USP 797: What to Do When the FDA Comes Knocking on the Door of Your Cancer Center

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Oncology practices are considered producers of sterile drugs, and fall under the standards set forth by the US Pharmacopeial Convention (USP)'s "General Chapter 797 Pharmaceutical Compounding—Sterile Preparations"[1] (USP 797). Any regulatory or accreditation entity, including state professional boards, state licensing or legislative bodies, health networks, or clinical research networks, could choose to enforce compliance with the USP 797 standards. The FDA has taken the stance that USP standards are enforceable, but when the FDA performs inspections, it uses Current Good Manufacturing Practices, the same rules it applies to pharmaceutical manufacturers.

Since the Fungal Meningitis Outbreak of 2012 and the subsequent passage into law of the Drug Quality and Security Act, the FDA has made frequent inspections of retail compounding pharmacies. The 2013 Drug Quality and Security Act gives the FDA greater jurisdiction and enforcement capabilities related to drug safety. The FDA's purview was pharmacy operations, but it has stepped up the training of its inspectors and the frequency of the inspections, and, more recently, it has expanded its reach into hospital inpatient pharmacies, and even a hospital cancer center and a medical oncology private practice.

When the FDA shows up, they do not provide advance notice. The majority of private oncology practices have no plan for or experience with an FDA inspection, but after the recent unprecedented incursion, some advanced planning may be in order. In June 2016, FDA inspectors appeared for a 3-day inspection in a private oncology practice 6 days after a patient's family member posted allegations of inappropriate chemotherapy handling on a public physician-rating website. It is important for practices to have a plan of action for such surprise inspections. There is a process that you should follow, as well as the FDA. Failure to have a plan of action could result in exacerbating the situation.

What to Expect When FDA Inspectors Arrive

FDA inspectors are federal criminal investigators; their purpose for visiting your practice is to determine whether they observe practices or processes that could result in your being charged with violating the Federal Food, Drug, and Cosmetic Act (FDCA), which is a federal crime.

They may be in street clothes or in full uniform; they frequently have military or bureaucratic backgrounds, which often define their demeanor and approach to authority. Often more than 1 investigator will arrive, typically 2 or 3 investigators, but sometimes more.

For all official FDA inspections, the investigators must present Form 482 on their arrival at your facility every day on which they inspect. If the FDA investigators do not immediately present Form 482 for you to sign upon their arrival, you should ask for it before they begin to inspect. If they say they did not bring Form 482, suggest that they leave and return only when they have the form.

Typically, the investigators inspect the practice from 3 to 14 days, and usually not on consecutive days. They typically avoid weekends; if they come on a Saturday or a Sunday, you likely have a serious problem, an adverse event, a complaint, or a report against you.

Your inspectors may have never inspected a pharmacy or a physician office that handles sterile or hazardous drugs: expect them to take frequent breaks to call their district office for instructions.

Although FDA inspectors are low-level federal bureaucrats and are not decision makers, they have individual personalities; they may attempt to bully or intimidate, which you can document and complain about.

Conversely, they may appear warm, approachable, and friendly, but you must not let down your guard; remain professional, courteous, and respectful at all times, but maintain an arm's-length posture, and do not allow yourself to be lulled into a false sense of comfort or security. Never forget that their purpose for being there is to determine whether you are violating federal law. Everything you say, and everything they see, can be used against you in a court of law.

Train Your Staff

Your personnel must know what to expect. Practice. Conduct drills. Then practice more, and conduct more drills. You should not expect your team to perform well without practice. Do not allow it to be the case that the first time the staff ponder an obvious question is when the FDA asks it.

For example, if the FDA inspectors approach your staff with, "So, according to your standard operating procedures (SOPs), how often do you wash your hands? How long do you wash them? What do you use to wash them with?" These questions should not be "stumpers," and should never lead to stammering, even by the newest nurse who just qualified for sterile compounding.

Your receptionist should ask to review the inspectors' credentials when they present themselves at your door, purporting to be with the FDA.

Teach your staff to provide a full and complete answer to the precise question that was asked. Give "no-frills" replies—no sarcasm, no irony, no eye-rolling; state the facts and stop talking. In our culture, silence is difficult to tolerate, and we tend to want to fill uncomfortably long pauses. Accreditation surveyors and government investigators are trained in stone-faced "staring contests," and your staff need to be just as good at it. Anxious babbling by staff is almost always to your detriment.

On their arrival, get the FDA investigators physically situated. Do not leave them "cooling their heels": greet them promptly. They are trained to view inordinate delays as an indication that you have "something to hide."

Immediately state that you are a healthcare facility, and that you are subject to USP standards, not to Current Good Manufacturing Practices, the standards held for manufacturers of drugs, which are also inspected by the FDA.

Put them in a conference room or in another space with an uncluttered table and semicomfortable chairs, but perhaps without any windows.

Have a policy that states that nonemployees are prohibited from moving through your workspace unescorted. Inform them that you have that policy, and show it to them. If you do not have one, create one today, to be prepared before they arrive. Emphasize that you or your proxy must be present for all excursions outside their space.

When you walk with them, have a note-taking or a voice-recording device and a camera. If you do not have these, acquire them now. If they take photos, try to take a duplicate photo of the setting from a similar angle.

