



Overhauling Compliance and GMPs

Jill Wechsler

FDA is making changes in inspection processes, postapproval changes, and 21 CFR Part 11 policies to streamline oversight and improve product quality.

FDA is moving boldly and aggressively to update and revise systems for ensuring manufacturer compliance with good manufacturing practices (GMPs). In announcing progress on its initiative to improve regulation of pharmaceutical manufacturing in February, the agency put on hold its controversial electronic record keeping policy and shifted oversight for warning letters from the field to FDA centers. Agency officials also rolled out significant changes in plant inspection policies, a new process for making postapproval manufacturing changes, and other actions designed to encourage modernization of production systems. These initiatives are part of FDA's broader move to develop a risk-based approach to GMP regulation of pharmaceuticals, which was launched in August 2002.

The GMP overhaul is headed by the Center for Drug Evaluation and Research's (CDER) director Janet Woodcock, but also applies to biological and veterinary drugs. As described in a six-month progress report (see www.fda.gov/cder/gmp/index.htm), the initiative involves dozens of staffers in FDA centers, district offices under the Office of Regulatory Affairs (ORA), and the commissioner's office who are developing a broad range of policies. Another update is expected in six months as FDA gains input from industry and other parties (see sidebar, "Working together").

Reinventing inspections

A major thrust of the program is to make the GMP inspection process more efficient. FDA acknowledges that limited resources prevent it from inspecting every manufacturing plant, warehouse, and packaging facility every two years, as required by statute. The agency consequently seeks to target inspections to higher-risk facilities and to

streamline the inspection process itself. Last year, CDER implemented a systems-based inspection program for drugs that focuses inspections on key aspects of a manufacturing process instead of covering the entire plant. The current initiative continues this approach by identifying those higher-risk facilities that should be at the top of the inspection priority list, including

- sterile drug manufacturing operations
- prescription drug manufacturers (excluding medical gas repackagers)
- new registrants not previously inspected.

The agency aims to inspect those higher-risk facilities every two years while visiting the thousands of medical gas repackagers much less often.

The next step is to develop a more complex risk-based model for prioritizing sites for inspection. This process will consider additional risk factors such as extent of patient exposure, type of formulation, and GMP-compliance record of the company. FDA aims to concentrate its resources on those facilities in which noncompliance is most likely to yield the greatest adverse public health consequences, explained David Horowitz, director of CDER's Office of Compliance. His office was reorganized recently to create a Division of Compliance Risk Management and Surveillance. This division will identify high-risk facilities that require more frequent inspections and relate risk data to oversight activities.

In addition to refining inspection priorities, FDA is making significant changes in who conducts inspections, evaluates GMP violations, and determines appropriate enforcement action. These important initiatives will introduce the following key aspects.

Establish a pharmaceutical inspectorate. Similar to the Team Biologics program for biotechnology products, FDA plans to form teams of specially trained inspectors to visit manufacturing facilities. Instead of a central cadre that inspects plants across the country, as with Team Biologics, multiple pharmaceutical inspection teams in ORA district offices will conduct preapproval as well as GMP inspections. FDA hopes to enroll 15–25 drug inspectors in the program by June.

Jill Wechsler

is *Pharmaceutical Technology's* Washington editor, 7715 Rocton Ave., Chevy Chase, MD 20815, tel. 301.656.4634, jwechsler@advanstar.com

Add product specialists to inspection teams. CDER specialists will be more available to participate in field inspections when needed. This is likely to occur for manufacturers using unique delivery technologies such as a new patch. A special process analytical technology (PAT) inspection group will review facilities implementing new production systems. It remains to be seen whether an increased use of specialists slows down inspections, delays approvals, or is too costly, as some fear. If so, FDA may look for ways for specialists to advise inspectors without actually participating in site visits.

Reduce disputes involving inspection deficiencies. FDA is encouraging manufacturers to discuss with investigators any observations listed on a 483 inspection report that a company feels are unjustified scientifically. The aim is to resolve issues early where possible and avoid listing incorrect observations. FDA also will test whether allowing a 48-hour delay in issuing a 483 could resolve scientific and technical issues that arise late in inspections and thus reduce citations and warning letters. The

agency plans a 12-month pilot to determine whether such a delay allows inspectors to consult with FDA experts. The agency hopes that this approach will encourage the use of new technologies, instead of the “don’t use” approach adopted by firms to avoid technical disputes with field inspectors.

