

Guidance for Industry on Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

0910-[NEW]

SUPPORTING STATEMENT

Terms of Clearance: None.

A. Justification

1. Circumstances Making the Collection of Information Necessary

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 compounding facility 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 section 310.305 of title 21, Code of Federal Regulations (or any successor

regulations). This guidance explains electronic reporting of adverse events in accordance with 21 CFR 310.305 with respect to outsourcing facilities.

Under the 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 follow-up 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.

2. Purpose and Use of the Information Collection

The guidance implements provisions added to the FD&C Act in the DQSA in which Congress created a statutory category of “outsourcing facilities” that compound human drugs. Section 503B of the FD&C Act requires compounders that register with FDA as outsourcing facilities to report adverse events, and this guidance describes adverse event reporting for outsourcing facilities.

3. Use of Improved Information Technology and Burden Reduction

FDA published in the Federal Register of June 10, 2014 (79 FR 33072), a final rule requiring electronic submission of certain postmarketing submissions. Under the final rule, which went into effect on June 10, 2015, persons subject to mandatory postmarketing reporting requirements (including reporting requirements under 21 CFR 310.305) are required to submit postmarketing safety reports to FDA in an electronic format that the Agency can process, review, and archive.

4. Efforts to Identify Duplication and Use of Similar Information

The requirements do not duplicate nor are they similar to any current requirements for outsourcing facilities.

5. Impact on Small Businesses or Other Small Entities

Economic Staff of FDA's Office of Policy, Planning, Legislation, and Analysis (OPLA) estimates that approximately 15% of outsourcing facilities would be considered small businesses. The information being requested in the final guidance, Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act, is needed for the intended use of the data. Most of the information requested in this guidance is specifically required by section 503B of the FD&C Act or 21 CFR 310.305.

6. Consequences of Collecting the Information Less Frequently

The regulation referenced in section 503B, 21 CFR 310.305, requires manufacturers of unapproved prescription drugs to report serious, unexpected adverse events to FDA within 15

calendar days of the initial receipt of information. Such adverse events can be signals for serious public health concerns, such as outbreaks resulting from drug contamination, or could signal serious quality problems at the firm that if corrected promptly could prevent an outbreak. FDA evaluates reported adverse events to determine what follow-up action is appropriate. Collecting adverse events less frequently would not be consistent with 21 CFR 310.305 and would not be sufficient for FDA's need to evaluate adverse event reports in a timely way.

7. Special Circumstances Relating to the Guidelines in 5 CFR 1320.5

There are no special circumstances relating to this information collection. The submission of proprietary, trade secret, or other confidential information is addressed under section 10 below.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In accordance with 5 CFR 1320.8(d), FDA published a 60 day notice for public comment in the FEDERAL REGISTER of February 19, 2015 (80 FR 8872). FDA received 7 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, 21 CFR 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 21 CFR 310.305, FDA should amend this regulation.
- Several commenters noted that 21 CFR 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 to Issue One 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, 21 CFR 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 21 CFR 310.305.
- Amending the regulation 21 CFR 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 health care 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 health care 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 follow-up 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 follow-up and investigation period, and an immediate decision on a recall.

FDA Response to Issue Three: The applicable regulation, 21 CFR 310.305, provides a 15-day timeframe for reporting an adverse event and an additional 15-day timeframe to submit a follow-up 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 21 CFR 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 approved new drug application.

FDA Response to Issue Six: This additional language is unnecessary because the guidance cites the regulation 21 CFR 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*

pursuant to section 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 Ten: 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 Ten: 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 API’s 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. . . .”

¹ See 21 CFR 310.305(g).

Issue Eleven: 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 Eleven: 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 Twelve: 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 pursuant to individual prescriptions, they are permitted to do the same kind of activities as facilities compounding under section 503A. Holding facilities that engage in the same conduct to different standards is “illogical and arbitrary and capricious.” If FDA determines that 503A facilities should not be required to adhere to the same adverse event reporting requirements as outsourcing facilities, an outsourcing facility that compounds pursuant to individual prescriptions should not have to report adverse events associated with individual preparations.

FDA Response to Issue Twelve: 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 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 distinguish between patient specific and non-patient specific compounded products.

