



FDA Launches Major Review of CGMPs

Jill Wechsler

FDA officials seek to revise manufacturing standards and the plant inspection process to better reflect risk parameters and scientific developments.

The escalating battle between pharmaceutical manufacturers and FDA about compliance with current good manufacturing practices (CGMPs) portends a major overhaul of manufacturing policy. Manufacturers have been complaining about inconsistent and unpredictable enforcement of FDA rules by agency staffers and field inspectors. The uneven enforcement has led to strong enforcement actions, including consent decrees and multi-million-dollar fines. As a result, public health has been affected by plant closings, product recalls, shortages of important therapies, and delays in FDA approval of new drug applications (NDAs).

To avoid protracted disputes, manufacturers are demanding better clarification of GMP policies and improvement in the conduct of field inspections. FDA officials counter that strong legal action is needed because some recidivist manufacturers ignore repeat citations and refuse to comply with regulations (see sidebar "FDA cracks down on GMP violations," page 19). They argue that companies have not invested the necessary resources to ensure the reliable production of safe and high-quality medical products. Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), has commented frequently in the past year about an increase in manufacturing-related problems. She also has voiced concern that outdated GMP policies may deter US manufacturers from adopting innovative production technologies that could efficiently ensure product quality.

With frustration mounting on both sides, FDA deputy commissioner Lester Crawford announced a high-profile initiative in August to reevaluate CGMP policies that apply to human and animal drugs and biological products. The effort aims to focus GMP enforcement on high-risk products,

revise GMPs to encourage new manufacturing technologies, and develop more-consistent and predictable agency policies to ensure drug quality and safety. Mindful that the last major revision of FDA GMP regulations occurred nearly 25 years ago, Woodcock and colleagues in FDA's Center for Biologics, Evaluation, and Research (CBER); Center for Veterinary Medicine; and the Office of Regulatory Affairs (ORA) have been working since June to launch the initiative, "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach."

Factors driving change

The need to take a new regulatory approach to how FDA ensures product quality reflects significant changes in drug manufacturing and in government regulatory processes during the past two decades. These changes include:

A growing number of products. Manufacturers are producing a larger number of pharmaceutical products that are playing an increasingly sophisticated role in providing quality healthcare. This development has focused public attention on adverse events related to prescription drug use and has expanded the range of products and organizations overseen by FDA.

Fewer FDA inspections. FDA has conducted fewer manufacturing inspections because resources are limited for ORA field activities. Woodcock noted that FDA conducted more than 4200 GMP inspections in 1980 but only approximately 1400 last year. FDA now visits most manufacturing plants every five or six years instead of biennially, as recommended by FDA policy. Consequently when FDA inspectors finally show up, they often find numerous problems, and by that time many of the problems are difficult for manufacturers to resolve easily.

Advances in technology. Advances in pharmaceutical sciences and manufacturing technologies are offering new methods for industry and FDA to ensure product quality. CDER is promoting a process analytical technology (PAT) initiative to encourage manufacturers to adopt new systems

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that can increase manufacturing efficiency and improve quality control (see *Pharmaceutical Technology's* "Washington Report" column, February 2002). FDA plans to implement the PAT initiative during the next several years.

A change in emphasis. An emphasis on risk-based regulation aims to match the degree of government oversight with the magnitude of risk associated with public use of a regulated product. With resource limitations preventing FDA from providing a uniformly high level of oversight for all regulated products and manufacturing facilities, the agency increasingly seeks to emphasize risk-based control-point analysis. This approach has shaped new policies for FDA oversight of foods and medical devices and provides a model for regulating drugs and biologics. One likely result is more-frequent inspections of plants that produce injectable therapies than of plants that produce other dosage forms.

International harmonization. The globalization of the pharmaceutical industry has fostered a 10-year effort to develop common international standards for drug testing and quality assurance. This effort has streamlined the drug regulatory process but emphasizes the need for FDA to ensure that any new manufacturing policies mesh with continuing harmonization efforts.

First steps

FDA's GMP reappraisal process is expected to take at least two years. Several proposals will shift more responsibility for manufacturing compliance from field inspectors to FDA centers. The agency has outlined many long-term goals but plans to begin the process with the following initial actions:

External review. FDA plans to conduct an external review of its current GMP enforcement program and agency product-review practices. Outside consultants would examine the agency's management capabilities and scientific approach to both the application-review process and the GMP-inspection program. The aim is to ensure a consistent, integrated systems approach to regulation so that FDA's pre-approval chemistry, manufacturing, and controls (CMC) review fits with its plant-inspection program.

Discussion. FDA personnel aim to meet with manufacturers, pharmaceutical scientists, and other interested parties to discuss scientific concerns and assess innovative technologies and approaches.

