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

May 19, 2015

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(*Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* – Draft Guidance for Industry)

Dear Food and Drug Administration,

Pentec Health, Inc. ("Pentec") submits this Comment Letter in response to the Draft Guidance *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (the "Draft Guidance") as it provides guidance on the implementation of Section 503B of the Drug Quality and Security Act (the "DQSA"), which amends the Federal Food, Drug and Cosmetic Act ("FFDCA").

The patients that Pentec serves have unique and serious medical needs. Established in 1983 and headquartered in Boothwyn, Pennsylvania, Pentec has grown to be a leader in providing intradialytic and intraperitoneal parenteral nutrition therapies for dialysis patients, as well as providing specialized care for patients with implanted intrathecal pumps. All of the medications Pentec provides to its patients are patient-specific, and are compounded based on individual prescriptions with strict adherence to USP <797> beyond-use-dating (BUD) for low, medium and high-risk medications. Because Pentec compounds a wide range of products to meet individual patients' needs, Pentec has extensive experience adhering to all three risk levels depending on the medications needed. The compounded prescriptions are stored at refrigerated temperatures and administered within 3 to 14 days, based upon their risk level.

Pentec applauds FDA's efforts to provide clarification on issues concerning adverse event reporting, and values the opportunity to provide feedback and input during this process. Pentec looks forward to working with FDA on this important issue.

1. Clarification regarding the goal(s) FDA hopes the Draft Guidance will accomplish

As an initial matter, Pentec wishes to address the purpose of the DQSA requiring an Outsourcing Facility registered under Section 503B of the DQSA (an "Outsourcing Facility") to submit adverse event reports to FDA. That is to say, Pentec hopes to better understand the goals FDA hopes to accomplish with the particular requirements it has proposed in the Draft Guidance.

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Pentec submits there are potentially two main categories of information that FDA seeks to obtain pursuant to the reporting requirements of the Draft Guidance.

First, FDA may be interested in knowing the sheer number of adverse events that occurred at each Outsourcing Facility. Said another way, FDA may be interested in identifying which Outsourcing Facilities have a demonstrated pattern of problems affecting many of its compounded products that may stem from, for example, poor quality and safety controls. This line of inquiry might help ferret out facilities whose poor practices may result in products that are dangerous to patients, *i.e.,* a facility or actor like the New England Compounding Center.

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. Indeed, 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, as proposed in the Draft Guidance.

Additionally, revising reporting requirements to meet this goal may be more realistic and reasonable given the nature of the information that Outsourcing Facilities have about specific adverse events. An Outsourcing Facility would not necessarily know which patient received which drug, unless it was compounded pursuant to an individual prescription. Indeed, Pentec expects that most Outsourcing Facilities make the majority of their preparations to be supplied to healthcare providers or facilities rather than pursuant to a prescription, so the only way an Outsourcing Facility would learn of the occurrence of an adverse event is if it is reported to the Outsourcing Facility by a patient or a healthcare provider. Barring some kind of contractual obligation, healthcare providers would not be required to provide this information to the Outsourcing Facility that compounded the drug. Healthcare providers are in a better position to know about the occurrence of adverse events. Accordingly, it may be advantageous to seek to collect this information from those individuals with better access to the information, perhaps through submitting reports to MedWatch and supplying copies of those reports to the Outsourcing Facility. Under this scenario, the Outsourcing Facility could then submit an adverse event report to FDA, reference the fact that the occurrence was already reported, and provide additional information about the product. This arrangement has the advantage not just of streamlining the reporting process, but also helps ensure consistency and eliminate the possibility of duplicate reporting. What's more, having only one report submitted rather than two would ease the administrative burden placed on FDA's already-strapped resources.

The second category of information FDA may be seeking to collect is data about problems caused by particular compounded products, active pharmaceutical ingredients ("APIs"), and

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other components of compounded products. If this is, in fact, the information FDA seeks to collect in order to create a database of adverse events linked to such substances, Pentec suggests that such database may be of limited value because Outsourcing Facilities can compound based on an individual prescription. For this reason, information about one-off compounded products may be of questionable value because of the unique formulation of each product. It would, in effect, be comparing apples to oranges.

