



Regulatory Beat: FDA Moves to Streamline GMP Inspections

Fewer field offices and inspectors will increase reliance on manufacturers to ensure product and process quality

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The continued squeeze on funding for the US Food and Drug Administration is prompting the agency to shut down regional offices and some field facilities as one way to make more efficient use of its limited resources. A streamlined inspection program also will try to identify those drug manufacturing sites most in need of frequent oversight, while reducing inspections for less risky facilities. Highly-trained inspectors will be able to assess modern manufacturing systems more efficiently, and field staff will work more closely with FDA Center reviewers to better understand company quality control systems.

These changes in FDA inspection operations fit the agency's Pharmaceutical Quality in the 21st Century initiative, which encourages broader industry adoption of quality control and risk management methods that can better assure quality drug production and distribution with less direct oversight by the agency. Instead of frequent, in-depth plant inspections, FDA aims to initially verify a manufacturer's process control and quality system and followup periodically with more efficient audits, commented FDA deputy commissioner Janet Woodcock. Under the "desired state" of pharmaceutical manufacturing, regulators will use risk-based approaches to make regulatory decisions and further streamline the inspection process, she explained at a March workshop on pharmaceutical quality initiatives co-sponsored by FDA, American Association of Pharmaceutical Scientists (AAPS), and International Society of Pharmaceutical Engineers (ISPE).

STREAMLINING ORA

The reorganization of FDA's Office of Regulatory Affairs (ORA) has been in the works for several months and now is nearing implementation, according to Margaret Glavin, FDA associate commissioner for regulatory affairs. ORA is eliminating its regional structure and closing seven of its 13 field laboratories, a move that has generated controversy since first announced last December. The current plan is to "phase out" labs in Detroit, Denver, Kansas City, Philadelphia, San Francisco, San Juan (PR) and Winchester (MA); laboratories will remain open and will be expanded in Atlanta, Seattle, Jamaica (NY), Cincinnati, Jefferson (AR), and Irvine (CA).

This downsizing of ORA reflects cuts in budget and staff. FDA's field force has dropped from 4,000 in 2003 to some 3,400 today. ORA inspected 2,411 drug facilities in the US and abroad last year, compared to more than 2,600 in the three previous years. Similarly, the agency inspected 1,826 biologics facilities last year, down from about 2,000 in previous years.

FDA's budget proposal for 2008 allots much of ORA's budget increase to food oversight, relying on prescription drug user fees to maintain the current level of drug manufacturing oversight. To bolster its resources, FDA has proposed a reinspection user fee that would collect \$23 million and add 100 field staffers to revisit manufacturing facilities cited for violations in initial good manufacturing practices (GMP) inspections.

ORA's streamlining plan is scheduled to go into effect Oct 1, 2007, unless sidetracked by opposition, which is surfacing within the agency as well as among manufacturers. In addition to nervous field staffers, industry fears more difficulty in contacting field officials and getting answers to specific questions. And members of Congress

have voiced opposition to closing FDA labs at a time of increased public concern about food contamination and medical product safety.

NEW APPROACHES TO QUALITY ASSURANCE

FDA officials would like to shift the focus from counting the number of plant inspections to evaluating how well it can ensure medical product quality and safety. This approach involves adopting efficient strategies for targeting inspections to more high-risk operations likely to have the greatest impact on public health and safety. In addition to a "significant decline in resources for inspections," noted David Horowitz, ORA deputy associate commissioner for compliance, more complex manufacturing processes require more expertise to evaluate.

Moreover, FDA regulatory operations suffer from industry efforts to sidestep the rules, Horowitz commented at the pharmaceutical quality workshop. Industry compliance with GMPs "is bad and getting worse," he said, noting that manufacturers are "studying for the test"—correcting specific deficiencies but not investing in systems that can avoid problems and correct root causes. Modern manufacturing and technological developments provide opportunities for both FDA and industry to establish quality-oriented approaches, Horowitz added, and risk management can better focus and target regulatory and manufacturing activities to "get the most bang for the buck."

FDA is working to help manufacturers adopt innovative approaches for assuring that drugs meet quality standards, as seen in its final guidance on quality systems approaches published last September. Additional guidances will clarify approaches for aseptic processing, process validation, investigating out-of-specification test results, and manufacturing standards for Phase 1 clinical supplies. The anticipated Q-10 standard from the International Conference on Harmonization (ICH) will further describe approaches for harmonizing quality systems on a global basis. FDA also plans to revise its regulations governing Part 11 and GMPs.

MODERN INSPECTORATE

A key ORA initiative is to improve the knowledge and training of pharmaceutical field inspectors so that they better understand sophisticated quality management systems and risk management approaches they encounter at production sites. FDA has improved the operation of its Team Biologics cadre that inspects biotech manufacturing facilities, with an eye to implementing quality management systems approaches. This includes establishing metrics to better assess team performance and to determine the need for improved training and qualification of team members. FDA is working with the Pharmaceutical Quality Research Institute (PQRI) to evaluate Team Biologics operations and its impact on manufacturers, according to Mary Malarkey, director of the Office of Compliance and Biologics Quality in the Center for Biologics Evaluation and Research (CBER).

Similarly, FDA is establishing a Pharmaceutical Inspectorate (PI) to handle inspections of drug manufacturing facilities. Following the Team Biologics model, this group of highly trained individuals will have the knowledge needed to evaluate facilities that have adopted the latest scientific and technological innovations for assuring drug quality. ORA and the Center for Drug Evaluation and Research (CDER) are working hard to build a cadre of 50 certified PI members by 2007. PI members would spend 80% of their time conducting drug quality inspections, compared to about 25% for regular field inspectors.

WEIGHING RISKS

A main approach for utilizing FDA resources more efficiently is to target inspections and oversight to industry operations most in need of FDA scrutiny. CDER has established a risk-based site selection program for identifying those drug manufacturing facilities to schedule for GMP inspection, based on a range of risk factors associated with products, processes, and facility characteristics. ORA now plans to extend this risk-based model to better target Team Biologics inspections to high priority situations. The long-term goal, says Horowitz, is to develop more outcomes-oriented metrics for evaluating risk.

Another important component of FDA's more science-based inspection process is for field staff to collaborate more closely with Center product specialists and technical experts in evaluating a firm's risk management programs, product and process knowledge, process capability, and quality system robustness. This approach for drugs builds on long-standing procedures in CBER. Postapproval GMP inspections of biotech manufacturers have been performed by Team Biologics together with CBER product specialists for the past decade, Malarkey commented. Such integration begins as early as the investigational new drug application (IND) stage, and is particularly important for dealing with complex and innovative technologies.

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