Partnering Well With CSP Outsourcers

What to ask your vendor

With the FDA now urging hospitals to acquire all their outsourced compounded sterile products (CSPs) from facilities registered with the agency under Section 503B of the Food, Drug, and Cosmetic Act, it may be tempting to assume that all FDA-designated 503B compounders are created equal. After all, the section requires that these facilities must observe Current Good Manufacturing Practices (CGMPs) and provide the FDA with certain information about the products they compound; they're also subject to regular FDA inspection according to a risk-based schedule.

But there are no easy, one-step ways to choose a sterile compounding facility. "Generally, the 503B industry is not steeped in CGMP," said Stuart Hinchen, the founder and CEO of QuVa Pharma, a Sugar Land, Texas–based sterile compounding outsourcer focused on anesthesia, general medicine, cardiovascular, operating room (OR), ER, pain management and obstetrics. "They came into it late,

after the Drug Quality and Security Act [DQSA] was passed in 2013. Simply being a 503B facility is not enough."

It's also not enough to review the Form 483 reports—the notices from the FDA of their observations after inspecting a compounding facility. "Honestly, I don't get terrified when I see that a compounder has had a 483, because pretty much everybody is going to get *something*," said Patricia Kienle, RPh, MPA, FASHP, the director of accreditation and medication safety at Cardinal Health. "What I *do* get concerned with is the egregiousness of the issues, repeat violations and how the company has responded to the FDA."

After a Form 483 is issued, the FDA may also issue a Warning Letter, which indicates that higher level agency officials have reviewed the observations and that a serious violation may exist. If the sterile compounding partner being considered has a warning letter (or letters), it should be a cue to look even more closely. "A Warning Letter is a red flag, although not necessarily a disqualifier," said James Hussey, the executive vice president of Athenex Pharmaceuticals, a 503B manufacturer of specialty and generic products with U.S. headquarters in Buffalo, N.Y. "Read the Warning Letters carefully. In a number of cases, you'll see that the FDA has recommended that the company hire a consultant to help them develop CGMP. That tells you that the compounder does not even have the internal expertise to get to CGMP—and if you see that, I'd recommend that you walk away."

Similar to Form 483s, recalls can be informative but also should not necessarily eliminate a compounder from consideration. "There are certain matters outside of the control of a production facility," said Jason McGuire, the vice president for quality and regulatory affairs at Fagron North America (JCB Labs/Fagron Sterile Services), an FDA-registered 503B compounding outsourcer based in Wichita, Kan., that specializes in ophthalmology, corticosteroids, OR syringes, and other high- and medium-risk pharmaceutical preparations. "Examples may include adverse events related to poor hygienic practices or facility protocols not being followed by the end users. When a customer complaint is made, the production facility may not have all the information related to the clinical facility. However, out of extreme caution, it may be decided to initiate a recall instead of risking potential patient harm."

"Even in Big Pharma, we see recalls. It's not possible to eliminate 100% of that risk," agreed Paul Yamamoto, RPh, the corporate pharmacist and general manager at California- and Colorado-based Leiters, a 503B outsourcing facility focused on ophthalmology and hospital-based products. "But it is important that your outsourcing facility quarantines and holds product, and does not rationalize releasing a product when the data suggest otherwise." (See the sidebar for additional considerations in choosing an outsourcer.)

One Health System's Strategy For Vetting 503B Outsourcers

Over the past year, Mission Health, a six-hospital health system serving western North Carolina, has evaluated three potential 503B sterile compounding outsourcers. Of the three potential vendors, only one was ultimately chosen.

"As with many other institutions facing significant drug shortages, we're trying to find partners who can meet our needs," Josh Powell, PharmD, Mission's pharmacy operations manager, told *Pharmacy Practice News.* Dr. Powell's tips for 503B vendor review:

Start with the FDA. Analyze the information available on the FDA's website, including 483 reports and recalls. Dr. Powell agrees that 483 reports alone are not a red flag against a particular outsourcer, and concurs with the recommendation to steer clear of companies that have been warned by the FDA to seek a consultant's help with Current Good Manufacturing Practices. "If you're searching for a consultant after the fact, that means you missed something pretty significant to begin with."

Check the catalog. After identifying promising outsourcers, determine whether the company can provide the drugs you need. "These facilities often want to know that you're going to remain with them if that particular drug shortage or shortages are resolved," Dr. Powell said. "Sometimes they may say that they can't support you unless you're willing to open up to more items in their catalog."

Request documentation. Now it's time for the paperwork. Dr. Powell always asks for items such as quality reports, FDA registration and state licensures, and Certificates of Analysis.

Never skip the site visit. But only schedule one after thoroughly vetting the company. "Multiple site visits can be burdensome in terms of cost as well as time of your pharmacy staff," he said. "We gather all our documentation and only visit the facilities that we know we would approve contingent on a good site visit."

Don't let them see you coming. Many compounders will offer to pay for your travel expenses and arrange the visit. "We want to see the pharmacy when they're not ready for us," Dr. Powell said.

Rely on ASHP. "After we've collected our data and conducted our site visit, we use the ASHP outsourcing assessment tool to round out our discussion," Dr. Powell said. He cautioned that some facilities already have the tool filled out for their customers. "It's important to use the tool yourself first and *then* compare it to the facility's answers."