Issue Thirteen: 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 Thirteen: 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 follow-up action is appropriate. Collecting adverse events at longer intervals would conflict with the 15 calendar day submission timeline required under 21 CFR 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 Fourteen: One commenter noted that an outsourcing facility would not necessarily know which patient received which drug, unless it was compounded pursuant to an individual prescription. Most outsourcing facilities make the majority of their preparations to be supplied to healthcare providers rather than pursuant to 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 Fourteen: 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 health care 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 Fifteen: 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 Fifteen: 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 health care 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 Sixteen: 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 Sixteen: 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 Seventeen: 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 Seventeen: 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 requires outsourcing facilities to report adverse events. Reporting by healthcare providers is voluntary and not the subject of this guidance.

Issue Eighteen: Two commenters asked if, after complying with the reporting requirement, FDA will require any additional information or follow-up 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 Eighteen: The draft guidance describes the requirement under 21 CFR 310.305(c)(2) that all serious, unexpected adverse drug experiences shall be promptly investigated by the outsourcing facility and a follow-up 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 Nineteen: 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 follow up, 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 Nineteen: 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 Twenty: 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 Twenty: 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 Twenty-One: 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 Twenty-One: 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 Twenty-Two: 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 Twenty-Two: 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 21 CFR 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 Twenty-Three: One commenter suggests using the MedWatch form 3500 voluntary reporting instead of the mandatory 3500A reporting form.

FDA Response to Issue Twenty-Three: FDA disagrees with this comment. Section 503B requires that outsourcing facilities report adverse events. Therefore, voluntary reporting mechanisms such as the form 3500 would not be appropriate for outsourcing facility adverse event reporting.

Issue Twenty-Four: 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 Twenty-Four: 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.

9. Explanation of Any Payment or Gift to Respondents

There is no payment or gift to respondents associated with this guidance.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of the information submitted under these requirements is protected under 21 CFR part 20. The unauthorized use or disclosure of trade secrets is specifically prohibited under Section 310(j) of the FD&C Act. FDA will not disclose any information that is considered a trade secret and prohibited under section 310(j) of the FD&C Act.

11. Justification for Sensitive Questions

There are no sensitive questions associated with this guidance.

12. Estimates of Annualized Hour Burden and Costs

12a. Annualized Hour Burden Estimate

Under the guidance, outsourcing facilities must submit to FDA electronically adverse event reports within 15 calendar days of receiving information about a serious, unexpected adverse event and must submit a follow-up report within 15 calendar days of receipt of new information about the adverse event, or as requested by FDA. The reporting Form FDA 3500A is approved by OMB control number 0910-0291. A copy of the current labeling of the compounded drug product must be included.

Under 21 CFR 310.305(f), entities subject to the regulation must maintain for 10 years the records of all adverse events required to be reported under 21 CFR 310.305, including raw data and any correspondence relating to the adverse event. 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.

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

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

Table 2.—Estimated Annual Recordkeeping Burden

Type of Recordkeeping	Number of Recordkeepers	Number of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
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Records of adverse events, including records of efforts to obtain the data elements for each adverse event report	55	1	55	16	880
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12b. Annualized Cost Burden Estimate

The industry burden estimate calculated above would result in labor costs. FDA OPLA’s Economics Staff estimates that adverse events are generally submitted and records are maintained by a regulatory affairs manager, and that labor hours are valued using the mean hourly wage of \$63.89 as reported by the U.S. Department of Labor, Bureau of Labor Statistics, 2013 Employment Occupational Statistics for Management Occupations (SOC 11-0000) in Pharmaceutical and Medicine Manufacturing (North American Industry Notification, NAICS, code 325400). Wages are further adjusted for benefits and overhead, for an average hourly labor cost of \$127.78 ($\63.89×2). Using this wage rate times 60.5 hours calculated above for this information collection and 880 hours for recordkeeping, equals approximately \$120,177.09 in labor costs.

13. Estimates of Other Total Annual Cost Burden to Respondents and/or Recordkeepers/Capital Costs

There are no capital, start-up, operating, or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

We estimate approximately 1.0 FTE (\$275,000) to receive adverse event reports submitted by outsourcing facilities and conduct an initial evaluation of the reports.

15. Explanation for Program Changes or Adjustments

This is a new data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no plans for tabulation and publication and project time scheduling.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

The OMB expiration data will be displayed where required.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.