On January 8, 2014, Margaret A. Hamburg, MD, Commissioner of Food and Drugs, sent a form letter to hospital pharmacists. That doesn’t happen very often. But Dr. Hamburg had something of critical importance to say: She encouraged the pharmacists to ask the compounding vendors they deal with to register with the Food and Drug Administration (FDA) under a new program called “503B” authorized by the Drug Quality and Security Act (DQSA).

Congress passed the DQSA in November 2013. Its compounding provisions grew out of the catastrophic events of late 2012, when contaminated compounded steroid injections made by the New England Compounding Center (NECC) caused a fungal meningitis outbreak leading to infections in more than 750 individuals and the deaths of 64 people across 20 states. The FDA had inspected NECC facilities and found suspect conditions, but had failed to force the company to make the kind of improvements that would have prevented the fungal meningitis disaster. Part of the FDA’s failure was related to enforcement limitations it faced under provisions in the Food, Drug, and Cosmetic Act. The new, voluntary 503B program allows compounders who ship nonpatient-specific prescriptions of sterile and (maybe) nonsterile compounded pharmaceuticals to register with the FDA and be held to much higher standards than NECC and others in that category ever had to meet. The FDA will regulate and inspect 503B pharmacies, and the 503B list is supposed to be a de facto FDA “Good Housekeeping” seal of approval. As of early May, 42 compounders were listed on the FDA website as having registered.

But on its website, the FDA provides all sorts of cautionary clarifications as to the reliability of 503B outsourcing facilities. It says purchasers will have “assurance that conditions at that facility met applicable current good manufacturing practice [cGMP] standards at the time of the inspection” if the facility has had “a recent satisfactory FDA inspection.” But only nine of the 42 pharmacies on the list have had an inspection since registering this year. In each case, the FDA issued a Form 483 as a result of the inspection. The FDA website says: “An FDA Form 483 is issued when investigators observe any significant objectionable conditions. It does not constitute a final agency determination of whether any condition is in violation of the FD&C Act or any of our relevant regulations.” Many of the other 42 have received Form 483s in the past few years, and some of them then got warning letters from the FDA.

So hospital pharmacists looking to the 503B list, per Dr. Hamburg’s urging, can be excused for being a bit perplexed at what looks not so much like a “Good Housekeeping” seal of approval but rather a list of pigs in a poke. Some of the facilities on the list may have floors that one could eat off of. Others may have floors that one wouldn’t want to walk on.

Skepticism Toward 503B Registrants

The International Academy of Compounding Pharmacists (IACP) “is very disappointed with FDA’s current actions on recommending that stakeholders only do business with 503B registered outsourcing facilities even while acknowledging that such registration alone does not guarantee any safer compounded medications or promote public health,” states David G. Miller, RPh, the IACP’s Executive Vice President and CEO. “FDA is blatantly recommending that stakeholders do business with facilities that have fulfilled no other safety requirements except simply filling out paperwork to register with the FDA.”

Some hospitals realize the limitations of the 503B list. Where resources are available, they are double-checking the outsourcing facility’s bona fides.

“We also have an annual on-site evaluation of our compounding vendors,” explains George Hill, RPh, MBA, Catholic Health Initiative’s Director of Pharmacy Services. “We discuss FDA communication specific to their facility at that time. We have developed a checklist of items we evaluate at our on-site inspection. Our annual inspection includes an independent auditor and a pharmacist with expertise in USP 797 standards,” the U.S. Pharmacopeia guidelines that cover compounding of sterile preparations. “Every two years we include an additional inspector who has a microbiology background and consulting experience advising pharma with sterile manufacturing process. We expect corrective action plans based on the on-site inspections and we incorporate resolution of corrective action planning into our vendor agreements.”