Warning letter reviews. FDA centers will provide a scientific and technical review of all drug CGMP warning letters that are issued from FDA's field offices. ORA assumed responsibility for issuing inspection warning letters several years ago to reduce delays in disseminating them. The present challenge is to expand CDER's involvement in developing warning letters without impeding the process of communicating manufacturing deficiencies to industry. Earlier this year, FDA's general counsel began to review all warning letters for potential legal problems, a process that is expected to continue.

Dispute resolution. FDA plans to establish a technical dispute resolution process. Technical experts from FDA's

FDA cracks down on GMP violations

FDA has ratcheted up enforcement of GMP standards in recent years, partly to offset streamlined oversight of low-risk manufacturing changes and modified CMC filing requirements. However, instead of finding increased voluntary compliance, agency inspectors and compliance officers are discovering extensive GMP violations that warrant strong legal action. For example, in May 2002 Schering Plough (Union, NJ) signed a consent decree with FDA agreeing to comply with measures to ensure that products made in its New Jersey and Puerto Rico plants comply with GMPs. Schering paid a record \$500 million fine to disgorge profits made on drugs produced during the past three years at its violative facilities. Much of the fine will cover FDA's cost of conducting 13 inspections at four Schering plants since 1998, and the company is expected to spend an equally large amount updating facilities and systems, expanding staff training, and engaging experts to bring its operations into full GMP compliance.

Other manufacturers also have felt the heavy FDA-enforcement hand. In May the agency negotiated a GMP consent decree with Watson Laboratories related to violations at its Corona, California plant. Abbott Laboratories paid a \$100 million disgorgement penalty

as part of a 1999 consent decree. Wyeth was hit with a \$30 million penalty two years ago to resolve manufacturing problems at various plants. Eli Lilly and Warner-Lambert negotiated earlier consent decrees with FDA to resolve GMP issues.

FDA officials acknowledge that efforts to ramp up fines and take legal action against industry leaders are intended to encourage broader corporate compliance with manufacturing standards. Early this year, FDA general counsel Daniel Troy announced that his office would examine all warning letters before their release to determine whether the agency was taking sufficiently strong legal action against those manufacturers that failed to correct problems despite repeated citations for GMP violations and warning letters.

FDA also is using GMP violations as a reason to delay NDA approvals. In July, Eli Lilly executives acknowledged that the company might be delayed in bringing three new products to market because of difficulties resolving manufacturing concerns raised by plant inspectors in a March 2001 warning letter. Other manufacturers are experiencing similar difficulties.

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centers will participate in an ongoing forum for addressing manufacturing concerns and perceived inconsistencies among agency offices and the field force.

Implementation of 21 CFR Part 11. CDER will gain the lead responsibility for implementing 21 CFR Part 11, FDA's electronic-signature and electronic records

policy. This responsibility was shifted to ORA in an effort to establish uniform policies for electronic filing systems throughout FDA. The highly complex nature of electronic submissions and the extensive implementation of these policies for drugs are prompting the agency to put the problem back in the hands of CDER experts, with continued involvement of other centers and ORA.

Improve the plant-inspection process. Last year, CDER launched a new systems-based GMP inspection program designed to enhance oversight of manufacturers' quality control systems. The program requires that inspections focus on a few key production systems to determine whether the operation is under control. Following a successful initial pilot program, CDER expanded the program in February 2002 to all US and international drug establishment inspections.

FDA soon will explore additional ways to improve manufacturing oversight. One proposal is for CDER drug product specialists to accompany field inspection teams, particularly for visits to sites that produce innovative products or that have experienced manufacturing difficulties. FDA also is seeking to enhance the operations of Team Biologics to make this ORA inspection program for biotech manufacturers more timely. A future initiative may be to establish dedicated cadres of pharmaceutical inspectors similar to the Team Biologics approach. A special field force assigned to pharmaceutical inspections could be trained more extensively about guidance policies and would be better equipped to handle more-complex or problematic products and organizations.

Facilitate manufacturing changes. Manufacturers would be encouraged to improve production processes by reviewing which manufacturing changes require FDA prior review and approval. The agency aims to expand the use of comparability protocols and other procedures that can document product quality and safety with reduced FDA oversight.

Enhance FDA expertise. FDA seeks to improve its expertise in scientific and technical areas by expanding training for agency staffers, hiring more employees with expertise in pharmaceutical engineering and industrial pharmacy, and leveraging outside expertise.

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Overhaul or update?

These initiatives will help Woodcock's GMP steering committee determine the need for significant revisions in CGMP regulations. Agency officials generally believe that the current rules are sufficiently flexible to permit FDA to define new manufacturing policies and approaches through guidances, although some rule changes may be in order.

FDA leaders must decide soon whether it will continue work on a May 1996 proposal for revising GMPs, an initiative that aimed to expand and improve manufacturer process validation. The proposal generated numerous comments from industry, many complaining that the new rules were too specific and would be costly to implement. FDA is continuing to evaluate these comments and is weighing whether the regulatory proposal should be included in the current reevaluation effort or if it should be abandoned altogether.

