



GMP Update

Reducing Obstacles to Innovation

Jill Wechsler

FDA offers new policies to encourage modern manufacturing approaches and automated systems, to simplify postapproval changes, and to avoid problems with sterile products.

For the past year, FDA officials have been emphasizing the importance of basing regulations and policies on “efficient, science-based risk management.” In a strategic action plan that was released on 20 August 2003, the agency reiterated its aims to reduce health risks to the public by overhauling and updating methods for manufacturing medical products and to clearly communicate enforcement policies. Last month, FDA commissioner Mark McClellan announced policies that further implement FDA’s risk-based approach to regulating good manufacturing practices (GMPs) for human and animal drugs and biologics.

FDA launched a two-year “Pharmaceutical CGMPs for the 21st Century” initiative in August 2002. The goal is to spur industry adoption of innovative manufacturing technologies and to relate agency oversight of pharmaceutical quality to the risk associated with products and processes (1). FDA announced progress in several key areas in February 2003 (2) and unveiled further proposals last month. These proposals encourage manufacturers to adopt innovative production technologies, while clarifying policies for implementing Part 11 electronic records and electronic signatures, for managing postapproval changes, and ensuring the quality of sterile drugs produced by aseptic processing (GMP progress report, guidances, and other documents are available at www.fda.gov/cder/gmp/index.htm).

FDA also is making changes in its plant inspection program. It is establishing a special cadre of highly trained field staff to inspect pharmaceutical facilities and revising its preapproval inspection program to focus on more high-risk products and processes. The agency also is instituting a program for discussing and resolving scientific and technical disputes that are related to GMP issues. These topics and other enforcement innovations will be discussed in next month’s Washington Report.

Rewriting Part 11

FDA has been struggling for years to set standards and rules for how manufacturers should ensure the integrity of electronic records and signatures that replace paper documents that are required by FDA for a variety of purposes. The agency adopted final regulations that implemented 21 *CFR* Part 11 in March 1997, only to face continual complaints from the industry that the rules were too costly to carry out and discouraged the use of electronic technology, innovative manufacturing, and information systems. Issues came to a head recently as FDA inspectors began to cite firms for noncompliance with Part 11 during GMP inspections, and companies indicated that they would go back to paper-based record systems to avoid Part 11-compliance problems.

In response, FDA launched a broad review of Part 11 and computer validation issues as part of the agency’s risk-based regulatory initiative. A first step (August 2002) was to shift lead responsibility for overseeing Part 11 to the Center for Drug Evaluation and Research (CDER). In February 2003, FDA withdrew several earlier guidances on specific Part 11 components and issued a draft policy announcing its intent to adopt a more-relaxed enforcement posture for this complex policy. Although manufacturers remained responsible for ensuring the integrity of electronic records, FDA said it would use enforcement discretion in applying Part 11 to computer system validation, audit trails, record retention, and legacy systems. FDA stated that “merely incidental” use of computers would not trigger Part 11 requirements.

Now FDA has decided to start over with Part 11 by launching a formal rule-making process to revise the policy, an initiative that will take several years to accomplish. The main task is to revise the preamble to the rule to clarify its scope and intent, explains CDER Director Janet Woodcock.

In the meantime, the agency issued a final guidance for manufacturers to follow while the Part 11 rewrite goes on. The guidance aims to clarify points that were raised in the hundreds of comments that were filed by regulated parties—Part 11 affects electronic records related to clinical research, labora-

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tory testing, data submission to the agency, as well as manufacturing.

The September 2003 final guidance reiterates that FDA does not intend to strictly enforce compliance with requirements for validating computerized systems; maintaining computer-generated, time-stamped audit trails; and ensuring future access to records and copies of records. FDA also will use discretion in calling for legacy systems (those operational before 20 August 1997) to meet Part 11 requirements. Manufacturers must continue to maintain and submit electronic information that meets requirements in predicate rules calling for controls on electronic records systems, written policies, and system checks to ensure the integrity of electronic records and data. Additional guidance may be issued on specific issues during the lengthy rule-writing process.