Not only did the DQSA change the outsourcing regulatory landscape, it also made some adjustments in the in-hospital or in-retail compounding environment. It did that by making changes to Section 503A of the Food, Drug, and Cosmetic Act, which has been around since 1997. It regulates in-pharmacy compounding, and puts state boards of pharmacy in control of policing that compounding. That will remain the case: State boards will continue to inspect hospital and community pharmacies that compound.

The constitutionality of the provisions originally included in 503A have been challenged in federal court over the years, and some of them were set aside. Given that shaky legal ground, the FDA never clearly defined the 503A provisions over the years they were in effect. That led to confusion, at times, as to...
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whether state boards of pharmacy or the FDA should inspect and/or regulate pharmacies doing various kinds of compounding. The DQSA ostensibly cleared up that confusion. The FDA issued draft guidance on implementation of both 503A and 503B in January 2014. Both draft documents gave pharmacy providers cause for concern and raised as many questions as they answered.

“It is unfortunate the FDA is not moving faster to clarify some of these issues, but I am sure they have a process to follow,” says T.J. Johnsrud, RPh, president of Nucara, a pharmacy company with four 503A pharmacies in three states. Johnsrud explains that he is considering starting a 503B pharmacy but has received conflicting answers on such things as whether they can manufacture nonsterile compounds and which drugs they can make. “It is not clear whether the FDA is going to require compliance with the pharmacy industry cGMP or something else. It would be helpful if they made it easier to do small-batch, sterile compounding. That is why we haven’t pulled the trigger.”

The DQSA’s key provision established the new 503B federal regulatory program for bulk compounders such as NECC that can voluntarily register as “outsourcing facilities.” Any companies selling bulk compounded drugs without first receiving a prescription for a particular patient theoretically should register voluntarily. If they do not, they are supposed subject to the same requirements that conventional drug manufacturers such as Pfizer, Merck, and the rest have to meet, and failure to satisfy those requirements, in areas such as GMPs, opens the compounder to heavy penalties, also approved by the DQSA. Again, pharmacies that prepare only patient-specific compounded drugs—although there is some undefined leeway in that regard—will be regulated by each state’s board of pharmacy.

503B List Open to Interpretation

As of early May 2014, 42 pharmacies had registered under 503B. Those 42 are a tiny fraction of the bulk pharmacies that hypothetically, because they provide nonpatient-specific medications, should voluntarily register. On one hand, the 42 deserve considerable credit. They have raised their hands and said they want to be held to a higher standard. However, the DQSA told the FDA to develop a set of cGMPs specifically for 503B pharmacies. Those practices have not been proposed, so the FDA is starting to inspect the 42 against standards that are not yet in place. “I have spoken to some of the pharmacies on the list of 42 and know some are spending hundreds of thousands of dollars to upgrade their facilities,” says Joe Caballeiro, RPh, Associate Director of Pharmacy at the Accreditation Commission for Health Care, which accredits pharmacies.

Still, the list of 42 503B outsourcing facilities would give anyone reason for pause. For example, the first compounder on the list of 42 is Advanced Pharma, Inc., of Houston, Texas. It registered on January 22, 2014. The FDA completed an inspection on March 17, 2014, and issued a Form 483. It discusses a number of shortcomings at the Houston facility, including some in the category of procedures to prevent microbiological contamination of sterile products.

Bourjois Abboud, RPh, MBA, President of Advanced Pharma, says those kinds of observations—and they are common on Form 483s issued to many of the 42—should give potential hospital pharmacist customers pause for concern. But he explains that Advanced Pharma, like many of the others, is in the process of transitioning from an environment where it complies with USP 797 to one where it complies with FDA GMPs written especially for 503B pharmacies. Those have not even been published yet, which means 503B registrants such as Advanced Pharma are not sure what FDA inspectors will be looking for. “So the important thing to ask is, what is a 503B pharmacy’s response to a 483, and what corrective action is it taking,” Abboud states. Soon he expects to complete a significant expansion to the present facility that began in 2013 with the speculation of FDA governance and GMP standards. This expansion represents a seven-figure investment that he feels puts his company ahead of the yet-to-be-issued standards, Abboud says.