FDA policy makers also are reviewing a proposal to clarify agency policy for aseptic processing, another hot topic already on the GMP revision agenda. FDA issued a draft guidance about this matter two years ago to update a 1987 policy and has worked with the Parenteral Drug Association and other manufacturer groups to develop consensus about acceptance criteria for media fill of parenteral products. FDA has developed a concept paper about the issue that spells out its preferred approach. This document is slated for review

by CDER's Pharmaceutical Sciences Advisory Committee at its meeting in late October.

Another GMP initiative now underway involves updating FDA standards for assessing uniformity and homogeneity of pharmaceutical powder blends. This topic has been a prime focus of the Product Quality Research Institute (PQRI), which brings together brand- and generic-drug manufacturers, academics, and FDA scientists to assess scientific and technical concerns related to drug manufacturing. The organization issued a proposal in March to revise FDA policy for verifying uniform drug content by shifting from frequent testing of the blend to more sampling of finished or intermediate drug dosage units. Consequently, FDA withdrew a controversial 1999 draft guidance that emphasized blend sampling. Agency staffers have raised some technical questions about the PQRI recommendation, but manufacturers believe they can resolve the problems quickly so a revised blend proposal can be released by the end of the year.

PQRI leaders seek to play a significant role in the GMP-revision initiative. The organization recently established its Manufacturing Technical Committee to address PAT-related issues. Broadening the PQRI portfolio to include GMP issues is “a logical extension” of efforts to develop appropriate standards to ensure the continued manufacture of high-quality pharmaceutical products, according to Tobias Massa, executive director of regulatory affairs at Eli Lilly and chair of the PQRI Scientific Steering Committee. Pharmaceutical Research and Manufacturers of America also strongly endorses FDA’s GMP review and has formed an internal working group to respond to agency proposals.

Continuing enforcement

FDA officials insist that the agency will maintain strong GMP enforcement activity as it adopts a more risk-based approach to GMPs. Even though some GMP violations may not pose direct safety risks, the agency believes that compliance fail-

CDER to regulate biotech therapeutics

In a surprise move, FDA deputy commissioner Lester Crawford announced last month that the Center for Drug Evaluation and Research (CDER) will assume responsibility for reviewing and regulating all pharmaceutical products, including biotech therapies now overseen by the Center for Biologics Evaluation and Research (CBER). The consolidation of new drug regulation was unexpected but is not a radical idea. FDA frequently has combined and separated oversight for drugs and biologics in the past.

The decision to shift oversight of biotech therapeutics to CDER in part reflects the continued maturation of biotech manufacturing and quality control processes. The shift also arises from a strong desire from industry for greater consistency in how FDA regulates drugs and biotech therapies. However, some industry executives are concerned about difficulties that may arise from the change. Biotech companies’ greatest fear is that the shift to CDER will open the door to generic biologics. Although Crawford said there would be no legislative change in the

statutory governance of biologics, which currently sets a high barrier to generic versions, these products now will be regulated by CDER officials who are more familiar with generic drug policies than their colleagues in CBER.

FDA is expected to implement its new regulatory structure during the coming year. The switch will be orchestrated by a high-level working group headed by FDA senior associate commissioner Murray Lumpkin, who previously headed CDER’s new drug application review and approval process. CDER director Janet Woodcock and CBER director Kathryn Zoon will participate, along with a cadre of their top aides and representatives of FDA administrative offices. The group will address how the shift will alter the prescription drug user fee program, how it will affect biotech therapies already on the market, and what FDA policies and practices will be altered. Next month, *Pharmaceutical Technology’s* “Washington Report” column will examine the consolidation plan more fully.

ures can create situations that threaten product quality and the integrity of the FDA regulatory system. The main objective of CGMP requirements, the agency explains in its GMP initiative, is to ensure that the American public does not have to wait until injuries or deaths related to drugs or medical products occur before FDA can intervene. GMP requirements aim to “prevent such harms by building quality into the design and production of pharmaceuticals and thereby reducing the risks that deficient drug products will be produced.”

The challenge is to find middle ground between agency micromanagement of manufacturers and overly vague GMP policy. Manufacturers believe that more-specific policy guidance will help them both avoid GMP problems and challenge uneven and unfair citations by field investigators. At the same time, overly specific regulations are likely to generate complaints that FDA is too inflexible and inhibits innovation.

Some industry executives acknowledge that the current battle about GMPs reflects a decline in manufacturer compliance. “Companies have let things slip a little,” one manufacturing expert commented. Industry mergers and new product development have absorbed the attention of corporate executives, who tend to regard manufacturing problems as a black box that they don’t understand.

FDA’s GMP initiative aims to address these trends and tensions. The goal is to gain consensus from manufacturers and regulators about science-based standards that reflect product risk and FDA capabilities. FDA officials acknowledge that they can do a better job of defining agency expectations for industry and communicating policies to field inspectors and center staffs, and manufacturers maintain that they can comply better if they understand the rules. **PT**

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