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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No. FDA 2014-D-2138—Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act – Guidance for Industry

Avella Specialty Pharmacy ("Avella") is pleased to submit comments to the Food and Drug Administration ("FDA") in response to the Draft Guidance for Industry titled Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (the "Draft Guidance"), which provides guidance on the implementation of Section 503B of the Drug Quality and Security Act ("DQSA").

Avella serves thousands of patients with unique and challenging medical needs throughout the United States. Founded in 1996 as a single pharmacy located in Phoenix, Arizona, it has since expanded to include a national distribution facility, community-based pharmacies in eight states, and a wholesale division. Avella is devoted to clinical excellence and patient education and engagement. Among other treatment areas, Avella is a national specialty and compounding pharmacy with unique expertise in ophthalmology treatments, and was the first ophthalmology pharmacy in the nation to earn the Pharmacy Compounding Accreditation Board's Seal of Accreditation. A portion of the ophthalmology medications Avella provides are customized to meet specific patients' unique medical needs. In 2014, Avella registered with FDA as an Outsourcing Facility in accordance with Section 503B of DQSA.

Avella is committed to working with FDA and state boards of pharmacy to ensure proper standards for facilities engaged in compounding. It is our understanding that aspects of DQSA are focused on improving oversight of human drug compounding, and FDA's Draft Guidance is a step toward implementing those aspects of DQSA. Avella appreciates FDA's efforts in developing and issuing this Draft Guidance and providing the opportunity for public comment. While Avella acknowledges that a number of Draft Guidance provisions are appropriate, Avella believes that portions of the Draft Guidance lack clarity, are superfluous, and could be overly burdensome. As a registered Outsourcing Facility, this Draft Guidance is of particular concern to Avella. Avella believes that the Draft Guidance will be significantly improved by modifying it as explained in this Comment Letter. For this reason, Avella wishes to raise a number of questions and issues with respect to FDA's Draft Guidance.

1. The Focus of FDA's Guidance Document is Unclear

Recognizing and reporting adverse events is a very important aspect of entity oversight. Avella seeks clarification from FDA as to the scope of the Draft Guidance. Avella understands that

there are two distinct areas that FDA may be seeking to monitor through adverse event reporting. The first is to monitor and identify issues with particular outsourcing facilities. For example, facilities whose practices may fall below a recognized standard and put the products compounded in those facilities at risk. The second is to monitor and address issues with specific products or their components. For example, issues with specific Active Pharmaceutical Ingredients ("APIs") or bulk drug substances. Avella believes FDA's concern is likely focused on the former issue in this context. However, Avella seeks clarification from FDA as to which aspect this Draft Guidance is intended to address.

If the focus is the former, the Draft Guidance disclosure requirements go too far. For example, if FDA's focus in on specific issues with Outsourcing Facilities, information such as patient information, a reporter, or drug information would not be needed by FDA. Instead, these issues could simply be addressed through the recordkeeping and facility inspections, to which Outsourcing Facilities are already subject under the Federal Food, Drug and Cosmetic Act ("FFDCA"), and a much simpler reporting requirement. Additionally, by focusing on the Outsourcing Facility, the reporting obligations could be completed by simply reporting to FDA on whether there were any unexpected, serious adverse events associated with the Outsourcing Facility's products. This would reduce the amount of resources required on FDA's behalf.

If the focus is the latter, unlike in a FDA-approved manufactured product, compounded products have a number of components and APIs, so it may be difficult for the Outsourcing Facility or a reporter to tie a serious, unexpected adverse event to a specific component or API. In addition, Outsourcing Facilities may not be in the best position to report problems with specific API. For example, specific patient information may not be available to the Outsourcing Facility, as many of the products an Outsourcing Facility compounds are not for a specific patient. Additionally, there is concern about an Outsourcing Facility's ability to determine if a serious, unexpected adverse event was due to its compounded product or API in the compounded product, as opposed to another drug or product, especially when a patient may be taking multiple drug products. Finally, the Outsourcing Facility may not have access to or knowledge of the other drugs that a patient took or was taking at the time of the event.

Further, the adverse event data the Draft Guidance is seeking may not provide enough information to indicate to FDA whether the product itself has a problem or if the facility has a problem. Avella also questions whether this is the most efficient and/or beneficial method FDA could pursue to meet these reporting goals. Avella suggests utilizing the FDA's Medwatch 3500 voluntary reporting process.

In addition, Avella also seeks clarification about the type of products these requirements would govern. As Outsourcing Facilities are not limited to compounding drug products, Avella would like to know if the reporting requirements will apply to Outsourcing Facilities' other activities, *e.g.*, products that are repackaged by an Outsourcing Facility.