Further, seeking to connect an adverse event to individual components of a compounded drug may be difficult simply due to the fact that compounded products, by their definition, have at least two, and sometimes multiple components. As will be discussed in greater detail below, linking an adverse event to a particular component of a compounded product may simply be an exercise in guesswork. Finally, the Draft Guidance does not mandate identifying all components of a compounded product in all instances, so information that FDA collects in this regard may run the risk of being incomplete.

2. Identical reporting obligations should be required of facilities compounding under Section 503A

One of Pentec's primary concerns about the Draft Guidance is that it imposes uneven reporting requirements on similarly-situated facilities engaging in the same activities. Because Outsourcing Facilities can compound drugs pursuant to an individual prescription, they are permitted to do the same kind of activities as facilities compounding under Section 503A of the FFDCA ("503A Facilities").

Holding facilities that engage in the same conduct to different standards is not just illogical, it is arbitrary and capricious.

As FDA is no doubt aware, its actions—like the actions of all agencies—may be set aside if they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law."[1] An agency acts arbitrarily when it applies different standards to entities engaging in the same conduct.[2] Indeed, "[g]overnment is at its most arbitrary when it treats similarly situated people differently."[3]

Under the Draft Guidance, 503A Facilities would not be required to report any information to FDA about adverse events, but Outsourcing Facilities are obligated to comply with extensive adverse event reporting requirements. Said another way, the Draft Guidance proposes to treat similarly situated entities—those engaging in compounding drugs pursuant to an individual prescription—differently even though they will be performing the same activities.

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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 Diagnostics, 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)).

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If FDA intends to treat these entities differently, it must provide a sufficient reason for doing so.[4] The Draft Guidance does not specify a rationale for this disparate treatment.

This arrangement—503A Facilities' not being required to provide any adverse event reporting to FDA—was troubling to members of the FDA Pharmacy Compounding Advisory Committee who expressed this concern during its February 2015 meeting. Requiring more safety reporting by an Outsourcing Facility is counterintuitive given that they must comply with more stringent safety standards. The likelihood of product quality problems arising in drugs compounded by an Outsourcing Facility is likely less than those compounded by 503A Facilities because Outsourcing Facilities must adhere to current good manufacturing practices ("cGMP"), which are not required of 503A Facilities.

FDA has the ability to remedy this disparity. FDA could require adverse event reporting by 503A Facilities through the Memorandum of Understanding that FDA has proposed be executed by states. While there are many options for implementing this requirement, one such possibility would be to require 503A Facilities to report to the relevant state board of pharmacy, which would then supply this information to FDA. By implementing this kind of reporting requirement, both state and federal regulators would have a full picture of the occurrence of adverse events, and would be better equipped to conduct oversight that best achieves their primary goal – ensuring patient safety.

If FDA determines that 503A Facilities should not be required to adhere to the same adverse event reporting requirements as Outsourcing Facilities, Pentec contends that the Draft Guidance should be changed to provide that an Outsourcing Facility that compounds pursuant to individual prescriptions need not engage in adverse event reporting in connection with these individual preparations. Employing a different standard to facilities engaging in the same activity is unreasonable, and would result in uneven data collection by FDA, thereby providing federal regulators an uneven and incomplete picture of safety concerns.

3. Unrealistic expectations about information that an Outsourcing Facility can provide

As referenced earlier, Pentec is concerned that the information required to be reported in the Draft Guidance may not be available to an Outsourcing Facility, and that other individuals and entities may be better sources for this information.

As an initial matter, an Outsourcing Facility simply may not have sufficient information to comply with the Draft Guidance's proposed reporting requirements. An Outsourcing Facility can only report the information that it has, and it may not be in the best position to provide the

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[4] *See, e.g., El Rio Santa Cruz Neighborhood Health Ctr., Inc. v. Dep't of Health & Human Servs.*, 300 F. Supp. 2d 32, 42 (D.D.C. 2004), *aff'd*, 396 F.3d 1265 (D.C. Cir. 2005) ("It is axiomatic that 'an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so.'") (quoting *Indep. Petroleum Ass'n of America v. Babbitt*, 92 F.3d 1248, 1258 (D.C. Cir.1996)) (emphasis added).

