will also be available in either hard copy or on CD–ROM, after submission of a Freedom of Information request. Written requests are to be sent to Division of Freedom of Information (ELEM–1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857.

Dated: July 29, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015–18969 Filed 7–31–15; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2015–N–0001]

Surrogate Endpoints for Clinical Trials in Kidney Transplantation; Public Workshop

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public workshop.

The Food and Drug Administration (FDA) is announcing a public workshop entitled ''Surrogate Endpoints for Clinical Trials in Kidney Transplantation.'' The purpose of the public workshop is to discuss potential surrogate endpoints for clinical trials for drugs and therapeutic biologics used in kidney transplantation, with a focus on endpoints in conditions that represent unmet medical needs. This public workshop is intended to provide information and gain perspective from health care providers, academia, and industry on the role of various laboratory, histologic, and other endpoints used to evaluate patient and allograft outcome in clinical trials for kidney transplantation.

Date and Time: The public workshop will be held on September 28, 2015, from 8 a.m. to 6 p.m.

Location: The public workshop will be held at the Residence Inn Marriott, 2850 South Potomac Ave., Arlington, VA 22202. Web site: *http://www.marriott.com/hotels/travel/wasry-residence-inn-arlington-capital-view/.* (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register.**) Seating will be available on a first-come, first-served basis.

Contact Person: Ramou Pratt, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6193, Silver Spring, MD 20993–0002, 301–796–3928 or 301–796–1600.

Registration: Mail or fax your registration information (including name, title, firm name, address, telephone and fax numbers) to Ramou Pratt (see *Contact Person*) by September 25, 2015. Registration is free for the public workshop. Early registration is recommended because seating is limited. Registration on the day of the public workshop will be provided on a space-available basis beginning at 8 a.m.

If you need special accommodations because of a disability, please contact Ramou Pratt (see *Contact Person*) at least 7 days in advance.

SUPPLEMENTARY INFORMATION: FDA is announcing a public workshop entitled ''Surrogate Endpoints for Clinical Trials in Kidney Transplantation.'' The purpose of the workshop is to discuss potential clinical or surrogate endpoints and biomarkers for clinical trials for drugs and therapeutic biologics in kidney transplantation. The input from this public workshop will help in developing topics for further discussion and may serve to inform recommendations on potential surrogate endpoints in clinical trials for kidney transplantation. The Agency encourages individuals, patient advocates, industry, consumer groups, health care professionals, researchers, and other interested persons to attend this public workshop.

This workshop is part of the Agency's program to facilitate the development of surrogate endpoints, clinical endpoints, and other scientific methods for predicting clinical benefit, in accordance with section 901 of the Food and Drug Administration Safety and Innovation Act, titled ''Enhancement of Accelerated Patient Access to New Medical Treatments,'' which was signed into law on July 9, 2012. During the workshop, there will be a discussion on potential surrogate endpoints and their ability to predict clinical benefit.

This public workshop will include discussion of allograft histology and biomarkers, laboratory measures of outcome, and other endpoints that may serve as surrogates for patient morbidity, graft function, and patient and graft survival. Related topics for discussion will include clinically relevant risk factors and prognostic factors in the kidney transplant population. Patient selection and enrichment strategies (inclusion/exclusion criteria) will be considered. The public workshop will include scientific discussion on the following topics:

- Surrogate endpoints and accelerated approval
- Unmet medical need in kidney transplant patients
- Histology: Findings on kidney biopsy (including protocol biopsies)
- Laboratory measurements and outcomes, surrogates and biomarkers
- Patient selection criteria and enrichment strategies
- Risk factors and prognostic factors
- Medication adherence

Transcripts: Please be advised that as soon as possible after a transcript of the public workshop is available, it will be accessible at *http://www.regulations.gov.* It may be viewed at the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. A transcript will also be available in either hard copy or on CD–ROM, after submission of a Freedom of Information request. Send written requests to the Division of Freedom of Information, U.S. Food & Drug Administration, 5630 Fishers Lane, Rm. 1033, Rockville, MD 20857. Transcripts will also be available on the Internet at *http://wcms.fda.gov/FDAgov/Drugs/NewsEvents/ucm449248.htm* approximately 45 days after the workshop.

Dated: July 29, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015–18957 Filed 7–31–15; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2014–D–2138]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Guidance for Industry on Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by September 2, 2015.

