Prioritize FDA Inspection Readiness

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A decade ago, questions still lingered among pharmacies concerning whether FDA had a legal right to conduct an inspection of their facility. After all, Section 704 of the Federal Food, Drug, and Cosmetic Act (FDCA) seems to exclude (at least to a degree) a pharmacy from FDA's inspection authority, and compounding pharmacies typically were regulated solely by state boards of pharmacy. After the compounding disaster in 2012 involving New England Compounding Center (NECC), however, FDA made it abundantly clear—through words and actions—that it has full legal authority to inspect pharmacies (see the **SIDEBAR**).

Since the beginning of 2013, FDA has published on its website the results of hundreds of compounding pharmacy inspections conducted throughout the United States.[4] Many inspections have resulted in regulatory actions such as FDA Form 483s (reports of FDA's inspection "observations" of allegedly violative conditions), warning letters, requests for product recalls, damaging press releases, FDA requests to cease sterile compounding operations, and court-ordered consent decrees and injunctions. The potential for a legal or regulatory action resulting from an inspection is a reality; thus, it is important to maintain a strong response plan to avoid such an outcome.

Inspection Preparation

Given FDA's increased scrutiny of compounding pharmacies over the past several years, compounders should be prepared for an agency visit at any time. This is especially true for pharmacies compounding sterile drugs, which has been a priority of FDA; however, FDA inspects nonsterile compounding pharmacies as well. As FDA typically does not announce that it intends to inspect a pharmacy premises, it is important for a pharmacy to establish internal procedures or SOPs detailing how to respond to an inspection. These procedures do not need to be shared with FDA. Some basic considerations when preparing for an FDA inspection include the following:

- When FDA arrives at the pharmacy, a designated employee should ask the investigators for their credentials. FDA usually will not permit credentials to be photocopied or photographed, but the full name of the investigator should be recorded along with his or her contact information. Typically, the inspection will include two investigators; in some cases, a state board of pharmacy employee will accompany them.
- The investigator will also present an FDA Form 482, Notice of Inspection, which sets forth FDA's authority to inspect the premises. If the investigator does not show an FDA Form 482 or says he or she is with the Office of Criminal Investigations, immediately contact outside legal counsel.
- As part of the inspection SOP, assign a designated room or area where the investigator is to meet with staff, review documents, or ask questions. The investigator should not leave this area, nor have unfettered access to the pharmacy.

Rather, the investigator must be escorted to any pharmacy locations and be accompanied at all times by a designated employee.

- The pharmacy may ask the investigator questions about any aspect of the inspection, especially if FDA's own questions, comments, or observations are unclear. One individual should be identified to field questions from the investigator to ensure that questions are answered appropriately. The designee should understand the parameters of the inspection and be familiar with the policies and procedures related to compounding operations.
- The investigator will ask questions during the inspection, but FDA cannot compel a response to questions posed, especially if the response requires any guessing or speculation. Employees should not engage in communications with investigators unless they are specifically designated to speak and have been asked to respond to a question.
- When responding to FDA's questions, respond only to the question asked, and do not offer or otherwise volunteer information in addition to that necessary to respond to the question. Similarly, it is critical to respond truthfully to FDA's questions.
    - Note that any responses may be admissible as evidence in legal proceedings that may follow the inspection. Furthermore, knowingly submitting materially false information to FDA—whether in writing or as oral statements—is a criminal violation.
- The pharmacy should designate a different individual to take notes during the inspection process, including but not limited to, questions asked, statements made, requests for documents, comments made by the investigators, and responses to the same. These notes should be preserved in a separate file that contains all inspection related documents.
- If asked to sign anything during the inspection, consult with legal counsel before doing so. It is also wise to notify counsel when FDA shows up to inspect the facility, in the event the inspection does not go as planned.

Inspection Scope

Pharmacies typically do not know or otherwise learn why FDA has determined to inspect their pharmacy. However, FDA is more likely to inspect pharmacies that engage in higher risk activities such as sterile compounding or have a history of prior inspectional findings, state activity or complaints, or adverse events. Regardless of the impetus, FDA inspections seek to find evidence of insanitary and other conditions that would render compounding violative of the law.

FDA's 2020 Insanitary Conditions Guidance for compounding facilities should be read as an inspection "checklist."[5] This final guidance document applies whether the entity is operating pursuant to FDCA Section 503A, or is an outsourcing facility operating under Section 503B. Inspections may be routine or surveillance inspections, or inspections for cause (ie, a complaint or adverse event). FDA bases the guidance on the multitude of compounding pharmacy/facility inspections it has undertaken since late 2012. The guidance clearly states that compounders must comply with the adulteration provisions in FDCA Section 501(a)(2)(A). FDA clarifies that a drug is adulterated "if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health." FDA has cited compounders via

Form 483 observations and warning letters for violations of the act's adulteration provisions since late 2012. FDA typically states that if compounding has occurred under insanitary conditions, then other exemptions under Section 503A–such as exemptions from FDA's new drug approval provisions, adequate directions for use, and current Good Manufacturing Practice regulations (cGMP)–do not apply.