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information FDA would like because there is no obligation of a patient or the patient's healthcare provider to report information about the occurrence of an adverse event to an Outsourcing Facility. Absent a contractual obligation mandating that the purchaser of a compounded product inform an Outsourcing Facility of an adverse event, there is no mechanism to require that this information be provided. This situation is exacerbated by the fact that an Outsourcing Facility may not always sell a compounded product directly to the end user. Accordingly, even if there were a contractual reporting obligation between an Outsourcing Facility and the buyer, the reporting obligation may not be with the one party best equipped to know about the occurrence of an adverse event – the patient who is the end user.

To be sure, Pentec has every intention and wish to comply with any and all adverse event reporting requirements, and would promptly provide such information in an effort to improve patient safety. But there are significant barriers to providing the information requested. Requiring other parties to provide this information—for example, the physician who prescribed the drug, the healthcare provider who administered the drug, or the facility where the drug was administered—may prove more effective. Additionally, requiring such reporting by those who are closer in time and proximity to the administration of the drug and the occurrence of the adverse event may help eliminate the possibility of over-reporting. Other healthcare providers may already report the occurrence of an adverse event, thereby opening the door to duplicate and unnecessary reporting.

The chance that another may report an adverse event to MedWatch raises additional questions. First, if a report of an adverse event is submitted to MedWatch without the relevant Outsourcing Facility's knowledge, could the Outsourcing Facility simply provide FDA a copy of the report rather than submitting a separate and duplicative report? Additionally, would there be a consequence to an Outsourcing Facility that does not report an adverse event because another individual or entity reported it directly to MedWatch?

4. Difficulties of attributing adverse event to the drug compounded by an Outsourcing Facility

Pentec wishes to bring to FDA's attention what it believes to be problems with how the Draft Guidance advises to identify the drug product suspected of triggering the adverse event.

The Draft Guidance instructs that if an adverse event "involves multiple suspect drug products that are compounded by the same outsourcing facility, the outsourcing facility should submit only one report that notes the drug product considered most suspect by the reporter. If the reporter views each drug product as equally suspect, the outsourcing facility should submit only one report that lists all of the drug products as suspect."[5]

[5] Draft Guidance, lines 219-225.

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Pentec wishes to understand how FDA envisions a determination could be made about which drug or which component of a compounded product is the "suspect drug product." Given the fact that a compounded product contains more than one component, Pentec is unclear how an Outsourcing Facility, or the patient's healthcare provider, would know with certainty which component of the compounded product, or which component of which product, is suspect.

What's more, an Outsourcing Facility would face significant challenges in its efforts to identify the suspect product because it may have an incomplete picture of the circumstances under which the drug was administered. The patient may be taking multiple drugs or undergoing other therapies that were started or stopped before the adverse event occurred but after the Outsourcing Facility provided the compounded drug. Simply put, an Outsourcing Facility is not in a position to have access to this information. Additionally, the Outsourcing Facility may have received incomplete information about the patient's medical history and other treatments, further hindering its ability to accurately assess the identity of the suspect product. Finally, the Outsourcing Facility would have no control over how a drug is administered, and improper administration may be material to the occurrence of the adverse event.

Pentec also suggests that it may be advisable to require that an adverse event report identify all the APIs contained in a compounded drug, and the manufacturers thereof. Providing this information may help illuminate the existence of problems from compounded drug products that stem from contaminated or otherwise problematic components.

Finally, 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, and as discussed above, 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. Once again, the patient's healthcare provider may be in a better position to provide this information.

In short, an Outsourcing Facility faces multiple and significant barriers to being able to comply with the requirements mandated by the Draft Guidance. Pentec suggests that the Draft Guidance would be improved by making revisions to address these concerns.

5. Additional questions/clarification sought by Pentec

In addition to the issues and questions identified above, Pentec seeks further information and clarification on a number of issues:

a. Types of events to be reported

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Additional details clarifying the characteristics of adverse events that must and should be reported would be of great benefit to Outsourcing Facilities seeking to understand the nature of the information FDA wishes to be reported.