If you have good relations with your state board of medicine—members, inspectors, or both—consider inviting them to join the inspection.

Promptly Call Your Risk Management or Legal Department

If you find yourself occupied, ensure that your trusted assistant knows the number and name of your attorney and contacts the law office as soon as possible. It may cost some money, but consider having your attorney come right away.

The choice of attorneys is critical—the lawyer you use for drawing up your will or reviewing contracts probably thinks that USP 797 is that latest airplane from Boeing. You would not hire a sterile compounding pharmacist who has never heard of USP 797, so why would you use an attorney who does not understand the issues related to USP 797? If your attorney has some learning to do on the subject, you are at legal risk while the attorney "crams for the exam," and, worse, you are paying the hourly rate while the attorney is studying. Know your solution ahead of time.

Release of Records

There are limits to the records that the FDA is legally entitled to review, but if you are not aware of these limits, you cannot "undo" letting the investigator see them. You have the legal right to discuss the release of records with your expert attorney, and you should exercise that right before you share any prescription or patient-specific information.

Set Up an Internal "War Room"

You gave the investigators their private space, but you should also reserve a corresponding private space or a "war room" for your leaders and staff, where you can communicate confidentially and compile the many required documents for review by the inspectors. You can also use this space to strategize and instruct your team regarding what they should say, and how they should behave.

Documentation

Have your policies (SOP manual) always in easy reach. Failure to have reviewed USP 797 and established SOPs should not be an option if you are handling sterile or hazardous drugs. The FDA investigators are accustomed to having your SOPs brought to them as soon as they have settled in the practice.

Have your Corrective and Preventive Action (CAPA) binder or your quality system binder always accessible. The FDA investigators expect these binders to be presented to them in a timely manner.

Presenting SOPs, CAPA log, and quality oversight documents in an expeditious manner underscores that you "live and breathe" these key documents, and that they are always nearby. If your documents are kept electronically, provide the investigators a personal computer for use in their confined space. Ensure that the computer restricts "user permissions" to guests of their status. It would be very poor form for the FDA investigators to be able to launch your enterprise software from the computer you allocate for their use.

Validation

You and your staff need to understand clearly that the FDA inspectors do not know what you do, or how you do it; they could not step in and do the job of any of your staff, because they have not been trained to do so. The investigators should not enter your qualified air environment until or unless they have gone through (and passed) your organization's training for gowning and garbing.

However, what they do know is validation; that is not something healthcare professionals are trained in, but we do need to immerse ourselves in it and come up to speed. The investigators will be focused on process, and will be carefully observing and documenting any variances from the SOPs.

FDA Problem Reports

An uneventful inspection results in no further official forms; that is, if you "pass," your reward is that you will not receive Form 483. The bad news is that, as of this writing, more than 275 pharmacy organizations and a growing number of other producers of sterile products underwent inspection and received Form 483.

At the end of your inspection, you will most likely be issued Form 483, and the investigators will probably inform you of this at their exit. Form 483 is a legally important document and should never be ignored.

Writing a reasonable response to Form 483 requires a background in the terminology and expectations of the FDA, and unless you have made yourself an expert, you should retain an expert to help you in crafting your response.

Your response to Form 483 must pass the test of "reasonableness": do not promise a rapid, impossible timeline for correcting what the investigators found; addressing their observations is a process, not an event.

After responding to Form 483, you must execute what you promise, and you will be held to it; the FDA investigators will be back, and you want to avoid repeat observations.

After your response is evaluated, the FDA may issue a Warning Letter. A Warning Letter has great legal significance, because this is how the FDA informs you that you may be in violation of FDCA, and can be a precursor to prosecution for federal crimes, such as misbranding or adulteration.

Referral Letter to Your State Professional Board and Other Licensing Agencies

A referral letter to your state board of pharmacy and other licensing agencies is a very good thing: it means that the FDA is signing off your case, at least for now. They will publish your "deficiencies" on the Internet and therefore to the world, and they will write a letter to your state board that states that your sterile compounding processes are poor, but subsequent enforcement carries over to your state board, which does not hold you to the Current Good Manufacturing Practices standards, but it is likely to enforce USP 797 standards. State professional board referrals are better than being left in "Form 483 limbo," waiting for the warning letter that may never arrive.

Be Prepared

All healthcare facilities, including oncology practices, are subject to the standards set forth in USP 797. If not the FDA, many other entities are likely to challenge your compliance and adherence to these standards. Preparing for a possible FDA inspection will serve you well for any other challenge that may come along.

FDA inspections can be triggered by almost anything—a filed complaint, an inquiry from another agency, media coverage, an internal whistle blower complaint, or a targeted audit plan for certain organizations.

Because a massive, multistate, fungal infection contamination killed and sickened hundreds of people, agencies such as the FDA have ramped up their training and ranks of inspectors for sterile drug producers, including healthcare providers and private physician offices. Ideally, you will never have to put into action a preparation plan for a surprise FDA inspection. But if the FDA comes knocking, your preparation will be invaluable.

Reference

1. US Pharmacopeial Convention. *USP 797 Pharmaceutical Compounding—Sterile Preparations*. September 2015. www.usp.org/sites/default/files/usp_pdf/EN/USPNF/usp-gc-797-proposed-revisions-sep-2015.pdf. Accessed October 10, 2016.

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