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202–395–7285, or emailed to *oira_submission@omb.eop.gov*. All comments should be identified with the OMB control number 0910—NEW and title ''Guidance for Industry on Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act.'' Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: FDA PRA Staff, Office of Operations,Food and Drug Administration, 8455 Colesville Rd., COLE–14526, Silver Spring, MD 20993–0002, *PRAStaff@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Guidance for Industry on Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act OMB Control Number 0910—NEW

In the **Federal Register** of February 19, 2015 (80 FR 8872), FDA announced the availability of a draft guidance for industry entitled ''Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act.'' On November 27, 2013, President Obama signed the Drug Quality and Security Act (DQSA) into law (Pub. L. 113–54). The DQSA added a new section 503B to the FD&C Act (21 U.S.C. 353b). Under section 503B(b), a compounder can register as an outsourcing facility with FDA. If the conditions outlined in section 503B(a) of the FD&C Act are satisfied, a drug compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility is exempt from certain sections of the FD&C Act, including section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use) and section 505 (21 U.S.C. 355) (concerning the approval of human drug products under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)). Drugs compounded in outsourcing facilities are not exempt from the requirements of section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice for drugs).

Under section 503B(b)(5), an outsourcing facility must submit adverse event reports to FDA in accordance with the content and format requirements established through guidance or regulation under 21 CFR 310.305 (or any successor regulations). This guidance explains electronic reporting of adverse events in accordance with § 310.305 with respect to outsourcing facilities.

Under § 310.305(c)(1), manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved new drug or abbreviated new drug application, including, as set forth in the guidance, outsourcing facilities must submit to FDA adverse event reports within 15 calendar days of receiving the information and must submit followup reports within 15 calendar days of receipt of new information about the adverse event, or as requested by FDA. Outsourcing facilities must submit the adverse event report in an electronic format that FDA can process, review, and archive (collection of information is approved by OMB control number 0910–0291). A copy of the current labeling of the compounded drug product must be provided.

Under § 310.305(f), entities subject to the regulation must maintain for 10 years the records of all adverse events required to be reported under § 310.305. The outsourcing facility should also maintain records of its efforts to obtain the data elements described in the draft guidance for each adverse event report.

In the **Federal Register** of February 19, 2015 (80 FR 8872), FDA published a 60-day notice requesting public comment on the proposed collection of information. FDA received seven comments on the draft guidance, several of which raised issues pertaining to the information collection provisions in the draft guidance. The issues raised are addressed below.

Issue One: Several individuals submitted comments related to the requirement described in the guidance that outsourcing facilities report adverse events that are both serious and unexpected and the recommendation in the guidance that outsourcing facilities report all serious adverse events, regardless of whether they are unexpected. Specifically:

- One commenter noted that the applicable regulation, § 310.305, defines an ''unexpected'' adverse drug experience as an adverse drug experience ''that is not listed in the current labeling for the drug product.'' The commenter indicated that this definition is not easily applied to unapproved drugs, as such products lack uniform FDA-reviewed language, meaning products with the same active ingredient may list different adverse events in the labeling, or no adverse events at all.
- One commenter indicated that instead of strongly recommending that outsourcing facilities report all serious adverse drug experiences to the FDA, the FDA should require such reporting.
- One commenter stated that reporting all serious adverse drug experiences (not just those that are both serious and unexpected) should be required, rather than ''strongly recommended,'' and because reporting all serious adverse events is not currently required under § 310.305, FDA should amend this regulation.
- Several commenters noted that § 310.305 only requires reporting of serious, unexpected adverse events, but the draft guidance suggests that outsourcing facilities should report all serious adverse events. They stated that FDA is reaching beyond what the regulations allow, and this suggestion will lead to confusion to what must be reported and what is suggested. FDA should narrow reporting to unexpected adverse events.