The Draft Guidance references 21 C.F.R. § 310.305(b)'s definition of "serious adverse drug experience,"[6] but the Draft Guidance provides that only a serious, unexpected adverse drug experiences must be reported.[7] However, the Draft Guidance suggests that an Outsourcing Facility should report all serious adverse experiences, not just those that are considered unexpected.[8] Pentec believes that Outsourcing Facilities would benefit from further clarification of the nature of which events must be reported versus those that FDA would like to be reported.

b. Reconciling reporting requirements imposed by FDA and by state regulators

Pentec seeks clarification concerning how the reporting requirements proposed by the Draft Guidance would interplay with reporting requirements imposed by state boards of pharmacy.

As FDA is undoubtedly aware, state boards of pharmacy generally require Outsourcing Facilities to obtain some kind of state license[9] and have jurisdiction over them. In the event a state board of pharmacy has adverse event reporting requirements that apply to an Outsourcing Facility, does satisfying the adverse event reporting requirements contemplated by the Draft Guidance preempt the requirement to comply with a state reporting requirement? Must an Outsourcing Facility report to both federal and state regulators?

c. Follow-up and/or enforcement concerning adverse event reports

After an Outsourcing Facility complies with the requirements proposed by the Draft Guidance, Pentec requests information about whether FDA will impose any additional reporting or follow-up requirements, and what actions, if any, FDA will take vis-à-vis a reported adverse event.

After complying with the reporting requirement, will FDA require any additional information or follow-up activity by the Outsourcing Facility that submits the report? For example, would the Outsourcing Facility be required to provide information about the adverse event to healthcare providers or others who purchased the same or similar product? If the adverse

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[6] Draft Guidance, line 259.
[7] Draft Guidance, lines 125-126.
[8] Draft Guidance, lines 128-131.
[9] For example, in Ohio an Outsourcing Facility must be licensed as a Wholesale Distributor of Dangerous Drugs with an outsourcing facility classification. *Guidance Document: Registering as a 503B Outsourcing Facility*, OHIO STATE BOARD OF PHARMACY, http://pharmacy.ohio.gov/Documents/WDDD/General/Guidance%20Document%20-%20Licensing%20Outsourcing%20Facilities%20in%20Ohio.pdf.

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event does not trigger reporting requirements imposed by the applicable state board of pharmacy, must the Outsourcing Facility notify the state board?

Additionally, Pentec wishes to know what action, if any, FDA will take following the reporting of an adverse event. Will such reporting trigger inspections or any kind of additional scrutiny by FDA? Does the filing of an adverse event report automatically mean FDA will undertake any kind of formal enforcement action, or any other follow up? Will FDA notify the state board, or otherwise disclose the adverse event to the public, healthcare providers, purchasers or others? Pentec understands that the Draft Guidance provides that Outsourcing Facilities are subject to FDA inspections, which can include a review of adverse event information received by the Outsourcing Facility,[10] but will submitting a report subject the Outsourcing Facility to additional inspections?

d. Clarity regarding recordkeeping requirements

Pentec also seeks additional information to clarify the recordkeeping requirements proposed by the Draft Guidance.

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.[11] Pentec wishes to know 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 perhaps another date?

Additionally, Pentec requests that FDA clarify if there are any requirements concerning how or where these records must be maintained. Other than complying with HIPAA and other patient confidentiality requirements, does FDA expect to provide additional guidance on the maintenance of such records?

e. Standard operating procedures for adverse event reporting

Finally, Pentec wishes to inquire whether FDA anticipates requiring Outsourcing Facilities to adopt common standard operating procedures ("SOPs") governing the reporting of adverse events.

Pentec contends that having standardized SOPs issued by FDA may help ensure consistency both in the frequency of reporting, the information reported, and how this information is provided. Maximizing such consistency, to the extent possible, will undoubtedly make this information more valuable to FDA, and eliminate administrative and technical difficulties associated with accumulating and synthesizing such information. To that end, Pentec wishes to know if FDA will provide additional guidance or standards clarifying the "written

[10] Draft Guidance, lines 329-333.
[11] Draft Guidance, lines 337-342.

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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?[12]

Pentec wishes to thank FDA for its efforts on this issue, and to reiterate its commitment to working with FDA to develop effective and reasonable policies that promote patient safety.

Sincerely,

Joseph Cosgrove
Chairman, President & CEO

[12] Draft Guidance, lines 329-333.