Promoting process analytical technology (PAT)

One reason for revising Part 11 is to en-

courage the pharmaceutical industry to adopt advanced computerized systems for drug manufacturing. FDA scientists have been working with the industry and systems experts for several years to devise a regulatory policy that will spur voluntary implementation of cutting-edge pharmaceutical manufacturing and quality assurance technologies as part of its PAT initiative.

The need for pharmaceutical companies to follow the lead of semiconductor makers and other high-tech industries in using more-precise and more-efficient manufacturing systems has become a favorite theme of Commissioner McClellan. In a speech at the National Press Club in August 2003, he noted that drug manufacturing processes have not received due attention in the pharmaceutical industry despite the potential for realizing large savings by reducing production costs. Manufacturing methods for many drugs have not changed in decades, McClellan commented, adding that improved regulations that are based on the

latest standards could encourage this process and change drug manufacturing from an "art form" to a science-based activity.

To achieve such gains, FDA unveiled a draft guidance in September 2003 that aims to reassure manufacturers that introducing new manufacturing technologies will not lead to regulatory impasses. The draft policy is "not a typical agency guidance," commented Ajaz Hussain, deputy director of CDER's Office of Pharmaceutical Science. Instead of explaining how to comply with a specific regulation, the PAT guidance ("A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance") describes a range of analytical tools that manufacturers could adopt to establish more-efficient and more-reliable production systems. The guidance also outlines FDA's plan to link its review of applications with PAT data to inspections of facilities with PAT systems to address regulatory issues efficiently and with expertise.

PAT involves systems for designing, an-

alyzing, and controlling manufacturing through the timely measurement of critical quality and performance attributes and processes to ensure final product quality, according to the guidance. It highlights opportunities for improving manufacturing efficiency by "building quality into products" through the use of process analyzers that can measure physical and chemical attributes of materials during processing. Gains in quality, safety, and efficiency could come from reductions in production cycle times and increased automation and real-time release.

Instead of writing new rules, FDA says that it can adapt current regulations to accommodate innovative technologies. The agency is forming a PAT team to coordinate the review of manufacturing data with GMP inspections of facilities that are adopting new technologies. FDA will provide special training and technical support for PAT review, inspection, and compliance staff and is encouraging manufacturers to communicate with the agency early on about plans to implement PAT approaches.

Harmonizing GMPs

The International Conference on Harmonization (ICH) will explore GMP harmonization as part of a discussion of risk-based approaches to drug quality design at the November 2003 ICH6 conference in Japan. At the July 2003 meeting of the ICH steering committee in Brussels, Belgium, a broad group of regulators and industry experts held a brainstorming workshop about this topic and agreed on the need to further address ways to harmonize elements of a life-cycle approach to quality-systems regulation.

The steering committee approved further work on

- pharmaceutical development incorporating elements of risk and quality by design
- incorporation of risk management into GMP compliance policies
- production of a quality-systems scoping document that will address areas of perceived differences among the three regions (United States, European Union, and Japan) regarding GMP issues.

Extending comparability protocols

Although manufacturers are most likely to adopt PAT technologies when building a new plant or production line, FDA says that innovative systems can be implemented for existing products by submitting a comparability protocol (CP) that outlines PAT research, validation, implementation strategies, and timelines. In other draft guidances, FDA offers advice to encourage the industry to develop and file more CPs to manage a broad range of manufacturing changes. The aim is to simplify the agency's postapproval regulatory process and curb the considerable re-

sources that FDA must devote to reviewing thousands of manufacturing supplements. This approach also can reduce the need for manufacturers to obtain prior approval from FDA before making routine changes in equipment, procedures, and ingredients that have little effect on product quality or safety.

In February 2003, FDA issued a draft guidance about developing comparability protocols for small-molecule drugs for humans and animals, including well-characterized synthetic peptides. The guidance describes the chemistry, manufacturing, and controls (CMC) information that is

required to create a protocol that could lower the level of the reporting category for a postapproval manufacturing change.

The new guidance offers similar advice for developing CPs for large molecules (i.e., protein-based drugs and biologicals, including more-complex peptide products). Since 1997, manufacturers have submitted more than 100 CPs to the Center for Biologics Evaluation and Research (CBER) to gain more predictability in making expected manufacturing changes for biologics. The new draft guidance builds on this experience and describes situations in which a CP might be useful (e.g., change in equipment size, raw materials, or production steps), when it would be inappropriate (e.g., a change requiring new clinical data, a product formulation, or a type of delivery system), how it should be submitted to FDA, and what data should be included. The guidance notes that a move to a new facility may be difficult to address in a CP because it could involve many changes that are hard to identify prospectively.

