A main objective of FDA's initiative to overhaul how it ensures high-quality pharmaceutical production is to apply more oversight and stricter rules to high-risk products and processes. This initiative involves revising FDA's field inspection program to use the agency's limited resources more effectively. FDA lacks the resources to monitor and inspect with equal vigilance the thousands of products and production facilities in its purview and has been conducting fewer good manufacturing practices (GMP) inspections in recent years. (The number of GMP inspections has dropped from more than 4000 in 1980 to approximately 1500 in 2003).

In response to the emergence of more-complex and diverse manufacturing operations for drugs and biologics, FDA is establishing a systematic risk-management approach to drug quality regulation that adjusts the level of regulatory scrutiny to fit the degree of product risk (see sidebar, “Defining risk and quality”). The agency is looking to set priorities based on risk factors for a range of regulatory policies. One option is to skip preapproval inspections for low-risk products and for companies with good compliance histories. FDA also is testing a risk-based site-selection model for selecting inspection sites overall. The Center for Drug Evaluation and Research (CDER) plans to test a pilot program in 2004 that evaluates risk factors that are related to the facility (including compliance history), type of drug product, and the level of understanding about the manufacturing process.

In a speech at the National Press Club in August 2003, FDA commissioner Mark McClellan highlighted how applying risk management to FDA's enforcement strategy involves targeting enforcement efforts at more-serious offenses. McClellan emphasized that FDA is serious about prosecuting individuals and organizations that break the law, particularly those that are involved in "more-sophisticated and large-scale criminal activity" that threatens public health. The commissioner promised to punish "bad actors" that refuse to comply with regulations by using enforcement actions and criminal prosecutions to "set a clear deterrent for illegal behavior."

**Overhauling inspections**

In addition to promoting a get-tough compliance posture, McClellan is emphasizing the need to improve FDA's pharmaceutical plant inspection program as part of its "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach" initiative (implementing documents are available at www.fda.gov/cder/gmp/index.htm) (1). An initial policy change in February 2003 was to give various FDA centers the authority to review GMP warning letters proposed by field inspectors. CDER and other FDA centers have been reviewing warning letters since March 2003 as one way to ensure that adverse findings are based on science, yield consistent findings, and are coordinated with FDA regulatory review programs. FDA is evaluating this process to assess if it is having the intended effect.

**Additional actions**

The following additional actions were proposed by FDA in September 2003.

**Reduce the number of preapproval inspections.** A first step in applying a risk-based approach to FDA's compliance program is to exempt certain low-risk drugs from preapproval inspection (PAI). FDA announced that it no longer will mandate field inspections for every application that involves a narrow therapeutic index therapy or a product on FDA's list of the top 200 prescribed drugs. The agency still may conduct PAIs for these products, but district field office managers will gain more flexibility to decide whether an inspection is necessary. The change is expected to reduce the number of PAIs overall, particularly for generic drugs and supplements, and allow inspectors to focus on more high-risk products and processes.

PAIs still will be conducted regularly for new molecular entities, priority applications, investigational new drug applications (IND), and a manufacturer's first application, companies that are experiencing GMP problems, and for various
problem situations. It will be up to the district office to decide, in consultation with CDER, if an application involves a low-risk situation that does not require a PAI.

Create a pharmaceutical inspectorate. Another new initiative is to raise the expertise of field officers who inspect drug production facilities as one way to gain more consistency in inspection results. FDA’s Office of Regional Affairs (ORA), which oversees the agency’s field force, plans to train approximately 50 investigators to form a pharmaceutical inspectorate (PI) during the next four years, starting with 25 investigators to be trained by the end of 2004. A memorandum of understanding between ORA and CDER outlines how PI members will be selected, trained, and assigned to inspections. The aim is for PI members to spend approximately 80% of their time performing drug inspections, both domestic and foreign, and to focus on facilities that use more-complex production technologies. Unlike Team Biologics, these individuals will be based in FDA district offices and will not travel around the entire country; ORA officials will determine where to base PI members as the program develops.

Include more drug review specialists in plant inspections. To better coordinate application review with GMP inspections, FDA also plans to include more product specialists on inspection teams. Such specialists may be review scientists in FDA centers or technical experts in ORA or other parts of the agency. The plan is to give them a larger role in conducting high-risk inspections, resolving technical issues, reviewing draft warning letters, and developing agency approaches for regulating and encouraging new manufacturing technologies.

A related initiative involves the formation of a specially trained review and inspection staff to oversee applications and GMP inspections of facilities that implement process analytical technology (PAT) systems. This program similarly aims to provide additional expertise in overseeing new manufacturing technologies.

