GMPs for Bulk Pharmaceutical Chemical Manufacturers: FDA Is Becoming More Demanding

FDA has focused substantial resources on upgrading pharmaceutical industry compliance with good manufacturing practice (GMP) over the past few years. Two enforcement actions in recent years have clearly boosted FDA's confidence in GMP cases. In an enforcement action against Warner Lambert, the company was forced to close all of its facilities and consent to FDA approved audits before recommencing operations. FDA won that showdown without actually having to litigate any of its GMP interpretations. In contrast, an enforcement action against Barr Laboratories proceeded to a court decision as Barr went the distance in trying to establish that its implementation of GMP was adequate. See U.S. v. Barr Labs, 812 F.Supp. 458 (D.N.J. 1993). The opinion provides a strong endorsement for FDA's conservative approach to the need to validate sampling plans and for all manufacturing decisions to be founded on soundly documented investigations.

A clear message having been sent to the finished pharmaceutical manufacturers, it appears that FDA is now turning its attention increasingly toward bulk suppliers. Facilities that have had favorable inspections over the years are now experiencing inspections with long lists of discrepancies. While most of the observations relate to the need for improved documentation and procedures, some have questioned long-standing procedures that will be costly to upgrade. As part of its ongoing program, FDA has released a revised draft of its Guidance for Industry--Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients (dated April 18, 1998, and available at http://www.fda.gov/cder/guidance/index.htm). This document follows up on a “discussion draft” released in September 1996.

FDA's authority to inspect manufacturers of active pharmaceutical ingredients (APIs) and to enforce GMPs by such establishments is not in question. Until FDA released the discussion draft cited above, however, the most relevant document that FDA had made available was entitled FDA Guide to Inspection of Bulk Pharmaceutical Chemicals. This guide was directed toward FDA's own inspectors. It made clear that bulk operations were different from finished dosage preparation and that more leeway was appropriate in inspecting such facilities. The codified GMPs at 21 C.F.R. Parts 210 and 211 (for finished dosage forms) were identified as an appropriate guide, particularly for final manufacturing steps that should be at the level of GMP required for finished pharmaceuticals. While that general message still gets lip service, the details have changed considerably. It appears that the recordkeeping expectations for a finished pharmaceutical manufacturer are being applied to all stages of bulk production.

One provision that may be particularly troublesome for bulk manufacturers is the need to use potable water, at a minimum, even for the early stages of production--with more stringent water requirements for latter stages. While water quality is an important issue, the reaction and processing conditions involved in many bulk operations are such that the time and money spent to achieve potable water quality before the water enters the bulk process is money down the drain.

The revised draft has some adverse implications with regard to storage requirements. It notes that a written program for stability testing should be followed that includes defined and controlled storage conditions specified on the label for the marketed product (e.g., temperature and humidity). In particular, FDA notes that “[w]here applicable, labeled storage conditions should comply with standard definitions for ‘Freezer,’ ‘Cold,’ or ‘Controlled...”
Room Temperature,’ as defined in the United States Pharmacopeia (USP)” or ICH guidelines. Large warehouses are unlikely to have adequate conditioned air to be acceptable.

API manufacturers should continue to evaluate their GMP compliance status in light of the revised API draft and be prepared with sound science-based support for continuing any practices that are not sanctioned. Manufacturers of excipients should also pay heed to this document since FDA notes that “much of the guidance provided [also] may be useful to the manufacturers of excipients.”

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