FDA will evaluate comments on this proposal (due on 4 December 2003) and the earlier draft guidance with an eye to issuing final versions in the coming year. The agency also plans to evaluate the number and types of manufacturing supplements that are submitted each year to identify further opportunities to coordinate review and inspection activities and to manage manufacturing changes without the need for prior FDA review or approval.

Revising aseptic processing

Somewhat unexpectedly, FDA issued another long-awaited guidance last month that clarifies policies for manufacturing sterile drug products that are produced by aseptic processing. Ensuring the quality and purity of these drugs and biologicals is a top priority for FDA's risk-based program. Because of their "high therapeutic significance," ensuring a steady supply of these medically necessary products is important, yet the need to meet very high quality standards has led to manufacturing and compliance problems, often creating critical drug shortages.

The new guidance aims to clarify FDA regulatory expectations to avoid such difficulties. It replaces a 1987 guideline that

generated years of debate regarding how best to ensure the purity and quality of sterile drugs where terminal sterilization is not possible. In September 2002, FDA issued a concept paper about the topic, which was discussed in October 2002 by FDA's Advisory Committee for Pharmaceutical Science and then reviewed in detail by an agency-industry working group that was formed by the Pharmaceutical Quality Research Initiative (PQRI). The group compiled information about current industry aseptic processing practices and developed recommendations for the specific topics and text of the concept paper.

The draft guidance addresses key issues such as personnel qualifications, cleanroom design, process design, quality control, environmental monitoring, and review of production records. The fairly lengthy document provides considerable detail about the design of aseptic processing facilities to control air quality, personnel, and material flow to prevent opportunities for exposure. Personnel training, quality, and monitoring are discussed in detail as well as process validation, laboratory controls, and sterility testing. Comments are due on 4 November 2003.

FDA worked hard to issue this guidance because sterile drug manufacturing is the number-one problem in the international arena, explains Woodcock. Many global companies make all their sterile products at one plant, which subjects the facility to inspections by a host of regulatory bodies. The hundreds of detailed rules for sterile drug production are widely disparate, and FDA hopes its proposal will encourage the development of an international approach.

More to come

In the coming months, FDA plans to explore risk-based approaches to sterile drug manufacturing and other production areas at several scientific workshops in the United States and overseas. This program aims to promote cooperation and collaboration in harmonizing international scientific standards about drug product quality and to encourage technological innovation around the world (see Sidebar, "Harmonizing GMPs").

FDA also is establishing additional collaborative arrangements with scientists and the industry to gain scientific and

technical information that is valuable for developing science-based regulatory policies. Last month, the agency announced an agreement with the National Science Foundation's Center for Pharmaceutical Processing Research to expand FDA's familiarity with innovative pharmaceutical manufacturing technology. FDA also has signed a cooperative research and development agreement with Pfizer to research chemical imaging applications in pharmaceutical manufacturing and quality assurance. The agency has commissioned a study that will identify factors that can predict manufacturing performance to help refine its risk-based site selection model for GMP inspections.

A main challenge for FDA in the coming year is to develop a quality-systems approach for its own review and compliance operations. The agency has formed three new working groups to move forward in this area. One group will develop a framework for integrating existing agency quality systems in its centers and field offices by establishing a common vocabulary, written procedures, record-keeping, and review processes. Another working group is preparing educational guidance documents for agency staffers. FDA also expects a report in March 2004 about ways to improve FDA practices for regulating pharmaceutical quality.

Although FDA has issued many of its planned guidances on GMP issues, Woodcock expects that additional technical issues will warrant further clarification through guidance documents. She and her colleagues will be evaluating GMP regulations, how rules for drugs compare with those for medical devices, and the GMP requirements of Europe and other international groups to identify differences and opportunities for harmonization. One important decision will be whether FDA should make broader revisions in FDA GMP regulations or continue to pursue its goals through the guidance-writing process.

References

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