FDA also is adding language to the 483 report to clarify that cited deficiencies are only “inspectional observations” and do not represent final agency determination of company compliance with GMP regulations. The aim is to help manufacturers and others understand that these observations are “just one piece” of the overall compliance process, explained ORA chief John Taylor.

Shift control of warning letters to centers. A major change is the transfer of authority for reviewing and issuing warning letters to CDER, Center for Biologics Evaluation and Research (CBER), and Center of Veterinary Medicine (CVM) from ORA. About 10 years ago, FDA transferred warning letter oversight from the centers to the field to

Working together

FDA will seek input from manufacturers on its GMP initiative at a workshop in Washington, DC, 22–24 April 2003. The session is cosponsored by the Product Quality Research Institute and will focus on

- defining risk and quality related to GMPs, including risk clarification and identification
- developing an integrated approach to review and inspection processes, for improving consistency in FDA operations, and for optimal use of specialists and inspectors
- implementing manufacturing changes without prior approval
- further discussion of manufacturing science and associated regulatory processes, including PAT.

speed up and gain uniformity in the compliance process. This latest change again seeks to reduce inconsistencies in warning letters, now citing those that arise from various approaches among ORA district offices. FDA’s chief counsel continues to have final clearance on warning letters, thereby centralizing agency authority and adding weight to final letters.

In CDER, Horowitz's compliance office will conduct a triage on warning letters proposed by district offices. Letters citing obvious violations may be sent immediately, and others that raise technical issues may be reviewed further by a cross-agency group, explains Woodcock.

Establish formal dispute resolution system. FDA plans to create a process for resolving those disputes arising from GMP in-

spection that cannot be resolved informally during or immediately following an inspection. A manufacturer may first request a formal review of a 483 citation by the district office, in consultation with the appropriate center. If the company disagrees with decisions at that level, it can appeal to a dispute resolution panel in the office of the commissioner. FDA is developing criteria for determining when an

issue involves scientific and technique issues suitable for dispute resolution; how and when a firm may seek such reviews; how FDA will resolve internal disagreements arising from such deliberations; and methods for disseminating information about resolved disputes.

The overall aim of these new policies is to prevent delay in the approval of new products because of technical disagreements that arise during inspections. FDA also hopes to avoid issuing invalid 483 observations and warning letters that lead to contracted disputes. At the same time, the agency wants to avoid pressuring a manufacturer to make what it considers unnecessary changes in production processes merely to gain agency approval.

Encouraging innovative changes

FDA officials believe that streamlining the inspection process and reducing needless disputes will encourage manufacturers to implement new production technologies designed to reduce manufacturing errors and promote quality production. Two years ago, FDA launched the PAT initiative, which promotes the use of new process monitoring and control technologies to improve manufacturing efficiency. A working group is developing a draft guidance on regulatory processes for applying PAT, and the agency has formed a PAT review inspection team to facilitate the oversight of such innovations.

The GMP initiative seeks to spur further use of new manufacturing technologies by making it easier for firms to implement postapproval manufacturing changes. FDA issued a draft guidance in February that clarifies how firms can develop comparability protocols (CPs) that may reduce the need for prior approval of changes in production systems.

Manufacturers have always been able to develop protocols for making certain routine chemistry, manufacturing, and control changes (CMC) such as revisions in packaging or expiration dates. During the past decade, CDER has developed the scale-up and postapproval changes (SUPAC) program that simplifies regulation of specified postapproval changes in manufacturing processes and systems for certain dosage forms. To facilitate changes for more-complex drugs made from biotechnology that do not lend themselves

to the SUPAC model, FDA issued guidances about how biotechnology companies can establish CPs to gain predictability for contemplated postapproval changes.

This new initiative clarifies how the CP approach can be used by manufacturers of conventional drugs, including animal drugs and generic products. The draft guidance spells out the basic elements of a CP, including acceptance criteria and tests, and analytical procedures to be used to document that certain changes do not adversely effect product quality. A CP would consist of a detailed plan for documenting such comparability and may be submitted as part of a new drug application or after initial product approval. It allows FDA to designate a reduced reporting category for a subsequent manufacturing change (i.e., a changes-being-effected supplement instead of prior approval).