FDA Response to Issue One: FDA responds as follows:

- FDA has clarified the guidance with regard to reporting adverse events that are considered ''unexpected.'' Specifically, the guidance now includes the following language to clarify the meaning of the term ''unexpected'' in the context of adverse events associated with compounded drugs: ''For example, if current labeling for a compounded drug product does not list any adverse drug experiences, all adverse drug experiences associated with the compounded drug product would be considered 'unexpected.' ''
- With regard to the recommendation that outsourcing facilities be required to report all serious adverse events, rather than just those that are considered both serious and unexpected, § 310.305, the regulation applicable to reporting of adverse events by all manufacturers of unapproved drugs, does not require reporting of all serious adverse drug experiences to FDA. Therefore, requiring outsourcing facilities to report all serious adverse events would be inconsistent with § 310.305.
- Amending the regulation § 310.305 would require a separate rulemaking, which is beyond the scope of this guidance document.
- With regard to the concern about possible confusion caused by FDA's recommendation that outsourcing facilities report all serious adverse events, the draft guidance states the

regulations require reporting of all adverse events that are both serious and unexpected, and that FDA is recommending that outsourcing facilities report all serious adverse events. Specifically, the draft guidance states that ''FDA strongly recommends that outsourcing facilities submit all serious adverse drug experiences'' (lines 128–131) and that ''the regulations require reporting of each adverse drug experience received or otherwise obtained that is both serious and unexpected . . . .'' (lines 103–104). FDA will further clarify this by adding the following italicized language: ''In addition, *although they are not required to do so,* FDA strongly recommends that outsourcing facilities report all serious adverse events. . . .''

Issue Two: Several commenters noted that FDA encourages, as appropriate, the outsourcing facility to attach to the report: (1) Hospital discharge summaries, (2) autopsy reports/death certificates, (3) relevant laboratory data, and (4) other critical clinical data, and that in case of a death, an outsourcing facility should also provide any available information on the event(s) that led to the death. The commenters stated it is unlikely that an outsourcing facility will be given access to the elements voluntarily by the healthcare facility where the serious adverse event occurred without being legally compelled to do so. A commenter also asked how a manufacturer, distributor, and/or supplier can obtain this information under the Health Insurance Portability and Accountability Act (HIPAA).

FDA Response to Issue Two: With regard to HIPAA, 45 CFR 164.512 describes situations under which a covered entity, *e.g.,* a healthcare provider, may use or disclose protected health information without the written authorization of the individual or the opportunity for the individual to agree or object. One of these situations is ''to collect or report adverse events'' to FDA (45 CFR 164.512(b)(1)(iii)(A)). However, although information about adverse events can be obtained under HIPAA, the guidance does not state that an outsourcing facility must obtain this information. Rather, the guidance states that attaching this information is encouraged. It should be provided if the outsourcing facility has the information, but the outsourcing facility is not specifically required to obtain this information. FDA has clarified in the guidance that the information should be provided to FDA if it is available. Specifically, the guidance now reads: ''In addition, as part of the adverse event report, we encourage, as appropriate, attachment of the following, if available: (1) Hospital discharge summaries, (2) autopsy reports/death certificates, (3) relevant laboratory data, and (4) other critical clinical data. In the case of a death, outsourcing facilities should also provide any available information on the event(s) that led to the death.''

Issue Three: One commenter noted that the period of 15 calendar days to submit an initial report of an adverse event and the 15 calendar days to submit a followup report is too long; that during this period illnesses, injuries, or deaths can result. The commenter also stated that this would likely also delay initiation of recall procedures, and that the time period for reporting should be no more than 48 or 72 hours, followed by an equally prompt followup and investigation period, and an immediate decision on a recall.

FDA Response to Issue Three: The applicable regulation, § 310.305, provides a 15-day timeframe for reporting an adverse event and an additional 15-day timeframe to submit a followup report. This is the maximum amount of time permitted. The guidance states that the regulations require reporting ''as soon as possible, but in no case later than 15 calendar days . . . .'' The preamble to § 310.305 notes that the manufacturer must usually obtain additional information about the product (*e.g.,* followup with the reporting physician or patient), and that reducing the time for submitting these reports would increase the number of incomplete reports. (51 FR 24478).

Issue Four: FDA should immediately share all adverse events reported with the home State regulator, so the State agency is also aware of potential problems at one of its licensee's facilities.

FDA Response to Issue Four: FDA intends to continue to work closely with its State partners on oversight of compounding, including improving and streamlining information sharing as much as possible. However, this recommendation is not relevant to this guidance document, which focuses on how outsourcing facilities should submit adverse event reports to FDA.

Issue Five: Two commenters asked how the reporting requirements proposed by the draft guidance interplay with reporting requirements imposed by State boards of pharmacy. The commenters asked whether, in the event a State board of pharmacy has adverse event reporting requirements that apply to an outsourcing facility, satisfying the adverse event reporting requirements described by the draft guidance ''preempt'' the requirement to comply with a State reporting requirement. They asked whether an outsourcing facility must report to both Federal and State regulators and noted that this could result in duplicate reporting.