Establish a formal dispute resolution procedure. Because disagreements about scientific and technical manufacturing issues do arise during GMP inspections, FDA has launched a program to resolve these issues efficiently and thus remove roadblocks that inhibit manufacturers from adopting new technologies. In September 2003, FDA unveiled a draft guidance for establishing a formal dispute resolution program. The policy describes several actions that manufacturers can take to resolve disagreements with plant inspectors and thus avoid unwarranted form 483 citations.

As a first step, FDA continues to urge manufacturers to seek clarification of disputes with the plant inspection team during the lengthy inspection process. Such discussions may occur as issues emerge or at the conclusion of an inspection when investigators usually meet with company management to discuss observations. FDA hopes that most scientific and technical disagreements can be resolved informally at this stage.
If a company and FDA fail to agree on a technical issue, and FDA issues a form 483 citation, a manufacturer can request to use the new two-tiered dispute resolution process.

However, if a company and FDA fail to agree on a technical issue, and FDA issues a form 483 citation, a manufacturer can request to use the new formal two-tiered dispute resolution process. The first tier involves referring the scientific or technical issue to the appropriate ORA district office within 10 days of the completion of an inspection. If ORA disagrees with the manufacturer, it will write up a review of the issue, usually consulting with the staff of the center involved.

If a manufacturer still disputes ORA's position, the company can move to the second tier and appeal the issue to an FDA dispute resolution panel. The panel will review the manufacturer's case and ORA's position and issue a report.

FDA anticipates that this dispute resolution program will be useful for addressing broad scientific issues such as the adequacy of a manufacturer's process and production control design activities, the appropriateness of a particular lot-testing or sampling scheme, or the adequacy of a company's investigation of an unexplained manufacturing discrepancy. FDA will launch a 12-month pilot program in January 2004 to test the new dispute resolution approach and then will refine the proposal and issue a final guidance in January 2005.

Changing compliance

To relate the frequency and intensity of plant inspections to risk factors, FDA is expanding its capabilities for assessing and analyzing data about product performance and manufacturer compliance history, according to David Horowitz, director of CDER's Office of Compliance (OC). To help implement new risk management approaches, CDER reorganized OC in January 2003 to create the Division of Compliance Risk Management and Surveillance. The new unit analyzes reports about GMP compliance and adverse events to identify high-risk products and manufacturers. One team in the division analyzes risk-related data by monitoring adverse drug event reports and field alerts and drug product-sampling surveillance. Another group keeps track of domestic and foreign drug manufacturers, repackers, and re-labelers and the products they make and distribute. The division then can use this information to identify products that
could expose consumers to high risks so that FDA district laboratories can analyze them for conformity to applications, compendial standards, or manufacturers' specifications.

Two other divisions continue the OC’s basic tasks. The Division of New Drugs and Labeling Compliance monitors adherence to labeling requirements, including the oversight of Internet claims, health fraud evidence, compounding, and imports and exports. The Division of Manufacturing and Product Quality remains responsible for overseeing foreign and domestic drug investigations, inspections, drug recalls, and GMP policy development. Division director Joe Famulare leads CDER’s efforts to revise and implement new policies related to electronic records and electronic signatures.

With this added expertise, OC is shifting its focus to concentrate on GMP inspections of facilities that make high-risk products. For the coming year, FDA plans to inspect 55% of high-risk drug plants, which includes 630 establishments that make sterile drugs, prescription drugs, or are new manufacturing facilities. The plan is to inspect approximately 100 new registrants, approximately half (200) of prescription drug facilities, and half (65) of 130 sterile drug products makers.

For the future, FDA is developing more-advanced risk-based models for selecting inspection sites on the basis of
- manufacturing process. More-complex processes such as aseptic filtration are more likely to experience problems that could have a serious effect on patients.
- product type. More oversight may be required for narrow therapeutic range drugs or products that treat the patient for a long period of time.
- facility-based factors. Plant compliance history is the key issue.

Within each of these three decision modules, the agency is developing risk-ranking and filtering techniques that weigh the risks related to each factor. This approach, which will require several years to implement, also may be useful in determining when a postapproval manufacturing change may or may not require a preapproval inspection.

The concept of risk management, explains CDER director Janet Woodcock, explicitly acknowledges that “some things
are more important than others”—in the laboratory, the plant, and the clinical area. FDA’s risk orientation aims to boost resources to handle the highest risks and to revise regulatory requirements to be proportionate to product risk. This approach will be particularly important as the industry moves away from the ‘90s manufacturing model geared to big blockbuster production and moves toward the development of drugs tailored to individuals. Small patient populations will require more flexibility in testing and production methods, and, according to Woodcock, “we’re all going to have to change.”

References