



[cGMP Home](#)
[FDA Home](#) | [Search FDA Site](#) | [A-Z Index](#) | [Contact FDA](#)

Summary Progress Report Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

Comments on this report or on the activities of this initiative should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket Number 03N-0059.

Electronic Management Comment Form: [Docket 03N-0059 - Pharmaceutical Current Good Manufacturing Practices for the 21st Century: A Risk-Based Approach](#)

A science and risk-based approach to product quality regulation, incorporating an integrated quality systems approach

Introduction

On August 21, 2002, FDA announced a major new initiative on the regulation of drug product quality. The two-year program, which applies to human drugs and biologics and veterinary drugs, has several ambitious objectives. One is to ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science and to encourage the adoption of new technological advances by the pharmaceutical industry. FDA will determine the best pathway to better integrate advances in quality management techniques, including quality systems approaches, into the Agency's regulatory standards and systems for the review and inspection processes. Additionally, risk-based approaches, that focus both industry and agency attention on critical areas, will be implemented. Finally, enhancements to the consistency and coordination of Agency drug quality regulatory programs will be made.

Current Progress

The initiative is overseen by an Agency steering committee with representatives from CBER, CDER, CVM, ORA and the Office of the Commissioner. CFSAN and CDRH are also involved in the Part 11 implementation. Working groups dealing with specific issues have been formed. The August 21 announcement included a number of "immediate steps," with planned completion at 6-months. FDA is now reporting on the overall progress of the initiative. In the six months since the announcement, steps have been taken to achieve both short and longer-term objectives.

The following planned six-month milestones have been completed:

21 CFR Part 11 implementation

FDA issued a Notice of Availability (NOA) of a draft guidance on Part 11 on February 20, 2003. The draft guidance clarifies the scope and application of the regulation and provides for enforcement discretion in certain areas that have been problematic. The Notice explains FDA's intent to reexamine Part 11, which may lead to revisions to clarify its scope and requirements. FDA encourages submission of comments on the draft guidance.

Encouraging innovation within the existing framework

Today FDA issued an NOA and draft guidance entitled "Comparability Protocols-Chemistry, Manufacturing and Controls Information." This guidance applies to nonprotein pharmaceuticals and veterinary drugs. Under appropriate circumstances, use of a comparability protocol can allow manufacturers to implement changes to their processes without submission of a prior approval supplement to the FDA. This facilitates continuous improvement and innovation. Related guidances are under development.

Center review of drug cGMP warning letters

Starting March 1, all drug cGMP warning letters will be reviewed by the relevant Center prior to issuance. This will help identify possible program inconsistencies and resolve them before warning letters are issued.

Implementation of a technical dispute resolution process for cGMP disputes

Today the Agency issued a progress report from the Dispute Resolution working group. The Agency seeks comments on the issues and processes discussed in the progress report.

FDA plans to consider and implement dispute resolution procedures for cGMP's that allow for discussion of scientific and technical issues, that bring the best technical expertise to bear on the particular issue, that allow for development of best practices and policies across FDA, and that improve transparency of the regulatory process.

Evaluating optimal mechanisms to effectively and efficiently communicate deficiencies

FDA will clarify the status of the observations that are noted on the FDA Form 483 form, and to highlight avenues for further discussion with FDA on the inspectional observations.

[Progress Report of the 483 Communications Working Group](#)

Holding scientific workshops with stakeholders

FDA will be holding the inaugural workshop on April 22-24 in Washington D.C. [Draft Agenda and Registration]. This workshop will provide an opportunity for in-depth discussion on four topic areas, namely:

- Risk-Based cGMP
- Integrated systems approach to the CMC review and cGMP inspections
- Post approval manufacturing changes
- Manufacturing science

Emphasizing a risk-based approach to the work planning process

In fiscal year (FY) 2003, FDA, using a basic risk management approach, identified three categories of potentially higher-risk pharmaceutical manufacturing sites for prioritizing inspections: sites making sterile drugs; sites making prescription drugs, and sites of new registrants not previously inspected by FDA.

By FY 04, FDA intends to have developed a more detailed risk model to help predict where FDA's inspections are most likely to achieve the greatest public health impact.

Effective January 27, CDER reorganized its Office of Compliance, creating a new Division of Compliance Risk Management and Surveillance to enhance the Office's capacity to implement risk management approaches.

CDER Office of Compliance Organizational Chart

Improving the operations of Team Biologics

CDER/ORa workgroups have been actively implementing improvements to the Team Biologics program including:

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

Including product specialists on inspection teams

FDA is issuing a progress report describing possible approaches on including product and technical specialists, with relevant expertise, to join inspection teams that do not yet include such specialists. This should assist the Agency in enhancing the technical quality and consistency of FDA inspection and further facilitate the adoption of innovative manufacturing technologies.