FDA Response to Issue Five: This guidance addresses requirements under the FD&C Act and FDA regulations. Outsourcing facilities may have independent responsibilities to report to State boards of pharmacy. FDA will clarify in the guidance that in addition to complying with federal adverse event reporting requirements, outsourcing facilities must comply with any applicable State adverse event reporting requirements. Specifically, FDA will add the following language: ''Certain state boards of pharmacy may also require outsourcing facilities licensed in their states to report adverse events. Outsourcing facilities must comply with any applicable state reporting requirements independent of and in addition to reporting adverse events as described in this guidance.''

Issue Six: One commenter proposed language clarifying that the regulations described in the guidance apply to products without an ANDA.

FDA Response to Issue Six: This additional language is unnecessary because the guidance cites the regulation § 310.305 and makes clear that it applies to manufacturers of prescription drug products that are not the subject of an approved drug application.

Issue Seven: With regard to the following statement in the draft guidance: ''Reports should be submitted as long as the outsourcing facility has information on at least the suspect drug and the adverse event'', one commenter recommended that FDA clarify that if a report lacks the four minimum data elements, the outsourcing facility should review the report for any potential safety issue.

FDA Response to Issue Seven: FDA believes that the draft guidance is clear that if the report lacks the four data elements, the outsourcing facility should continue investigating. The guidance states, ''If the outsourcing facility was not able to include all four of the data elements in its initial report, it should exercise due diligence to obtain information about any of the remaining elements.''

Issue Eight: One commenter suggested that FDA clarify that if an adverse event reporter does not identify a suspect drug, the outsourcing facility should submit a report that lists all drugs that the patient was taking as suspect.

FDA Response to Issue Eight: FDA does not agree with this suggestion. The guidance states that for an adverse event to be reportable to FDA, the outsourcing facility must have information on at least two data elements: An adverse event and a suspect drug. A suspect drug product is one that the initial reporter suspected was associated with the adverse event. If the reporter does not identify a suspect drug, the adverse event is not reportable. The outsourcing facility should not submit a report that lists each of the drugs the patient was taking as suspect drugs, as the comment suggests, if none of the drugs was identified as suspect by the reporter. In most cases, we believe that a reporter that contacts an outsourcing facility will be able to identify the suspect drug. It is unlikely that the reporter would have notified the outsourcing facility of the adverse event if it did not believe the compounded drug manufactured by the outsourcing facility caused the adverse event.

Issue Nine: Several commenters noted that under the draft guidance, when an adverse event cannot be directly determined to be associated with a specific drug, the outsourcing facility should identify and list all other medications to which the identified patient may have been exposed including information related to all compounded prescription preparations, brand and generic manufactured drug products, dietary supplements, and over-the counter medications that may have been taken by the patient. The commenters stated that requiring information on all drug products taken by a patient that may be ''suspect'' is unduly burdensome, especially when a compounded preparation is distributed to a medical center where multiple treatments and therapies are provided at any given time to an individual. An outsourcing facility may therefore have an incomplete picture of the circumstances under which the drug was administered. In addition, the outsourcing facility would also have no control over how a drug is administered, and improper administration may be material to the cause of the adverse event.

FDA Response to Issue Nine: FDA will clarify that the outsourcing facility should only include information on suspect drug products that the outsourcing facility is aware of from the reporter and the outsourcing facility's due diligence to obtain additional information. The outsourcing facility is not expected to report information that it does not have. Specifically, FDA will add the italicized language: ''In all cases, including those where not all of the drug products were made by the outsourcing facility, the report should include information on all suspect drug products *of which the outsourcing facility is aware.*''

FDA will also clarify that FDA will consider how the drug was administered, the patient's medical history, and any other relevant facts when investigating the adverse event. Specifically, FDA will add the following language: ''The outsourcing facility should include the information described in this guidance on suspect drug products and concomitant medications of which it is aware after exercising due diligence. For example, although an outsourcing facility should exercise due diligence to determine any concomitant medical products, FDA only expects that it report information about concomitant products that it is able to obtain from the reporter. Furthermore, as noted previously, the report or information submitted by an outsourcing facility issued in § 310.305 (and any release by FDA of that report or information) does not necessarily reflect a conclusion that the report or information constitutes an admission that the drug caused or contributed to an adverse effect.[1] When investigating the adverse event, FDA considers how the drug was administered, the patient's medical history, and any other relevant information.''