Johnsrud points out that under USP 797 the sterility of the finished product is emphasized as opposed to the facility and the process, which is what a cGMP additionally attempts to ensure.

Abboud emphasizes that he and other leaders in the bulk sterile compounding business have long wanted the FDA to regulate and inspect their facilities. That is because Advanced Pharma and other companies have been unable to sell products to hospital pharmacies in states that require in-office use, meaning that the hospital must be able to produce a specific prescription for each dose it purchases from an outside vendor. Now Advanced Pharma plans to market to hospital pharmacies in 48 states.

Inspections Have Turned Up Issues

There is no way to sugarcoat the Form 483s issued before and after January 2014 to almost all of the pharmacies on the 503B list. Almost all are designated “open.” The FDA explains that designation this way: “Open does not mean that FDA has determined that further action will be taken. It means only that a determination has not yet been made. If an action has been taken, it will be listed. Possible FDA actions may include: warning letter; seizure; or injunction.” The Form 483s paint a picture of endemic sloppiness.

The FDA inspected Allergy Laboratories, Inc., in Oklahoma City, Oklahoma, the third compounder on the list of 42, in April 2013. A Form 483 was issued as a result of that inspection. Then the FDA issued a warning letter on September 4, 2013. One paragraph from that letter states:

The deficiencies described in the Form FDA 483 issued at the close of each inspection referenced above and this letter are an indication of your quality control units not fulfilling their responsibility to assure the identity, strength, quality, and purity of your licensed biological drug products and intermediates. These serious deficiencies from the applicable regulations and standards described above, when viewed collectively, represent the extensive failure of your firm to maintain control over the manufacturing process, including 1) release of product, 2) monitoring of the process, 3) appropriate response to a failure in the process, and 4) process controls. These critical aspects of the operation are objectionable and accordingly, the agency lacks confidence in your firm’s ability to manufacture pure, potent, safe and effective products.

Rebecca Johnson, president of Allergy Laboratories, did not return phone calls.
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Cantrell Drug Company in Little Rock, Arkansas, has an open warning letter, while its president, Dell McCarley, PharmD, is president of the newly launched Specialty Sterile Pharmaceutical Society (www.sterilepharma.net). A Form 483 was issued to Cantrell Drug on November 2, 2013, and remains “open.” It includes numerous complaints, including entries in a section titled: “Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established.” Dr. McCarley did not respond to phone and e-mail requests to be interviewed.

The FDA has never inspected some of the registrants. A state regulatory agency may have done so, but no information in that regard is posted on the FDA website. The second registrant listed alphabetically that has never been inspected by the FDA is Banner Health in Chandler, Arizona. Repeated requests to the Arizona State Board of Pharmacy asking whether it has inspected Banner went unanswered.

Even if a hospital pharmacist does find a spotless 503B pharmacy, it is not clear what compounds he or she may purchase from that outsourcing facility. Johnsrud says he has heard conflicting reports about what a 503B pharmacy can manufacture. The 503B draft guidance document says the list of acceptable products will come into play if a potential compounded drug does not comply with the standards of an applicable USP or National Formulary monograph. If such a monograph does not exist, then the substance must be a component of an approved drug product. If the substance used is neither of the above, then the bulk substance must be included on a “positive list.”

The FDA first published a proposed positive list of such substances in 1999. That list contained 20 substances that the FDA initially recommended, and another 10 then still under FDA consideration. The FDA did not issue a final rule adopting the 30 substances or otherwise finalize the list. On December 4, 2013, the FDA withdrew that proposed rule and bulk substances list, stating it would reconsider the substances on the original list and requesting nominations for specific bulk substances to be included on a new list.