FDA states it is critical that compounding facilities avoid insanitary conditions and identify and remediate these conditions before they result in drug contamination and patient injury. The guidance provides numerous examples of insanitary conditions that FDA investigators have observed in compounding facility inspections. These include:

- Presence of vermin
- Visible microbial growth such as mold and bacteria
- Nonmicrobial contamination such as rust, glass shavings, or hair in a production area
- Handling beta-lactam, hazardous, or highly potent drugs (eg, hormones) without providing adequate containment, segregation, and cleaning of work surfaces, utensils, and personnel to prevent cross-contamination
- Production of drugs while construction is underway in an adjacent area without adequate controls to prevent contamination of the production environment and product

The guidance also includes:

- Examples of insanitary conditions in aseptic operations (including detailed gowning, procedures, and equipment)
- Cleaning and disinfection "best practices"
- Descriptions of insanitary practices concerning equipment and facilities, sterilization, cleaning, and disinfecting
- Procedures that facilities must follow (noted as "critical") to identify insanitary conditions, including routine environmental monitoring, certifying the ISO 5 workspace every six months, differential pressure monitoring, and conducting media fills
- Necessary corrective actions when insanitary conditions are found, which reads similar to Warning Letters issued to compounding facilities where FDA found insanitary conditions were present
- A list of conditions that should cause a pharmacy to immediately recall product and cease compounding (although FDA does not have independent recall authority absent intervention of a court)

Given FDA's reliance on this guidance, pharmacies engaged in either sterile or nonsterile compounding should ensure employees review and become well-versed in the guidance as it plainly sets forth FDA's expectations for both sterile and nonsterile compounding operations.

FDA Document Requests

As the FDA inspection continues, the investigator may ask to review documents or make copies of documents. In this case, the responsible pharmacy employee should make a copy of the item for FDA and retain a copy for the pharmacy's inspection record. The employee should also create and record on a log the documents provided to FDA, including the number of pages of each item provided.

Items Requested

During recent pharmacy inspections, investigators have typically requested the following types of documents:

- Product labels
- Prescriptions (to determine whether the pharmacy complies with Section 503A's individually identified patient requirement)
- Lists of the sterile and nonsterile drug preparations that the facility compounds
- Compounding (ie, batch or production) records
- Any product testing data
- Environmental monitoring data
- Media fill testing results
- Written policies and procedures concerning compounding processes

There are key considerations to keep in mind when responding to FDA requests including:

- Do not write on, notate, or otherwise initial any copies of documents provided, unless dating or numbering the documents. Dating and numbering the documents chronologically including internal page numbering for the document should suffice (eg, FDA 6.10.14: 1 pg. 1, FDA 6.10.14; 1 pg. 2, etc.).
- Do not permit the investigator unsupervised access to records, documents, or files. Likewise, do not permit access to document storage areas for the investigator to search independently for requested documents.
    - Remember that the investigator is not permitted to review financial data, sales data (other than shipment data), pricing data, or personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to the FDCA) per FDCA Section 704.
- Review documents carefully before providing them to FDA. If the investigator asks to review (but not copy) certain documents, take notes of the documents reviewed. Resist the urge to provide documents that are not specifically requested.
- FDA investigators often ask for documents in electronic form. While electronic document production may seem less burdensome, there is a risk that such data could be manipulated (consider Excel spreadsheets, for example). There is no legal requirement to produce documents to investigators in electronic form, unless they are required records and the facility's policy is that the electronic versions of records are the official copy. Do not produce electronic records unless the production of hard copy documents is not feasible or is impracticable. Ensure that an exact copy of any electronic data or records that are furnished to FDA is maintained; make a copy of the media on which such data or records are provided.

- Before the investigator leaves each day (the FDA inspection may last multiple consecutive or non-consecutive days), request a meeting with the investigator to review any observations they have made and to identify any problems they have encountered. Once the investigator leaves the facility, review the day's inspection with all the other employees in attendance. Pay particular attention to any deficiencies noted by FDA, or items that may need correction or clarification upon FDA's return. If items can be addressed and promptly corrected (eg, update or write a new SOP), undertake these tasks immediately and show the correction to the investigator prior to the conclusion of the inspection. This quick action may avert the issuance of an FDA observation for the particular issue at the inspection's conclusion.

Product Samples

The FDA may request samples of drug products, which is within the agency's authority. The pharmacy representative should attempt to obtain information from the investigator concerning the intended analysis. If the investigator requests samples, retain a duplicate sample from the same batch in order to conduct an independent, third-party test. If FDA does not provide information as to the specific tests that will be run on the sample, instruct the third-party laboratory to test for sterility, identity, potency, endotoxins, and particulates.