Issue 10: Two commenters asked how, given that a compounded product contains more than one component, could an outsourcing facility or the healthcare provider know which component of the compounded product, or which component of which product, is suspect. Compounded products have a number of components and active pharmaceutical ingredients (API), so it may be difficult for an outsourcing facility to tie a serious, unexpected adverse event to a specific component or API. A commenter also noted that FDA should require that an adverse event report identify all the APIs contained in a compounded drug and the APIs' manufacturer(s).

FDA Response to Issue 10: The guidance makes clear that the minimum data element for reporting is the suspect drug product, and not a suspect component. (See section III.B.3 of the draft guidance.) We agree with the suggestion that the outsourcing facility should identify in its adverse event report all of the APIs contained in a compounded drug and the APIs' manufacturer. The guidance states that all known components of a suspect drug product should be reported. It states that, ''[i]f the compounded drug product contains multiple components (*e.g.,* excipients, drug substances, finished dosage forms), the outsourcing facility should list each component and its manufacturer. . .''

Issue 11: One commenter noted that as indicated within the guidance document, FDA is not prepared nor has the necessary infrastructure in place to receive electronic reports of adverse events despite having such a system already available for other registered entities including manufacturers. The commenter asked that the FDA provide an implementation schedule to all currently registered outsourcing facilities outlining the anticipated date of an electronic adverse event reporting system as soon as possible.

FDA Response to Issue 11: This final guidance describes the process for outsourcing facilities to report adverse events to FDA electronically. The electronic reporting system is ready for outsourcing facilities to use, and, therefore, the issue raised by this comment is now moot.

Issue 12: Two commenters stated that this draft guidance imposes uneven reporting requirements on similarly-situated facilities (*i.e.,* outsourcing facilities operating under section 503B and pharmacies operating under section 503A of the FD&C Act) engaging in the same activities. Because outsourcing facilities can compound drugs issued in individual prescriptions, they are permitted to do the same kind of activities as facilities compounding under section 503A of the FD&C Act. Holding facilities that engage in the same conduct to different standards is ''illogical and arbitrary and capricious.'' If FDA determines that section 503A facilities should not be required to adhere to the same adverse event reporting requirements as outsourcing facilities, an outsourcing facility that compounds issued in individual prescriptions should not have to report adverse events associated with individual preparations.

FDA Response to Issue 12: FDA does not agree with this comment. The purpose of this guidance is to implement section 503B(b)(5) of the FD&C Act, which requires adverse event reporting for outsourcing facilities and does not address adverse reporting for compounding conducted under section 503A. Adverse event reporting for entities operating under section 503A of the FD&C Act is beyond the scope of this guidance. We also note that section 503B of the FD&C Act requires outsourcing facilities to report adverse events associated with all of their compounded drugs to FDA and does not

[1] See § 310.305(g).

distinguish between patient specific and non-patient specific compounded products.

Issue 13: One commenter noted that FDA may have written this guidance because it may be interested in knowing the sheer number of adverse events that occurred at each outsourcing facility. If this is the case, this kind of information could be collected by reporting the number of adverse events without the need for extensive detail about the affected patient or the components of the compounded product. This information could be collected through the recordkeeping and facility inspections that are already required of outsourcing facilities. Further, it may be more efficient to collect this information at regular intervals (*e.g.,* quarterly or biannually) rather than in relation to when the adverse event occurred.

FDA Response to Issue 13: FDA is not interested only in the number of adverse events associated with compounded drug products from a particular outsourcing facility, as the comment suggests. A single report of an adverse event can signal a serious public health concern, such as an outbreak resulting from drug contamination, or could signal serious quality problems at the outsourcing facility that if corrected promptly could prevent an outbreak. FDA evaluates each adverse event report to determine what followup action is appropriate. Collecting adverse events at longer intervals would conflict with the 15-calendar day submission timeline required under § 310.305 and would not be sufficient for FDA's need to evaluate adverse event reports in a timely way. Whether to require additional reporting or collect additional information is beyond the scope of the current guidance.

