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By Scott Sutton, PhD

Choosing a 503B Outsourcing Facility

Recent well-publicized compounding failures have prompted lawmakers and the Food and Drug Administration (FDA) to take measures to ensure medications are compounded safely, especially those compounded for outsourcing to hospital pharmacies or distributed nationwide. As a result of these compounding tragedies, Congress revised the Food, Drug, and Cosmetic (FD&C) Act, creating a new form of pharmacy–the Outsourcing Facility–under section 503B.[1] According to draft guidance issued by FDA in July 2014,[2] these 503B pharmacies function as limited pharmaceutical manufacturers and are required to observe an abbreviated version of current good manufacturing practices (cGMPs), as described in 21 CFR 211.[3]

Under section 503B, an outsourcing facility is defined as a facility at one geographic location or address that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of section 503B.[4] Outsourcing facilities:

- Must comply with cGMP requirements
- Will be inspected by the FDA according to a risk-based schedule
- Must meet certain other conditions, such as reporting adverse events and providing the FDA with certain information about the products they compound

An outsourcing facility can qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not the exemption from cGMP requirements.

The FDA urges hospital pharmacies to purchase compounded sterile preparations (CSPs) only from 503B outsourcing facilities (see **SIDEBAR**). To assist in that endeavor, FDA maintains a listing of currently registered 503B pharmacies on their Web site.[5] This list is updated regularly and includes the date of each facility's most recent inspection. Upon review of this list, it is clear that most registered 503B facilities are not compliant with significant portions of cGMPs. The majority of these pharmacies have received form 483s (observations questioned by a team of inspectors during an audit) or even warning letters (more serious compliance problems that must be resolved immediately). This leaves the hospital pharmacist/purchaser with a dilemma: How can the hospital identify quality sources for required CSPs given that FDA expects purchasing only from 503B facilities, most of which have received 483s? Fortunately, hospital pharmacists have more information available than ever before regarding the operations of such pharmacies. Using such information to perform due diligence in evaluating outsourcing facilities is vital to ensuring the safety of CSPs.

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Understanding cGMPs

cGMPs have evolved over the past century in response to specific hazards affecting the public and are in place for good reason. The practices are intended to prevent the recurrence of issues that led to previous outbreaks (an excellent overview of the evolution of cGMPs is available at http://gmpnews.ru/wp-content/uploads/2010/05/History-gmp.pdf).[6]

Traditional pharmacies, designated as 503As, assign beyond-use dating (BUD) measured in hours for most CSPs, and when used immediately, CSPs do not allow for microbial growth to the same degree as pharmaceutical products, which typically have expiry dating measured in months. Conversely, 503B facilities may compound large batches of CSPs and store the batches before shipping to the customer. Because this scenario is akin to pharmaceutical manufacturing, it is prudent to take advantage of the hard lessons learned in the past that led to the development of cGMPs. Therefore, Congress has empowered FDA with the authority to enforce that 503B outsourcing facilities adhere to cGMPs.

Proactive documentation practices are essential to compliance with cGMPs. Ensuring there is a record of the compounding, testing, and storage of a CSP is vital to investigation should quality issues arise. Frequently, these are the only data available to assist in an examination of a problem.

Approaches to Choosing a 503B

Identifying an outsourcing facility from which to purchase CSPs may seem to be a daunting task; some hospitals may be inclined to give up and simply purchase medications from the lowest bidder, but this approach is strongly discouraged. Others may choose to believe that FDA's stepped-up focus on cGMPs is transient; that no significant safety problems exist; or that the 483s that have been issued are outside the scope of FDA authority (which may be a difficult position for a facility to defend) or insignificant, as they reflect only a lack of documentation, which can be corrected easily. These approaches are fraught with danger.

The FDA is now an integral part of the pharmacy landscape and 503B facilities are expected to comply with cGMPs. Moreover, arguing that 483 observations indicate nothing more than documentation issues reveals a significant naivety regarding the basic nature of cGMPs, for which documentation is the manufacturer's only proof of compliance. Those who minimize 483 citations are ignoring the underlying compliance issues the 483s highlight.

A third approach to identifying suitable outsourcing facilities is to review the outstanding issues pertaining to each of the pharmacies from which you are considering purchasing (483 reports and related documents are available on the FDA Web site[7,8]). Pay particular attention to facilities that received warning letters, as warning letters reflect an elevated level of concern by the FDA district office (warning letters are available with the list of 503B registrants[5]).

Once your review of the specific issues identified by FDA is complete, ask the outsourcing facility to share their reply to FDA, which should detail the pharmacy's resolution of the citations in the 483 report. Should the response to the FDA

SIDEBAR

FDA's Rationale for Purchasing from 503B Pharmacies

In a letter to hospital pharmacy last January, FDA urged purchasing agents to acquire CSPs from 503B facilities.[1] The arguments presented by FDA include:

> *If compounders register with FDA as outsourcing facilities, hospitals and other health care providers that purchase compounded drugs necessary to meet the medical needs of their patients can provide patients with drugs that were compounded in outsourcing facilities that are subject to cGMP requirements and increased federal oversight.*
>
> *As a purchaser of compounded drugs, you can play an important role in improving the quality of compounded drugs by requiring compounding pharmacies that supply drugs to your facility to register as outsourcing facilities. Once they register, you and the patients you serve can be assured that FDA will inspect these facilities on a risk-based schedule, hold them to cGMP requirements, monitor the adverse event reports they are required to submit to the agency, and require appropriate labeling.*

Operating under cGMPs is a new experience for pharmacies recently registered as 503B facilities. The requirements can be confusing, and the preliminary draft guidance published by FDA[2] may be interpreted by some as tentative.[3] But offsetting these concerns is the clear language in the FD&C Act describing FDA authority to conduct inspections of 503B facilities, which should help allay concerns on the part of hospital pharmacists and purchasers regarding the quality and safety of CSPs coming from these facilities.

References

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2. Food and Drug Administration. Guidance for Industry. Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (draft guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf. Accessed October 6, 2014.
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include arguments in favor of retaining current practice, a scientifically justifiable rationale must be included. More commonly, the response to FDA will convey an intent and commitment to rectify the situation that led to the particular observation and will include a timeline for completion. Finally, request a status report of progress toward resolving the issues in the 483 or warning letter.

By evaluating this information, the hospital pharmacist or purchaser can effectively assess the risk associated with procuring from a particular 503B facility. Of course, the possibility exists that an outsourcing facility will ignore a 483 report and perhaps even a warning letter, and as such, not develop a response or strategy. Alternatively, the facility may decide that all such correspondence with FDA is proprietary and will not share this information with you. Consider carefully such reticence when identifying which 503B outsourcing facility to trust with your patients' well being.

Conclusion

This is a transitional time for pharmacies, and often change is undertaken with some level of trepidation. Information is available to assist the hospital pharmacist or purchaser in determining which registered 503B facilities are best qualified to supply CSPs to hospitals. In fact, the argument could be made that more useful information is available now than ever before in the FDA inspection reports. Undertaking a robust review of 503B quality indicators, including form 483s, is a vital step prior to purchasing CSPs from outsourcing facilities. ■

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