Can pharmacists still compound those 30 drugs in the absence of an FDA list? Jim Smith, President of the Professional Compounding Centers of America, says:

To now preclude their use, after this prolonged period of permissible use, until finalization of a new list, would mean disruption for the physicians who prescribe these therapies and the untold number of patients who have come to rely upon them. Bulk substances that illustrate the importance of continued access include: betahistine, cantharidin, diphenylcyclopentenone, piracetam, and quinacrine HCl.

What Are “Limited” and “Inordinate” Under 503A?

While it is mostly hospital pharmacists who will be concerned about bulk purchases from 503B outsourcing facilities, both they and community pharmacists will have to pay attention to the new complexities evolving out of the tightened-up 503A program. Those new provisions have particular relevance for hospital pharmacies because one of them will detail the extent to which hospital pharmacies can distribute compounded drugs beyond a certain number (that metric is among the many things undetermined) to other hospitals or clinics in the health system that happen to be located across state lines from the pharmacy where the compounding takes place.

There will be two distinctions here. First, if the compounding pharmacy is located in a state that has not executed a memorandum of understanding (MOU) with the FDA, it can sell interstate no more than 5% of the total prescription orders dispensed or distributed by the individual or firm. The FDA is supposed to come up with a model MOU in conjunction with the National Association of Boards of Pharmacy. The FDA published a draft MOU back in 1999, but it was never finalized. If the state does sign an MOU, the hospital pharmacy does not face that 5% restriction.

The American Pharmacists Association (APhA) wants the FDA to reconsider the inclusion of the 5% limitation on compounded drug products as the default “non-MOU” metric. Its comments to the FDA say the agency needs to clarify how it will calculate “total prescription orders.” Is this calculated on a monthly, quarterly, or annual average basis? How is the baseline established, and if there is a temporary spike (e.g., for a drug in shortage), how would that affect a pharmacy’s compliance? Further, because the FDA has failed to provide any basis for this number, the 5% limit appears arbitrary at best.

Other elements in the draft guidance affect all state-regulated 503A pharmacies, not just those shipping interstate. One allows a licensed pharmacist or licensed physician to compound “in limited quantities before the receipt of a valid prescription.” There is no definition of “limited quantities.” The FDA has never defined that term, and the draft guidance doesn’t take a shot at doing so, either. The draft guidance also states that a pharmacist or physician should “not compound regularly or in inordinate amounts any drug products that are essentially copies of commercially available drug products.” “Inordinate amounts” is not defined either.

“This language has affected how much high-risk compounding we do internally. There may be some subjectivity surrounding how ‘compound regularly or in inordinate amounts’ can be interpreted,” states CHI’s Hill. “The draft guidance and all the events involving adverse drug events (ADEs) have caused us to examine our compounding practices more closely. We have advised our membership to use high-risk compounding only when other means of acceptable procurement have been exhausted.”

How Far Does FDA Authority Go Under 503A?

An equally fundamental question is what standards a pharmacy will be held to when compounding drugs on its own premises. Congress made it clear when writing the new 503B section that the FDA must make sure that outsourcing facilities are complying with USP chapters 795 and 797. It did not amend 503A to require the same for in-house, 503A pharmacies. “It would appear, absent Congressional action, FDA does not have the legal authority to enforce compliance with 795 and 797 for pharmacies exempt under 503A,” states the PCCA’s Smith. “PCCA fully supports compounding in compliance with USP 795 and 797, encourages states to adopt these standards (as many have), and provides significant training and education on the same; regulation and enforcement of these provisions should remain a matter of state, not federal law.”

The USP 797 issue is academic in many states, where com- continued on page 435
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pliance is required by the state board of pharmacy. That is the case in Iowa, Illinois, and Texas, according to Johnsrud, whose four sterile pharmacies operate in those states.

But the answers to many of the open questions about the new compounding landscape are clearly not academic. The longer confusion reigns, the more likely it is that another NECC type of problem will develop.

REFERENCES