Issue 14: One commenter noted that an outsourcing facility would not necessarily know which patient received which drug, unless it was compounded issued in an individual prescription. Most outsourcing facilities make the majority of their preparations to be supplied to healthcare providers rather than issued in a prescription, so the only way an outsourcing facility would learn of the adverse event is if it is reported to the outsourcing facility by a patient or a healthcare provider. Healthcare providers are in a better position to know about the occurrence of adverse events. Therefore, it may be advantageous for FDA to seek to collect this information from healthcare providers with better access to the information, through submitting reports to FDA and supplying copies of those reports to the outsourcing facility. The outsourcing facility could then submit the adverse event report to FDA, reference the fact that the occurrence was already reported, and provide additional information about the product.

FDA Response to Issue 14: Reporting by healthcare providers is not mandatory under the FD&C Act or its implementing regulations. Section 503B of the FD&C Act requires outsourcing facilities, and not healthcare providers, to report adverse events to FDA. We agree with the comment that healthcare providers have useful information on a patient, and for this reason encourage outsourcing facilities to contact the healthcare provider to obtain additional information on the patient. The guidance makes clear that outsourcing facilities must report adverse events that they are aware of; if they do not learn of an adverse event, there would be nothing for them to report.

Issue 15: Two commenters asked what the consequences are if a practitioner reports a serious, unexpected adverse event but the outsourcing facility did not because it was not aware of the adverse event. The commenters indicated that an outsourcing facility should be permitted to refer to a previously submitted adverse event report instead of being required to prepare a separate, duplicative report.

FDA Response to Issue 15: Outsourcing facilities are required to report serious unexpected adverse events that they are aware of, regardless of whether anyone else voluntarily reported them. The guidance states that ''failure to report adverse events by an entity that is registered in accordance with section 503B(b) is a prohibited act under section 301(ccc)(3) of the FD&C Act. Violations relating to this provision are subject to regulatory and enforcement action.'' If an adverse event associated with an outsourcing facility's product is submitted to the FDA voluntarily by an entity other than the outsourcing facility (a healthcare provider), the outsourcing facility, under section 503B of the FD&C Act, is still required to submit an adverse event report if it also became aware of the same adverse event report and it is reportable. During the review and analysis of case reports from the FDA Adverse Event Reporting System, FDA reviewers identify duplicate cases and treat them as one case report in their evaluation.

Issue 16: One commenter asked if there would be a consequence to an outsourcing facility that does not report an adverse event because another individual or entity reported it directly to FDA.

FDA Response to Issue 16: The outsourcing facility is required to report any adverse events of which it becomes aware, regardless of whether anyone else voluntarily reported it. The guidance states that ''failure to report adverse events by an entity that is registered in accordance with section 503B(b) is a prohibited act under section 301(ccc)(3) of the FD&C Act. Violations relating to this provision are subject to regulatory and enforcement action.''

Issue 17: Two commenters stated that the draft guidance fails to account for compounded drug products being used for off-label treatment. By failing to address this issue, the reporting requirements detailed in the draft guidance may not provide FDA with the information it seeks. Additionally, an outsourcing facility may not know how the compounded drug is to be used, thereby limiting its ability to provide a full and accurate accounting of the adverse event. The patient's healthcare provider may be in a better position to provide this information.

FDA Response to Issue 17: FDA disagrees with this comment. The concept of ''off-label treatment'' is not applicable to compounded drugs because compounded drugs are not approved and do not have approved labeling. FDA evaluates adverse event reports associated with compounded drug products for quality issues. Furthermore, section 503B of the FD&C Act requires outsourcing facilities to report adverse events. Reporting by healthcare providers is voluntary and not the subject of this guidance.

Issue 18: Two commenters asked if, after complying with the reporting requirement, FDA will require any additional information or followup activity by the outsourcing facility that submits the report. They asked if the outsourcing facility will be required to provide information about the adverse event to healthcare providers or others who purchased the same or similar product, and if the adverse event does not trigger reporting requirements imposed by the applicable State board of pharmacy, whether the outsourcing facility must notify the State board.

FDA Response to Issue 18: The draft guidance describes the requirement under § 310.305(c)(2) that all serious, unexpected adverse drug experiences shall be promptly investigated by the outsourcing facility and a followup report must be submitted within 15 calendar days of receipt of new information ''or as requested by FDA.'' The guidance does not direct the outsourcing facility to provide information about adverse events to any other entities. Whether the outsourcing

facility must also notify the State is a question of State law. The guidance makes clear that the outsourcing facility must comply with any State requirements. As described above, for clarification, FDA added the following language to the guidance: ''Certain state boards of pharmacy may also require outsourcing facilities licensed in their states to report adverse events. Outsourcing facilities must comply with any applicable state reporting requirements independent of and in addition to reporting adverse events as described in this guidance.''