2. Outsourcing Facilities are Not in the Best Position to Report Adverse Events to FDA

Outsourcing Facilities distribute and dispense products to a number of entities, including hospitals, physicians, long-term care facilities, and individual patients. Because Outsourcing Facilities may provide products to healthcare providers and not directly to patients, they may change hands without the Outsourcing Facility's knowledge. For this reason, the Outsourcing Facility may not have all of the information necessary to make a useful report to FDA. Health care providers are in a better position to meaningfully report because they have close contact with the actual patients receiving the drugs, and have significantly more access to pertinent information in the event of an adverse experience. Regardless, FDA, or any other governmental agency, has placed no affirmative requirement on health care professionals or recipients of these products to alert an Outsourcing Facility of a suspected adverse experience. Barring affirmative requirements on health care professionals, or other recipients of products, through an FDA-imposed mandate or a contractual obligation, it remains voluntary for practitioners to even inform an Outsourcing Facility of an incident. Avella reiterates that Outsourcing Facilities are only in a position to report as much as they know, which may be very little, so Avella questions the proposed program's likelihood of success. Avella recommends that health care providers and other recipients of these products be held responsible for reporting obligations as well.

Relatedly, Avella seeks clarification regarding the consequences involved if a practitioner makes a report of a serious, unexpected adverse event directly to MedWatch and the Outsourcing Facility does not because it was not aware of the occurrence. FDA should clarify both the consequences related to the Outsourcing Facility, and whether it is permissible for the Outsourcing Facility to refer to the MedWatch report submitted by the practitioner as opposed to submitting its own report and essentially duplicating the information reported. Avella recommends that the failure to report in a situation where there is a lack of knowledge of the event have no consequences to the Outsourcing Facility, and that the Outsourcing Facility be permitted to refer to the previously submitted MedWatch report instead of being required to prepare a separate, duplicative report.

3. Compounding for Off-Label Uses

Many specialty pharmacies compound products that may be used by health care professionals for off-label purposes. The Draft Guidance does not distinguish between the uses of products for reporting purposes. Avella is concerned that the reporting requirements, as they are discussed in the Draft Guidance, will not provide FDA with the pertinent information it seeks in the case of an adverse event. The Outsourcing Facility may have this information to provide to FDA in certain circumstances, but in others it may not know how the medication is being used or administered. As stated in the previous point and for this reason, health care professionals may be in a better position to report adverse events.

4. FDA's Draft Guidance Imposes Different Standards for the Same Activity

Compounding pharmacies that operate under FFDCA Section 503A ("503A entities") compound products for an identified individual patient based on receipt of a valid prescription order. Outsourcing Facilities are also permitted to compound drugs for an identified individual patient

based on receipt of a valid prescription order or notification. Although both entities engage in the same activity, 503A entities are not subject to this Draft Guidance with respect to reporting serious, unexpected adverse events. Jane Axelrad, Associate Director for Policy at the FDA's Center for Drug Evaluation and Research, confirmed the exclusion of 503A entities from this requirement during the FDA Pharmacy Compounding Advisory Committee meeting in February 2015. Avella seeks clarification on how FDA plans to address this issue for both safety and arbitrary and capricious reasons.

The application of adverse event reporting to Outsourcing Facilities and not 503A entities holds entities participating in the same activity to different standards and could be deemed arbitrary and capricious. As FDA is likely aware, the actions of agencies may be set aside if it is determined that they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law."[1] An agency is deemed to act arbitrarily when it applies different standards to entities engaging in the same conduct,[2] and the "[g]overnment is at its most arbitrary when it treats similarly situated people differently."[3]

Avella recommends that the Draft Guidance be amended to apply to 503A entities. In the event that FDA determines not to expand the Draft Guidance's applicability, Avella suggests that the products compounded by an Outsourcing Facility that are for an identified individual patient based on receipt of a valid prescription order or notification be exempt from the reporting requirements.

Avella notes that Outsourcing Facilities are arguably safer than 503A entities because they must comply with stricter safety requirements, *i.e.*, cGMP, and are subject to FDA inspections. Because safety is a concern for FDA, 503A entities (which the FFDCA exempts from complying with cGMP[4] and are held to less stringent safety requirements) should be subject to the reporting requirements.

5. The Draft Guidance Does Not Make Clear Which Types of Events Outsourcing Facilities Should Report

The Draft Guidance makes reference to a number of different types of adverse events. Although 21 C.F.R. § 310.305(b) defines "serious adverse drug experience," Avella would like to note that the regulation only requires reporting of "serious, unexpected adverse drug experience[s]." However, the Draft Guidance suggests that Outsourcing Facilities report ***all*** serious adverse drug experiences, not just those that are considered "unexpected."[5] Avella believes that FDA is reaching far beyond what the regulations allow, and is concerned that this suggestion will lead to confusion between what must be reported and what is merely suggested. For this reason, Avella recommends that FDA narrow reporting to the specific requirements of 21 C.F.R. § 310.305, *i.e.*, those serious adverse events that are unexpected.

