Q&A

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Q. What are the regulatory differences between an outsourcing facility (503B) and how does it differ from a hospital pharmacy (503A)?

The Drug Quality and Security Act (DQSA) was signed into law in 2013, creating Section 503B, following a meningitis outbreak caused by contaminated mass-produced compounded medications. Regulations required of 503B outsourcing facilities are much more rigorous as compared to 503A pharmacies.

- ***503A Pharmacies***
  - Dispense medications pursuant to a prescription.
  - Must comply with USP <797> when performing sterile compounding and <USP 800> when utilizing hazardous medications.
  - Licensed and inspected by state boards of pharmacy.
- ***503B Outsourcing Facilities***
  - Operate on a much larger scale by producing large batches of medications.
  - Must adhere to current Good Manufacturing Practices (cGMP) requirements (21 CFR Parts 210/211) (the same as drug manufacturers and much more rigorous than 503A requirements).
  - Registered and inspected by FDA.

FDA has published many guidance documents and are holding 503B registrants accountable to cGMP requirements to ensure the health and safety of patients who are prescribed medications in a hospital setting receiving medications from an outsourcing facility. Additionally, health system pharmacies that undertake 503B activities are also becoming acclimated to FDA requirements requiring cGMP compliance.

Q. What are the USP (United States Pharmacopeia) requirements for compounding sterile products (CSPs)and when will they become effective?

The USP, founded in 1820, is a regulatory authority that establishes legally enforceable standards applying to medications prepared for patients. Health system pharmacies must abide by USP <797> and USP <800> for compounded medications intended to be sterile.

USP <797> provides guidelines to reduce the contamination risk for compounded sterile preparations (CSPs). It is currently effective, however the version updated in 2019 will become enforceable in November 2023.

USP <800> provides guidelines for the safe handling of hazardous drugs to minimize occupational exposure risks to health care workers. Many states have opted to delay enforcement until the new version of USP <797> is effective.

Q. What are the key changes to USP <797> and what are the challenges for hospital-based pharmacies in meeting these requirements?

Evolving regulatory oversight is making it more difficult and more costly to safely and effectively compound drugs in-house. Some of the key changes in USP <797>, effective November 2023, are as follows:

- Any person entering a sterile compounding area, whether preparing a CSP or not, must meet the requirements.
- Designated person(s) must be assigned to be responsible and accountable for facility operation and personnel preparing CSPs.
- CSP Categories 1, 2, and 3 replace previous risk levels of low, medium, and high.
- Garbing competency requires three successful gloved fingertip (GFT) samples in succession.
- Media fill with post-GFT + surface sampling must be performed every six months (or every three months for Category 3).
- GFT: incubate at 30-35˚C for no less than 48 hours and then 20-25˚C for no less than five additional days.
- Media-fill: incubate at 20-25˚C and 30-35˚C for a minimum of seven days each (SOP defined order).
- ISO 8: > 20 ACPH (air changes per hour).
- Humidity: 60% or below.
- Cleaning agents used within the PEC (primary engineer control) must be sterile.
- Beyond Use Dating (BUD) maximum: 10 days refrigerated (unless additional testing performed to be Category 3).

Some of the challenges hospital pharmacies are facing are physical facility limitations including renovations to HVAC systems, cost of required upgrades, and limitations within the facility for additional space necessary.

Should a pharmacy choose to compound Category 3 medications to extend BUD, the following are additionally required:

- Increase use of sporicidal disinfectants.
- Increase in environmental monitoring.

- Use of all sterile garb.
- Stability determination.
- Increased personnel qualification.

Q. What medications are often outsourced to a 503B from hospital pharmacies?

Hospitals rely on outsourcing facilities to provide a variety of compounded medications, such as in the categories of pain management, anesthesiology/operating room, ophthalmic, antibiotics, and labor and delivery. Some of the most requested compounded medications include: Bupivacaine, Ephedrine, Epinephrine, Fentanyl, Morphine, Neostigmine, Norepinephrine, Oxytocin, Phenylephrine, Ropivacaine, Succinylcholine, and Vancomycin.