Issue 19: Two commenters asked what action, if any, FDA will take following the reporting of an adverse event. They asked if such reporting will trigger inspections or additional scrutiny by FDA, whether the filing of an adverse event report automatically means FDA will undertake any kind of formal enforcement action or any other followup, and whether FDA will notify the State board, or otherwise disclose the adverse event to the public, healthcare providers, purchasers, or others. A commenter also noted that if the purpose of the guidance is to monitor and identify issues with particular outsourcing facilities, the disclosure requirements go too far because information such as patient information, a reporter, or drug information would not be needed by FDA and can be addressed through recordkeeping and inspections.

FDA Response to Issue 19: When FDA receives a report of an adverse event associated with a compounded drug, FDA evaluates the report for appropriate action. In appropriate cases, FDA will contact the outsourcing facility or reporter for additional information, and if the report suggests a quality issue, FDA may initiate an inspection of the outsourcing facility and/or the reporter's facility, as appropriate. FDA may also contact such an outsourcing facility about initiating a recall or ceasing sterile operations if, for example, there is evidence that the firm may have released adulterated or misbranded drug products (*e.g.,* contaminated drug products) that could cause patient harm, or pursue regulatory action. In other cases, FDA may be able to determine that the adverse event resulted from the patient's underlying condition, improper administration, or concomitant product and not from a drug product compounded by the outsourcing facility. In the guidance, FDA has provided additional information about the actions that it takes upon receiving an adverse event report and why adverse event reporting is important. Specifically, FDA added the following language:

''Adverse event reporting for drug products compounded by outsourcing facilities is a critical mechanism by which FDA identifies signals of potential quality problems that may be associated with a particular drug or drug component, and which may have been caused by substandard conditions or processes at a facility where the drug or its components were made or handled. FDA needs to distinguish such cases from cases of medication error, hospital or clinic procedural problems, or quality issues associated with ingredients such as active pharmaceutical ingredients (APIs) or excipients. For example, several reports of adverse events in patients who received compounded drug products from the same outsourcing facility may be a signal of a quality issue resulting from a deficiency in the outsourcing facility's manufacturing processes. However, if several different outsourcing facilities report adverse events in patients who received drug products that contained the same API, this may suggest a quality problem associated with the API used in the compounded drug product.

An adverse event may be reported for reasons other than a quality problem. For example, it may be a side effect of taking the drug product, or may have resulted from lack of efficacy of the drug product, the patient's underlying medical condition, or use of a concomitant medication. To address the reported adverse event appropriately, FDA reviews information provided by the outsourcing facilities, such as the description of the circumstances associated with the adverse event such as the source of the drug and its ingredients, concomitant medications that the patient was taking, and relevant information reflected in hospital discharge summaries, autopsy reports/death certificates, relevant laboratory data, and other critical clinical data used to determine the cause of the adverse event.''

Issue 20: One commenter noted that the draft guidance requires that outsourcing facilities maintain for 10 years the records of all adverse events required to be reported, including certain specific information. The commenter asked when this 10-year period begins: From the date of the occurrence of the adverse event, the date the adverse event is reported to FDA, or another date, whether there are any requirements concerning how or where these records must be maintained, and whether FDA expects to provide additional guidance on the maintenance of such records

FDA Response to Issue 20: FDA clarified the guidance by adding the following language: ''The ten-year retention period for a particular record begins from the time that an outsourcing facility receives information (*e.g.,* a document with information about one of the four data elements).'' FDA does not feel that additional recordkeeping guidance is necessary.

Issue 21: One commenter requested clarification regarding the specific information that an outsourcing facility should keep in its records of an adverse event report. The commenter stated that if specific data are not available at the time of the report, FDA should specify that it is acceptable for those data to be missing from the record of the adverse event. In addition, FDA should clarify how outsourcing facilities should document their efforts to obtain the four data elements.