When removing samples from the premises, the investigator should provide an FDA Form 484 (which is the equivalent of a receipt) setting forth the type and quantity of the sample(s). Note that the pharmacy is not required to sign the FDA Form 484, even if asked to do so. Because the FDA is responsible for the cost of samples provided, the facility has the option to bill FDA for the same.

It is equally important to request the results of the FDA's sample testing. On occasion, the FDA will provide this information voluntarily, so be sure to ask for any test results following the conclusion of the inspection. If this approach is unsuccessful, request the test results via the Freedom of Information Act (FOIA). Information concerning how to submit a straightforward FOIA request is available on FDA's website and may be submitted online.[6]

Inspection Conclusion

At the conclusion of the inspection (which may last days or weeks), the investigator will conduct an exit interview to discuss their inspection findings and observations. Typically, this interview will not occur until after the investigator has consulted with FDA headquarters about the results of the inspection.

During the exit interview, the investigator may issue an FDA Form 483, Notice of Observations, which lists alleged deficiencies observed during the inspection. It is important to respond carefully to questions asked during the exit interview and avoid overstating intended remedial efforts. If an observation is unclear, request clarification from the investigator. In many cases, compounding pharmacies ask why FDA is treating the pharmacy as a drug manufacturer and holding the pharmacy to FDA's cGMP regulations. FDA typically holds pharmacies to its more stringent cGMP regulations required of drug manufacturers of FDA-approved products when it believes or otherwise determines during

the inspection that the pharmacy is not acting in compliance with Section 503A. Finally, prepare a written summary of the exit interview.

After the inspection, the pharmacy should prepare a file of all documentation resulting from the inspection, including but not limited to all written notes, documents copied, notations of samples taken, laboratory test reports, copies of any documentation provided by FDA, and responses to any FDA Form 483 Observations. The time period to respond is 15 working days (not including federal holidays or weekends). Lastly, submit a FOIA request for a copy of the Establishment Inspection Report, which is the investigator's detailed report of the inspection and contains more detailed information than the FDA Form 483 prepared by the investigator. Typically, FDA will not provide the Establishment Inspection Report until after the inspection is closed out and the observations have been remediated to FDA's satisfaction.

Conclusion

While FDA inspections of pharmacies are not commonplace, they can be quite challenging when they do occur given the FDA's aggressive approach to reviewing compounding practices, in particular sterile practices. Furthermore, these inspections are typically unannounced, leaving no time for preparation at the time of inspection. Thus, the best tool to ensure a smooth review process is the creation and consistent maintenance of a strong inspection protocol as part of facility's standard policies and procedures.

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SIDEBAR

FDA's Scope of Inspections

The NECC incident prompted strict enforcement of compounding protocols, with FDA's purview extending to any compounding pharmacy. The former FDA Commissioner stated as much in 2013:

The [NECC] fungal meningitis outbreak has caused the Agency to review our past practices with regard to our oversight of compounding pharmacies, and has led to some preliminary conclusions. In my view, even in the face of litigation and continuous challenges by industry to our authorities, we can nonetheless be more aggressive in pursuing enforcement actions against compounding pharmacies within our current limited authority. I can assure you that we are being more aggressive now. We have established an Agency-wide steering committee to oversee and coordinate our efforts, and we have taken several important steps to identify and inspect high-risk pharmacies that are known to have engaged in production of sterile drug products.[1]

Given the increase in frequency of FDA inspections in the last decade, it is important for compounders to keep in mind that FDCA Section 704(a) does in fact authorize FDA to enter pharmacy premises and conduct an inspection during normal business hours, as it is a facility where drugs are processed, packed, or held. FDA may inspect at least the facility, equipment, containers, labeling, raw materials, and inventory, notwithstanding the exemption from inspection for certain records maintained in the pharmacy set forth in § 704(a)(1). Thus, a pharmacy should not refuse the inspection.

Such refusal likely would be an independent violation of FDCA § 301(f) (ie, a "prohibited act"). Specifically, refusing to permit an inspection authorized by the FDCA is a criminal offense. FDA's pharmacy inspectional powers are now interpreted quite broadly, and may extend to:

"all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products which are adulterated or misbranded within the meaning of this chapter, or which may not be manufactured, introduced into interstate

commerce, or sold, or offered for sale by reason of any provision of this chapter, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this chapter."[2]

But FDA's inspection authority *does* have its (statutorily defined) limits. Importantly, FDA inspections *shall not* extend to "financial data, sales data (other than shipment data), pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to the FDCA)," and certain research data.[2] Compounding pharmacies (and drug manufacturers) are not required to make these types of records available for inspection, and this type of information may be redacted on records which FDA is otherwise entitled to see.

If a pharmacy objects to a notice of inspection (FDA Form 482), and if FDA believes that the pharmacy is engaging in acts inconsistent with the FDCA, FDA may obtain a warrant from a court, permitting FDA to enter the premises and inspect those documents and things within the scope of the warrant.[3]