

GMP Progress Report

Six months into its initiative to update manufacturing regulations, FDA announces a raft of changes covering warning letters, inspections, and comparability — plus a fresh start on Part 11

It's been six months since FDA declared its intention to make sweeping changes to the way the agency regulates pharmaceutical manufacturing and product quality. The first set of changes — many quite substantial — were announced in a February “progress report” (www.fda.gov/cder/gmp/index.htm). The agency put on hold its controversial electronic record-keeping policy, shifted oversight for warning letters from the field to FDA centers, and rolled out significant modifications of plant inspection policies.

Reinventing Inspections

A major thrust of the program is to improve systems for overseeing compliance with GMPs. One important change is to return to CDER, CBER, and CVM authority to issue manufacturing warning letters. About 10 years ago, FDA transferred warning letter oversight from the centers to the field for the sake of speed and uniformity in the compliance process. This latest change seeks to reduce inconsistencies in warning letters that arise from differing approaches among ORA district offices. FDA's chief counsel Dan Troy and his department will continue to have final clearance on warning letters to centralize agency authority and add weight to final letters. FDA centers will conduct

“triage” on proposed warning letters originating in district offices. Letters citing obvious violations may be sent out immediately, whereas others that raise technical issues may be reviewed by a cross-agency group.

To make the GMP inspection process itself more efficient, FDA seeks to target inspections to high-risk facilities. For the moment, the priorities are:

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

Next FDA aims to develop a “more complex” risk-based model that will concentrate FDA resources on facilities where noncompliance is most likely to yield the greatest adverse public health consequences. The model will include factors such as extent of patient exposure, type of formulation, and GMP compliance record of the company.

Although many of the changes apply more directly to drugs, new initiatives are prompting a reevaluation of the Team Biologics program for inspecting biotech manufacturing operations.

FDA plans to establish a “pharmaceutical inspectorate,” similar in concept to Team Biologics, with teams of specially trained inspectors. But instead of Team Biologics' central cadre that inspects biotech plants across the country, there will be multiple pharmaceutical inspection teams in ORA district offices that will conduct preapproval as well as GMP inspections. FDA hopes to enroll 15–25 drug inspectors in the program by June.

The drug inspection teams also will make greater use of CDER review specialists,

another Team Biologics practice. If this strategy slows down inspections, delays approvals, or is too costly, as some fear, FDA may look for ways to have specialists advise inspectors without actually participating in site visits.

While FDA is moving to incorporate some aspects of Team Biologics in a new model for drug inspections, CBER and ORA working groups are examining options for improving operations of Team Biologics itself through:

- adoption of an internal quality management system
- developing metrics to determine the impact of Team Biologics on industry
- standardizing training and qualification of the Core Team members
- risk-based work planning
- increased communications between headquarters and the field.

Resolving Disputes

Another goal is to prevent delays in approving new products caused by technical disagreements that arise during inspections. FDA is encouraging manufacturers to discuss with investigators observations listed on a 483 inspection report that a company feels are unjustified scientifically. FDA also will test whether allowing a 48-hour delay in issuing a 483 could reduce citations and warning letters by resolving scientific and technical issues that arise late in inspections. The agency hopes this approach will encourage companies to use new technologies, rather than adopt a “don't use” approach.

A more formal system will be used for disputes that cannot be resolved during or immediately following an inspection. A



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manufacturer can first request a review by the district office, in consultation with the appropriate center. If the company still disagrees, it can appeal to a panel in the office of the commissioner. FDA is developing criteria for determining what issues are suitable for dispute resolution, how and when companies may seek reviews, how FDA will resolve internal disagreements, and methods for disseminating information on resolved disputes.

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

Encouraging Innovative Changes

FDA hopes that streamlined regulation and dispute resolution will encourage manufacturers to implement new production technologies that can reduce manufacturing errors and promote quality. Toward that end, FDA launched the process analytical technology (PAT) initiative two years ago to spur use of new process monitoring and control technologies. A working group is currently developing a draft guidance on applying PAT, and the agency has formed a PAT review-inspection team to facilitate oversight of such innovations.

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

Previous guidances spell out how biotech manufacturers can use the CP process to gain more predictability for contemplated postapproval changes. This new initiative clarifies how manufacturers of conventional drugs, including animal drugs and generic products, can use CPs to gain FDA approval of a reduced reporting category for a subsequent manufacturing change.

Biotech manufacturers generally have found comparability protocols too complex and difficult to tackle before market approval, but FDA anticipates broader use

of this approach for small molecules. Manufacturers have until 20 April 2003 to comment on the proposal.

Starting Over on Part 11

One of the most significant announcements in the February progress report is that FDA has launched a broad re-examination of 21 CFR Part 11, its regulation for electronic record keeping and submissions.

In effect, it's back to the drawing board for Part 11. FDA spent years deliberating on this policy, which finally led to publication of regulations for implementing Part 11 in 1997 — regulations that generated voluminous objections for being too vague, too complex, and too costly to implement. 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 outcry.

Since FDA launched its GMP overhaul initiative last August, there have been several signals that a major change was under way. First responsibility for Part 11 was shifted from ORA back to CDER. Then on 4 February 2003, the agency withdrew a draft guidance on electronic copies of records to halt further industry review of the policy. A few weeks later, FDA issued its new draft guidance, which withdrew an internal compliance policy guide and other draft guidances on validation, a glossary of terms, time stamp requirements, and maintenance rules for electronic records.

Most important for manufacturers is the promise that field investigators will exercise "enforcement discretion" while agency officials reevaluate Part 11. 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 a secure and reliable manner. FDA recommends that manufacturers maintain audit trails or other security measures to ensure the reliability of records and validate computer systems that could affect product quality and safety or record integrity. Manufacturers also 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 its narrower approach to Part 11 will 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 in electronic format, but not to a computer used to produce paper printouts of electronic records or for other "merely incidental" uses.

FDA plans to publish a final guidance quickly to implement this discretionary oversight approach and to clarify its policy review process. The revision of Part 11 regulations will take at least two years to accomplish.

In addition to finalizing new draft guidances and implementing new inspection procedures, FDA officials plan to move forward with efforts to increase the quality of the agency's 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 Harmonisation. Agency officials will explore with colleagues related topics for harmonization at a meeting in Brussels this July. **BPI**

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 four key areas:

- 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 process analytical technology.