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[1] *AstraZeneca Pharm. LP v. FDA*, 713 F.3d 1134, 1139 (D.C. Cir. 2013) (quoting 5 U.S.C. § 706(2)(A)).
[2] *See*, e.g., *Bracco Diagnostic, Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997).
[3] *Id.* At 27-28 (quoting *Etelson v. Office of Personnel Mgmt.*, 684 F.2d 918, 926 (D.C. Cir. 1982)).
[4] FFDCA Section 501(a)(2)(B).
[5] Draft Guidance, at lines 123-131.

6. Reporting Requirements

A number of states require adverse event reporting for drug incidents. Avella would like to understand how federal reporting will be reconciled with state adverse events reporting requirements, as these requirements may vary. Avella is concerned that Outsourcing Facilities will be required to report to the state and to FDA, resulting in duplicate reporting and waste. For this reason, Avella recommends that FDA standardize reporting to reduce the likelihood of duplicate reporting and confusion among differing standards.

The Draft Guidance also addresses the required development of "written process for surveillance, receipt, evaluation, and reporting of adverse events"[6] pursuant to 21 C.F.R. § 310.305(a). This requirement is overly broad and FDA should either issue follow-up guidance or standards on the content and format of these written processes, or clarify that the method of documentation will be left to the discretion of the Outsourcing Facility.

7. The Draft Guidance Does Not Provide Clear Information About Post-Adverse Event Reporting Follow-Up

The Draft Guidance does not address follow-up actions or enforcement actions that FDA anticipates taking after receiving notice of an adverse event. Avella seeks more information about any anticipated actions.

a. Notice.

Avella seeks clarification on notification procedures. Many states already require that compounding facilities notify the state and other entities in the event of an adverse event report. Avella would like FDA to clarify if there is a notice requirement, outside of the notification to FDA and whom the Outsourcing Facility will be required to notify. For example, notifications to health care providers, purchasers and applicable state boards. In order to reduce duplicative notification, Avella recommends that FDA adopt a singular notification standard for both state and federal reporting requirements.

b. Follow-Up and Enforcement.

The Draft Guidance does not specifically address FDA follow-up or enforcement in response to a reported adverse event. For example, it is unclear if the reporting of a serious, unexpected adverse experience will trigger an inspection of the Outsourcing Facility, and if so, the applicable threshold for triggering such an inspection (*e.g.*, one adverse event or multiple). Again, Avella recommends that FDA focus on issues involving an Outsourcing Facility and not specific individual active ingredients. If this approach is taken, FDA's focus could result in a warranted inspection after a reported event. However, if FDA is focusing on active ingredients, an inspection of an Outsourcing Facility based on a reported event would not likely produce any meaningful data or results, as the Outsourcing Facility does not "produce" or "manufacture" the API in question.

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[6] Draft Guidance, at lines 331-332.

Outside of a potential inspection in response to an adverse event report, the Draft Guidance also fails to address additional follow-up action that FDA may take in response to an adverse event report, including formal enforcement action. Avella requests that FDA describe the types of enforcement action that FDA may take and under what circumstances FDA will take such action.

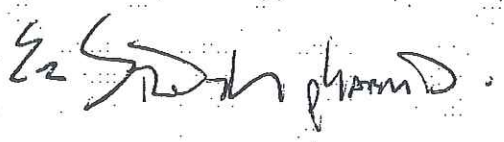
8. Recordkeeping

Avella seeks clarification regarding the specific information that the Outsourcing Facility should keep in its records in the event of an adverse experience report. If specific data points referenced in the guidance are not available at the time of the report, FDA should specify that is it acceptable for those same data points to be missing from the Outsourcing Facility's record of the adverse event. The Draft Guidance indicates that Outsourcing Facilities should "maintain records of its efforts to obtain the four data elements discussed in section III.B."[7] Avella recommends that FDA clarify how this information is best documented, and what information should be contained in the documentation to demonstrate efforts to obtain said information.

Conclusion

Avella appreciates FDA's efforts in developing and issuing the Draft Guidance and for giving Avella and others an opportunity to ask questions and provide comments. Avella believes that addressing the concerns raised in this Comment Letter and incorporating the above suggestions into the Draft Guidance will promote product integrity and safety, while minimizing the costs and burdens associated with implementation of regulations. If FDA has any questions, please feel free to contact Eric Sredzinski, EVP Clinical/Quality, Avella Specialty Pharmacy at 623-238-7072 or eric.sredzinski@avella.com.

Sincerely,



[7] Draft Guidance, at lines 340-342.