CPs may describe one or multiple CMC changes and will be more or less difficult to compile depending on the complexity of a product and the ability to characterize it. Drugs that are robust, fairly safe, and

sensitive to analytical procedures may be more suitable for this approach. FDA discourages using CPs for significant changes in product specifications, in formulation, in type of delivery system, in source materials, or in moves to a new site or facility that require a new GMP inspection. Protocols may be most useful in changing to equipment with a different operating principal, as could occur in implementing PAT.

Manufacturers will have to decide individually whether it makes sense to document the analysis and testing needed to file a CP. A firm may find it valuable to gain FDA agreement on a strategy for implementing manufacturing changes that the firm knows it wants to make. Biotechnology manufacturers generally have found CPs too complex and detailed to tackle before market approval, but FDA anticipates broader use of this approach for small molecules, comments Ajaz Husain of CDER, who heads up this project. Manufacturers have until 20 April 2003 to submit comments to FDA on the proposal.

Starting over on Part 11

The February GMP progress report announced that FDA has launched a broad re-examination of its regulation for electronic record keeping and submissions and will not enforce previously announced rules in this area for now. FDA issued a new draft guidance to explain its intent to narrow the approach for implementing Part 11 and will be lenient about requiring compliance with recent policies. The agency acknowledged that this effort "may lead to revisions to clarify its scope and requirements" of Part 11 for all FDA regulated products, including medical devices and foods, in addition to drugs.

In effect, it is back to the drawing board to develop a new policy for requiring validation and documentation of electronic recordkeeping systems. FDA has spent years deliberating this program that led to publication of regulations for implementing 21 *CFR* Part 11 in 1997. Unfortunately, the policy generated voluminous objections from manufacturers for being too vague, too complex, and too costly to im-

plement. The agency tried to clarify its approach in several draft guidances and numerous presentations, but recent efforts to enforce Part 11 rules during GMP inspections raised further outcries.

When FDA launched its GMP overhaul initiative in August of 2002, it signaled that a major change was underway by shifting responsibility for implementing Part 11 from ORA back to CDER. The agency then withdrew a draft guidance on electronic copies of records on 4 February 2003 to halt further industry review of the policy. As part of the agency's GMP progress report a few weeks later, FDA issued a new draft guidance. The draft withdrew an internal compliance policy guide plus other draft guidances about validation, glossary of terms, time stamps, and maintenance of electronic records.

Most important for manufacturers is the promise that field investigators will exercise enforcement discretion for regulating Part 11 while agency officials re-evaluate the entire rule. FDA "will not normally take regulatory action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of Part 11," the draft guidance states. The agency says it will continue to enforce electronic signature policies that apply to legacy systems as well as predicate rules that require records to be maintained and submitted in secure and reliable manners. FDA recommends that manufacturers maintain audit trails or other security measures to ensure the reliability of records and also validate computer systems that could effect product quality and safety and record integrity. Manufacturers should supply copies of electronic records as required by predicate rules and protect electronic records so that they can be retrieved if needed.

Agency officials explain that they will seek a more narrow approach to Part 11 to clarify that the policy does not apply to every use of a computer or information system by a manufacturer. For example, Part 11 would apply to records maintained by a company in electronic format but not to a computer that generates paper printouts of electronic records and other "merely incidental" uses of computers.

FDA plans to publish a final guidance quickly to implement this more discre-

Continued on page 120

Circle/eINFO 25

tionary approach to enforcing Part 11 and to clarify its policy review process. The revision of Part 11 regulation will take at least two years to accomplish.

In addition to finalizing the two new draft guidances and implementing new inspection procedures, FDA officials plan to move forward with efforts to increase the quality of its own regulatory processes. FDA is commissioning an outside study of effective business practices and policies that could apply to internal review operations. The agency also seeks to harmonize its GMP policies with international standards through continued discussion with regulatory authorities and manufacturers in the International Conference on Harmonization (ICH). Agency officials will explore related topics for harmonization with colleagues at an ICH July 2003 meeting in Brussels. **PT**