—*G.S.*

It's All in the Documents

To be in compliance with CGMPs, Mr. Hussey said, all sterile compounders should provide a Certificate of Analysis with every batch that includes the following items:

- sterility testing
- potency testing
- bacterial endotoxin testing

- testing for visible particulates
- visual inspection for container integrity

“This must be signed and dated by a registered pharmacist,” he said. “Ask to see these in writing and check to ensure that the batch number and lot number match. In some cases, a compounder will do a mockup C of A, but when you look, the lot number doesn’t match the product shipped. That means they did it one time, but not on every batch.” The compounder also should be able to show data confirming that the basic formulation of every product they’re compounding will remain stable for 90 days, he added.

An outsourcer’s quality assurance unit should have clear independence from the rest of the operation, Mr. Yamamoto said. “They must be given the responsibility of approving and rejecting all products. I’ve seen several 483s that say the quality entity was not given the authority to do this. Releasing product is not a decision that should be left in the hands of pharmacists—sorry, pharmacists. You need a variety of quality employees. Your chemists don’t do the microbiology methods; your microbiologists don’t review the chemistry data. There are many roles within the quality segment, and everyone there should be trained in CGMP.”

Multistep Process

Ensuring a supplier has an integrated system is itself a multistep process. It should start, if at all possible, with on-site audits. “You need to see the facility and validate with your own eyes what is going on,” Mr. Yamamoto said. “You should interact with the leaders in quality, production, pharmacy and compliance, and view their documentation. We’ve had customers ask us to complete paper-based surveys, but they don’t come close to giving you the information that you really need.”

Before the site visit, prepare by reviewing the FDA’s 483 reports on the supplier. “They are the best independent arbiter of what a supplier is doing. Look at what elements the 483 addresses,” Mr. Hinchen said. “Is there a problem with room certification, with the facility showing weakness? Is there an issue with aseptic practice, pointing to the production system? On your site visit, you can then ask focused questions about room certifications, about the calibration program, about whatever the 483s have identified.”

The company should be able to provide a written explanation to the pharmacist—the potential partner—as to what is being done to address any issues raised in the 483s, Ms. Kienle said. “If they have an explanation and a clear plan of action for correction, then [they shouldn’t be eliminated] from consideration. But if they say they don’t think that the 483 accurately represents what they’re doing, then I would be more concerned.”

There isn’t a single compounder in operation today that hasn’t had a recall or a 483 report, the experts reiterated. But most of the time, when there’s a breakdown in one of the pillars of a good sterile compounding operation, the other pillars should act as checks and balances on that one. “An integrated process means that you have controls all the way through, and that’s what you need to look for,” Mr. Hinchen said. “Don’t rely on glossy brochures.”

Mr. McGuire compared the integrated quality components of good sterile compounding with those that maintain human homeostasis. “The human body has 11 different support systems designed to maintain optimum physiological function. If any of those support systems malfunctions, it’s an indicator that you may not be 100% healthy. Similarly, the quality of a compounded sterile product is tied to the quality systems built into the entire process, and each part must be monitored, reviewed and found in working order prior to the product release.”

—Gina Shaw

7 Steps for Choosing a 503B Partner

If being certified as a 503B facility is a necessary, but not sufficient, prerequisite for an outsourcer to make your initial list of possible sterile compounders, and having an FDA Form 483 citation or even a recall isn’t necessarily enough to eliminate a company from contention, how should your hospital go about choosing an outsourcer? There are seven key components of an integrated quality management system for sterile compounders, according to Stuart Hinchen, the founder and CEO of QuVa Pharma, who stressed that you should be reviewing all of these steps with any outsourcer you’re considering.

1. Facility systems. This area involves room certification, maintenance and calibration of equipment.
2. Regulatory and pharmacy. This pertains to compliance with all relevant agencies, including state boards of pharmacy, the Drug Enforcement Administration, the Occupational Safety and Health Administration, and, of course, the FDA.
3. Validation. “This is where you’re proving—before you start manufacturing the product—that you have the process under control,” Mr. Hinchen said. “You’ve done stability studies: You know how the product is going to react in the container and that, at the end of its shelf life, it’s going to be as good as the day you put it out. This is very often not done in the 503B sphere.”
4. Materials. Before bringing any materials into the system, the outsourcer must do supplier qualification and testing. As it does business with its own suppliers, the outsourcer should continue to ensure those vendors stay in a state of compliance with the FDA and that each batch sent is in accordance with specifications.
5. Production. This critical component is all about sterility assurance, including cleanroom design, aseptic technique, operations under the hood, all the way to core building airflows. “It also takes into account cross contamination and segregation, and building monitoring systems so that you have something to tell you if you leave a door ajar,” Mr. Hinchen said.
6. Quality assurance. The outsourcer should have an independent quality unit that oversees what’s happening in the production system: reviewing aseptic practice, assembling documents to create a batch record, and ensuring that the appropriate people are signing off on processes.
7. Quality control. This involves final testing of the product for sterility, potency and presence of endotoxin. Although this aspect is getting the lion’s share of attention, Mr. Hinchen cautioned that it only offers 95% confidence. “Even if you’re following USP [U.S Pharmacopeial Convention Chapter] <71>, which sets out a sampling plan for sterility testing, in order to have 100% confidence in your product , you have to make sure all of these other systems are integrated and doing their job. You can’t latch onto one aspect of a program.”

—G.S.