improvement.

The establishments that will likely benefit most from the Quality Metrics Pilot Program will have the metrics definitions, send an email to OPQ-OS-QualityMetrics@fda.hhs.gov.

The establishments that will likely benefit most from the Quality Metrics Pilot Program will have the metrics definitions, send an email to OPQ-OS-QualityMetrics@fda.hhs.gov.

The following captures the proposed process for the Quality Metrics Pilot Program:

A. Procedures

1. FDA will collect statements of interest for participation in the pilot program beginning July 30, 2018. The pipeline will be open for about 30 days, or until 9 companies have submitted statements of interest.

2. FDA will select the first nine companies that follow the procedures set forth in section III.B and meet the criteria in the first paragraph of section III.A, per the first paragraph of section III.A, FDA would prefer that establishments for which Type C formal meetings and pre-ANDA meetings are unacceptable use this approach. Additionally, FDA is seeking participants that represent different sectors of the pharmaceutical industry, including companies that manufacture the following types of products: Brand, generics, biotechnology, APIs, and non-application products marketed under the OTC monograph system.

B. Procedures

1. To be considered for the voluntary Quality Metrics Pilot Program, a company should submit a statement of interest for participation to OPQ-OS-QualityMetrics@fda.hhs.gov. The statement of interest should include agreement to the selection criteria listed in section III.A. The following captures the proposed process for the Quality Metrics Pilot Program:

2. FDA will select the first nine participants that submit a statement of interest in participation meeting the selection criteria in the first paragraph of section III.A. While any covered establishment meeting the criteria may request inclusion in the pilot program per the first paragraph of section III.A, FDA would prefer that establishments for which Type C formal meetings and pre-ANDA meetings are not applicable use this approach. Additionally, FDA is seeking participants that represent different sectors of the pharmaceutical industry, including companies that manufacture the following types of products: Brand, generics, biotechnology, APIs, and non-application products marketed under the OTC monograph system.

C. Procedures

1. The company must be a covered establishment. A covered establishment is an owner or operator of an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a covered drug product, or an API used in the manufacture of a covered drug product. A covered drug product is: (1) Subject to an approved application under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or under section 351 of the Public Health Service Act (42 U.S.C. 262); (2) marketed pursuant to an OTC monograph; or (3) a marketed unapproved finished drug product. A covered establishment does not need to be involved in the physical manipulation of a drug.

2. The company must have a quality metrics program that has been developed and implemented by the quality unit and that is used to support product and process quality improvement. The established quality metrics program must include product-specific measurements and include at a minimum: (1) Lot acceptance rate or rejection rate; (2) validated out-of-specification rate; and (3) product quality complaint rate. If a product is manufactured at more than one location, these product specific metrics could be limited to operations at the participating covered establishment. To provide feedback on recommended changes in the metrics definitions, send an email to OPQ-OS-QualityMetrics@fda.hhs.gov.

The ideal participant in the Quality Metrics Pilot Program will have the following elements in their quality metrics program:

1. Quantitative measurement of quality metrics for the products and processes in the facility(ies) that are specific to the risks of the facility(ies), products, manufacturing processes, supply chain, and current business decisions (e.g., amount of product held in inventory or days on hand);

2. Certain quality metrics measured, such as lot acceptance rate or rejection rate per product, validated out-of-specification rate per product, product quality complaint rate, process performance and process capability per product, CAPA effectiveness, quality system timeliness, and on-time-in-full fulfillment of orders;
I. Background

More than a decade ago, FDA launched an initiative to encourage the implementation of a modern, risk-based pharmaceutical quality assessment system. As part of this initiative, and in recognition of the increasing complexity of pharmaceutical manufacturing, FDA developed a 21st century vision for manufacturing and quality with input from academia and industry. The desired state was described as follows: “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.”

There has been significant progress toward this vision in the intervening years as evidenced by programs and guidelines from FDA around major initiatives such as pharmaceutical development and quality by design, quality risk management and pharmaceutical quality systems, process validation, and emerging technology, among others. These programs and guidelines are intended to promote effective use of the modern pharmaceutical science and engineering principles and knowledge throughout the life cycle of a product. FDA sought input from industry on the establishment of an FDA Quality Metrics Program as another mechanism to promote continual improvement in manufacturing quality. FDA has also consulted with other stakeholders to identify mutually useful and objective quality metrics. The Agency heard that it should perform further studies of existing quality metrics programs and conduct additional discussions with stakeholders. Based on this input, CDER and CBER are initiating this 2018 Quality Metrics Site Visit Program to assist the Agency in understanding existing programs. This voluntary site visit program is designed to offer experiential and firsthand learning opportunities to CDER and CBER staff involved in the development of FDA’s Quality Metrics Program and to provide stakeholders with an opportunity to explain the advantages and challenges associated with implementing and managing a robust Quality Metrics Program. This notice invites pharmaceutical companies interested in participating in this program to submit a Quality Metrics Site Visit proposal.

II. The Site Visit Program

During a quality metrics site visit, CDER and CBER staff will observe how quality metrics data are gathered, collected, and reported to management. We anticipate 5 to 10 FDA representatives (involved in the development of FDA’s Quality Metrics Program) would participate in a site visit taking place over a 1- to 2-day period. To facilitate the learning process, the host establishment may present overviews of the development and management of their quality metrics program. The presentation(s) will allow the participating establishments an opportunity to showcase technologies that support their program.

CDER and CBER encourage covered establishments, including establishments that do not perform physical manipulation of drugs, engaging in the development and manufacturing of both active pharmaceutical ingredients (small and large molecules) and drug products to submit quality metrics site visit proposals. A covered establishment is an owner or operator of an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a covered drug product, or an active pharmaceutical ingredient (API) used in the manufacture of a covered drug product. CDER and CBER staff participating in this program will benefit by gaining a better understanding of current industry practices, processes, and procedures for quality metrics programs.

CDER and CBER identified a number of establishment types that are of particular interest to their staff. The following list identifies some examples of these establishments but is not intended to be exhaustive, mutually exclusive, or to limit industry response to the notice:

- Manufacturer of brand, generic, biotechnology, APIs, and non-application product(s) marketed under the over-the-counter (OTC) monograph system, and any combination of these products;
- contract development and manufacturing organizations;
- establishments with small and large portfolios; and
- establishments with past or current product availability issues (e.g., history of a drug supply issue, recall).

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