Progress Report of the Working Group on Product Specialists on Inspection Teams

Enhancing expertise in pharmaceutical technologies

The Agency has hired a number of experts, and is collaborating actively with academic and industry groups to harness available expertise

In addition to achieving the short-term milestones, the Agency has taken steps in the following areas:

International collaboration

- Senior FDA officials have discussed the initiative with drug regulatory authorities in other regions.
- In Sept 2002 the initiative was presented to the ICH steering committee, and the ICH plans to discuss possible topics for harmonization in July 2003 in Brussels.

Pharmaceutical Inspectorate

- ORa, CVM and CDER have agreed to the implementation of a "Pharmaceutical Inspectorate"
- The inspectorate will consist of specially-trained individuals who will spend a majority of their time in the

drugs cGMP area

- Members will co-train with Center staff
- The first members are anticipated to be on board by the end of FY 2003

Progress Report of the Pharmaceutical Inspectorate Working Group

Process Analytical Technologies (PAT) Initiative

This collaborative initiative between CDER, ORA and CVM is designed to address many of the objectives of the cGMP for the 21st Century Initiative. It identified, through public meetings and workshops, the benefits of PAT, and perceived/real hurdles to its introduction in manufacturing. This initiative is exploring how FDA can facilitate introduction of new process monitoring and process control technologies to improve manufacturing efficiencies. Draft guidance for industry on a regulatory process for applying PAT is currently under development and a review-inspection team has been assembled and is currently in a training and certification program. Additional information on this initiative is available at <http://www.fda.gov/cder/OPS/PAT.htm>

Contract

As part of the initiative to ensure that the Agency uses current business practices for risk and quality management, FDA will commission a study of 'effective' business practices and policies which could be applicable to FDA's business model. Such a study will assist the Agency in developing approaches that improve Agency effectiveness and efficiency, and that will positively impact on industry innovation and use of the latest advances in manufacturing science and technology to improve the overall public health.

Progress Report on Effective Business Practices and Policies in Other Organizations

Quality management system

FDA is planning to develop a quality management system for the regulatory processes associated with product quality regulation. The scope of this effort is still under consideration.

Further Steps

The steering committee expects to finish an overall plan for the initiative within the next four months. Work groups will continue to develop their projects. Topics that require further work by the steering committee include the definition of "quality" for pharmaceutical products, risk assessment, the role of the CMC review function, and the current regulatory structure for quality management systems. As was stated in the August announcement, the existing regulations appear to provide the flexibility to accommodate this initiative, but, FDA will consider various options for enhancing the use of quality systems approaches in FDA regulation of drug quality.

Criteria for evaluating the success of each working group, and for the initiative as a whole, are being developed.

The Future

Pharmaceuticals will have an increasingly prominent role in the health care of the future. The health of our citizens depends on the availability of safe, effective and affordable medicines. In the future, pharmaceutical manufacturing will need to employ innovation, cutting edge scientific

and engineering knowledge, and the best principles of quality management to respond to the challenges of new discoveries and ways of doing business such as individualized therapies or genetically tailored treatments. Regulation of the future will also need to meet these challenges, by incorporating new scientific information into regulatory standards and policies. Both industry and regulatory practices will need to be informed by the best techniques of risk assessment and management. "Pharmaceutical cGMPs for the 21st Century" is intended to jump-start progress into this future.

Pharmaceutical manufacturing is evolving from an art form to one that is now science and engineering based. Effectively using this knowledge in regulatory decisions in establishing specifications and evaluating manufacturing processes can substantially improve the efficiency of both manufacturing and regulatory processes. This initiative is designed to do just that through an integrated systems approach to product quality regulation founded on sound science and engineering principles for assessing and mitigating risks of poor product and process quality in the context of the intended use of pharmaceutical products. In this regard, the desired future state of pharmaceutical manufacturing may be characterized as:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- Continuous "real time" assurance of quality
- Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability
- Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product

Dockets

Comments in the initiative may be submitted to Docket number 03N-0059. However, comments on either of the two draft guidances should be submitted to the respective docket.

[Electronic Management Comment Form: Docket 03N-0059 - Pharmaceutical Current Good Manufacturing Practices for the 21st Century: A Risk-Based Approach](#)

[cGMP Home](#)

[FDA Home](#) | [Search FDA Site](#) | [A-Z Index](#) | [Contact FDA](#) | [Privacy](#) | [Accessibility](#)

FDA/CDER Web Management Team
Web page created by mau 2003-FEB-27.