Aside from these drugs, many hospital pharmacies may require other compounded medications when manufacturers of the comparable FDA-approved drug are unable to supply the market due to drug shortages. Inconsistent medication supply due to product recalls, drug shortages, and other drug supply chain disruptions, combined with the lack of visibility into drug supply and usage, create headaches for pharmacists and technicians, who waste valuable time hunting for new sources and changing suppliers, which also increases demands on other staff.

Q. Why can't a 503B help as soon as a drug goes on shortage?

It can, but only if it has already developed the shortage drug as a compounded drug, which takes extensive time and money and which may or may not make sense if a drug is not yet on the FDA's shortage list. The outsourcing facility must follow the process of the Drug Quality and Security Act, as well as guidance from the FDA, to commercializing a drug that complies with current Good Manufacturing Practice (cGMP). To fulfill these requirements, it usually costs approximately $160K and takes about six months to conduct the appropriate validation and stability studies before a 503B can bring a compounded drug to market with a reasonable expiry date. There is a risk the 503B assumes when investing the money and time to develop a drug that may only be on drug shortage for a short period of time (or may never go on shortage in the first place).

Q. Why do 503B have to allocate drugs to us when drugs go on shortage. Can't they just make more?

The simple answer is yes, they can produce more. However, in addition to the up-front investment of time and money to develop the compounded drug for a shortage scenario in the first place, there is a lot of work that must happen first to be compliant with 21CFR Parts 210/211, and there are only so many production slots available per week. As an example, if you want to increase a batch size to produce more units, all the documents associated with that batch change must be edited, reviewed, and approved before they can be deployed. Also, the supply chain department must acquire additional supplies to accommodate the larger batch size, and these new supplies need to be on site prior to the production run is made. This usually takes four to six weeks. This is why a 503B may ask you for a standing order, so the production and batch size are correct in the first place to appropriately supply the needs of each facility. When a drug shortage does occur, it does take the 503B the four to six weeks to be able to adjust to help supply additional product into the marketplace.

Q. What are some advantages to hospital pharmacies as a result of working with outsourcing facilities to provide medications?

Some advantages include a longer BUD as compared to USP <797>, as well as the assurance of a high-quality, reliable product due to the 503B employing repeatable, validated cGMP aseptic processes. The medications outsourcing facilities typically compound are provided in ready-to-use containers, with no additional compounding required by the hospital pharmacy or the clinician on the floor. These medications have been tested prior to distribution to ensure accuracy and reduce the risk of hospital-related compounding errors. Lack of standardization and inefficient in-house compounding can create waste, impact supply, and increase costs to health systems. A longer BUD reduces medication waste, which is critical during times of drug shortage. Additionally, pharmacists and technicians will spend less time compounding and more time participating in patient care activities. Staff shortages are currently at an all-time high and are exacerbated by allocating pharmacy staff to devote to compounding preparations.

Q. How do health-system pharmacies find a reliable 503B facility?

It is important for hospital pharmacies to know that not all 503Bs are equal when it comes to supply, quality and compliance, partnership, service, and innovation. A 503B organization with an experienced and trusted team of sterile manufacturing and pharmacy experts can be counted on to develop, compound/repackage, and deliver the high-quality, ready-to-use sterile products that health systems need. Be sure to engage 503B providers who are in good standing with state and federal regulatory agencies, such as FDA and state boards of pharmacy. It may be prudent to partner with several providers to meet the individual needs of health systems.

BIOGRAPHY

Barb Knightly, PharmD, RPh
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Barb Knightly, PharmD, RPh has over 25 years of pharmacy regulatory leadership experience, including sterile compounding, for both 503A pharmacies as well as FDA-registered 503B outsourcing facilities. Knightly completed her BS in pharmacy from Philadelphia College of Pharmacy and Science and received her doctor of pharmacy from the University of Kansas.