FDA’s Proposed 503B Draft Compounding Guidance Raises Concerns of All Kinds

Is the Bar Being Set Too High, or Too Low?

Stephen Barlas

Mr. Barlas is a freelance writer in Washington, D.C., who covers issues inside the Beltway. Send ideas for topics and your comments to sbarlas@verizon.net.

The Food and Drug Administration (FDA) will publish a final guidance document, ostensibly this fall, describing the requirements for outsourcing compounding pharmacies that register under the new 503B program established in the wake of the 2012 New England Compounding Center disaster.

The guidance has been eagerly awaited by hospital pharmacists, who are expected to purchase compounded products from 503B pharmacies that register with the FDA and, if they pass an inspection, receive the agency’s Good Housekeeping-like seal of approval. That inspection will be based on facility sterility, environmental, and other standards just a notch below the current good manufacturing practices (cGMPs) that big-name drug companies must meet. The final guidance will establish those standards. The 503B pharmacies that meet these standards will be able to sell sterile, compounded products in bulk—without first receiving individual prescriptions for individual patients—to hospital pharmacies and other purchasers, such as dialysis centers and nursing homes.

The FDA published draft guidance on potential 503B standards in July.1 It is not clear when the final guidance will be published, but the FDA is under the gun. However, the FDA must reconcile numerous conflicting views about the draft guidance from many players in the industry.

The International Academy of Compounding Pharmacists, which represents many of the 50 or so companies that have registered with the FDA under 503B, is worried that it will take the agency considerable time to publish final guidance (which is not legally enforceable anyway). In the meantime, the FDA presumably will inspect 503B registrants based on the cGMPs for conventional drug manufacturers such as Pfizer and Eli Lilly. But if the FDA eventually publishes less stringent cGMPs for outsourcing facilities, it is unlikely that the 50 current registrants would lower their standards. This would create a dual regulatory system: one set of tough cGMPs for early registrants versus looser 503B “lite” standards for pharmacies that wait for publication of the final guidance.

There are other concerns about the content of the draft guidance. Some, like Joseph Cosgrove, President and CEO of Pentec Health, complain the requirements are “arbitrary and capricious.” Others argue, in effect, that the requirements are too easy and that the FDA shouldn’t be giving 503B pharmacies any leeway beyond what Pfizer, Eli Lilly, and the rest of the big companies must provide in their cGMPs.

The primary focus of the FDA’s draft is on quality assurance for sterile drug products and the safety of compounded drug products more generally, with respect to strength (e.g., subpotency, superpotency) and labeling or drug-product mix-ups. So the guidance establishes requirements for clean-room air quality and monitoring, container handling, aseptic drug processing, testing incoming components, etc.

The FDA is clearly conscious of potential complaints that its requirements are too tough. In the area of laboratory testing of incoming components, for example, the FDA is considering allowing 503B pharmacies to outsource final release testing to a contract testing laboratory. That third-party lab would have to submit a drug master file (DMF) to the FDA with information on how it does its testing, the records it maintains, its quality assurance activities, and other procedures.

But Brad Goskowicz, Chief Executive Officer of Microbiologics, argues that the DMF provides only a description of what a laboratory intends to do. “It does not provide any assurance that laboratory protocols are followed,” he states.

Cosgrove, whose company is considering registering as a 503B pharmacy, thinks the draft guidance sets too high a bar. For example, when a 503B pharmacy compounding fewer than 10 doses for a single patient, based on a single prescription, it would not have to perform sterility testing on those 10 doses if the beyond use date (BUD) meets certain qualifications. Cosgrove wants a more expansive exemption, allowing more drugs to escape sterility testing. He suggests the FDA use the risk-based standards in the U.S. Pharmacopeia (USP) Chapter 797, Pharmaceutical Compounding—Sterile Preparations. Chapter 797 uses low-, medium-, and high-risk categories and establishes different standards for BUD timeframes. The FDA’s draft guidance picks up the “high-risk” standards without specifically mentioning USP 797, so the draft treats all 503B pharmacies as if they are doing high-risk compounding.

Another concern, voiced by industry players such as Jack Maniko, Director of Federal Legislative Affairs for Baxter International, Inc., is that the draft guidance fails to distinguish between sterile drug products that are compounded by combining licensed, commercially manufactured sterile drug products under aseptic conditions and sterile drug products that are compounded from nonsterile bulk active pharmaceutical ingredients (API). He thinks 503B pharmacies compounding products in the second category ought to be subject to cGMPs at the pharmaceutical-company level, with some exceptions for small batch sizes, patient-specific compounding, and products with rapid expiry.

One only has to visit the FDA website to find warning letters the agency has sent to compounding pharmacies this continued on page 758
year about unsanitary conditions and other problems. Continuing quality control issues argue for a comprehensive set of requirements in any final guidance from the FDA. Of course, "comprehensive" is in the eye of the beholder. Still, the FDA seems likely to adopt a fairly strict interpretation.

REFERENCES