FDA Response to Issue 21: FDA has clarified this in the guidance. Specifically, FDA added the following italicized language: ''If the outsourcing facility was not able to include all four of the data elements in its initial report, it should exercise due diligence to obtain information about any of the remaining elements *and should keep records of its efforts to obtain this and other relevant information (e.g., dates of discussions with the reporter to determine how many patients experienced a particular adverse event or dates of discussions with a healthcare facility to obtain contact information for an identifiable person who purports to have knowledge about the patient, adverse event, or drug involved).*''

Issue 22: One commenter asked whether FDA anticipates requiring outsourcing facilities to adopt common standard operating procedures (SOPs) governing the reporting of adverse events. The commenter noted that having standardized SOPs issued by FDA may help ensure consistency in the frequency of reporting, the information reported, and how this information is provided. The commenter asked whether FDA will provide additional guidance or standards clarifying the ''written processes for the surveillance, receipt, evaluation, and reporting of adverse events for the drug products it compounds as described in 21 CFR 310.305(a) and 211.198'' that it anticipates reviewing during inspections of outsourcing facilities.

FDA Response to Issue 22: Outsourcing facilities are required to develop and implement written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences as described in §§ 310.305(a) and

211.198. FDA will consider whether to provide additional guidance on SOPs, but outsourcing facilities are required to develop written procedures that enable them to fulfill their review, reporting, and recordkeeping obligations even if FDA does not provide such guidance.

Issue 23: One commenter suggests using the MedWatch Form FDA 3500 voluntary reporting instead of the mandatory Form FDA 3500A reporting form.

FDA Response to Issue 23: FDA disagrees with this comment. Section 503B of the FD&C Act requires that outsourcing facilities report adverse events. Therefore, voluntary reporting mechanisms such as the Form FDA 3500 would not be appropriate for outsourcing facility adverse event reporting.

Issue 24: One commenter asked for clarification about the type of products about which adverse event reports must be submitted, noting that outsourcing facilities often do more than compounding. The commenter asked whether the reporting requirements apply to other activities such as repackaging.

FDA Response to Issue 24: The guidance states that ''for purposes of reporting adverse drug experiences, the term *prescription drug products* includes any compounded drug product subject to the prescription requirements in section 503(b)(1) of the FD&C Act.'' Reporting for other activities such as repackaging will be addressed in separate guidance documents. For example, when finalized, FDA's draft guidance, ''Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities,'' will describe adverse event reporting for drug products repackaged by outsourcing facilities, if they will be expected to report adverse events associated with their repackaged products, as contemplated by the draft guidance.

Burden Estimates:

The total estimated reporting and recordkeeping burdens for the guidance are as follows:

We estimate that approximately 55 outsourcing facilities (''Number of Respondents'' and ''Total Annual Responses'' in table 1) will annually submit adverse event reports to FDA as specified in the guidance, and that preparing and submitting this information will take approximately 1.1 hours per registrant (''Average Burden per Response'' in table 1).

We estimate that approximately 55 outsourcing facilities (''Number of Recordkeepers'' in table 2) will annually maintain records of adverse events as specified in the guidance, and that preparing and maintaining the records will take approximately 16 hours per registrant (''average burden per recordkeeping'' in table 2).

FDA estimates the burden of this collection of information as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN [1]

Compounding outsourcing facility	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Submission of adverse event reports including copy of labeling and other information as described in the guidance	55	1	55	1.1	61

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

TABLE 2—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

Type of recordkeeping	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
Records of adverse events, including records of efforts to obtain the data elements for each adverse event report	55	1	55	16	880

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

Dated: July 28, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2015–N–0007]

Biosimilar User Fee Rates for Fiscal Year 2016

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the rates for biosimilar user fees for fiscal year (FY) 2016. The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Biosimilar User Fee Act of 2012 (BsUFA), authorizes FDA to assess and collect user fees for certain activities in connection with biosimilar biological product development, certain applications and supplements for approval of biosimilar biological products, establishments where approved biosimilar biological products are made, and a biosimilar biological product fee for each biosimilar biological product approved in a biosimilar biological product application.

BsUFA directs FDA to establish, before the beginning of each fiscal year, the initial and annual biosimilar biological product development (BPD) fees, the reactivation fee, and the biosimilar biological product application, establishment, and product fees. These fees are effective on October 1, 2015, and will remain in effect through September 30, 2016.

FOR FURTHER INFORMATION CONTACT: Rachel Richter, Office of Financial Management, Food and Drug Administration, 8455 Colesville Rd., COLE–14216, Silver Spring, MD 20993–0002, 301–796–7111.

SUPPLEMENTARY INFORMATION: