Progress in FDA's Drug Product Quality Initiative

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Impetus for Initiative:

- Modernization and continuous improvement in pharmaceutical manufacturing sector slow compared to other sectors
- Process efficiency low: Drives up costs
- Regulatory paradigm (cGMPs) not significantly changed over 25 years
- Regulators recognize need for risk-based approaches

Structure of Initiative

- All pharmaceutical products: drugs, biologics, veterinary drugs
- Cross Center: ORA, CDER, CBER, CVM
- Inspection and Review: All aspects of quality regulations

Common Goal of Stakeholders:

Reliable availability of high quality, efficiently produced drugs

Objectives of Initiative

- Encourage adoption by the pharmaceutical industry of new technological advances in manufacturing
- Facilitate industry application of modern quality management techniques to all aspects of pharmaceutical production & quality assurance
- Encourage implementation of risk-based approaches that focus both on industry and Agency attention on critical areas

Objectives:

- Insure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science

- Implement quality management in review and inspection processes

Plan for Initiative

- Two year project
- Constitute 16 working groups
- Implement immediate (6 month) and 1 year actions
- Final actions at 2 year mark

Six Month Time point: February 20, 20003

- Plans for pharmaceutical inspectorate
- Center review of warning letters
- Modifications to form 483
- Draft guidance: Part 11

Six Month Time point:

- Draft guidance on comparability protocols
- Announcement of plan for dispute resolution process
- Progress on PAT initiative

Second Progress Report:
September 3, 2003

First Year Accomplishments

- Issued draft guidances on comparability protocols for small molecules and proteins
- Workshop (with PQRI) April 22, 2003
- Issued final guidance on *Part 11, Electronic Records, Electronic Signatures—Scope and Application*- clarifies the scope and application of the Part 11 regulation and provides for enforcement discretion in certain areas

First Year Accomplishments
(continued)

- Implementation of a technical dispute resolution process for CGMP disputes- draft guidance issued and initiation of a 12-month domestic pilot program in early 2004

- FDA actively seeking to improve international standards for drugs through its efforts at supporting global harmonization, and collaboration with its public health counterparts in other nations

First Year Accomplishments
continued

- Issued draft guidance on *PAT—A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance*- intended to encourage pharmaceutical manufacturing and QA technologies

- Issued draft guidance on *Sterile Drug Products Produced by Aseptic Processing*- emphasizes current science and risk-based approaches, once final, this will replace the 1987 Guideline

First Year Accomplishments
continued

- Changes to FDA's inspection program:

  -Establishment of a Pharmaceutical Inspectorate- highly trained individuals within ORA who will devote most of their time to conducting human drug manufacturing quality inspections on prescription drug manufacturers and other complex or high risk inspections.

  -The Preapproval Inspection Compliance Program has been revised to give the field more opportunity to utilize a risk-based approach by allowing greater flexibility in determining whether a preapproval inspection is warranted.

First Year Accomplishments
continued

- FDA entered into several collaborations with industry, academia, and another government organization- will aid in enhancing FDA's scientific and technical capabilities, as well as help both FDA and industry to better focus activities and resources related to pharmaceutical product quality.

Next Steps: Topics for further consideration

- Develop definition of “quality” for a pharmaceutical
  - “Customer’s” point of view?
  - Fitness for use?
  - Availability?
- Definition of “risks” to quality
  - Draws on underlying science
  - Requires a model for risk

Next Steps: Quality Systems

- Internal: FDA Drug Quality Regulatory Program as a Quality System
  - Does the program operate in a coordinated fashion, as a system?
  - To what extent can the principles of quality management be applied to the operations of the program?

Next Steps: Quality Systems

- External:
  - To what extent do the existing regulations and guidances reflect current thinking on quality management practices?
  - To what extend do current standards (CMC and cGMP) reflect current thinking on quality management?

Next Steps: Quality Systems

- External:
  - To what extent do these standards promote/facilitate state-of-the-art quality management practices in industry?
  - To what extent, if any, do these standards impede industry?

Next Steps: Sources of Variability

- What does “design controls” mean for pharmaceuticals?
- What is the role of “process validation?”
- Need scientific evaluation of our conceptual understanding of the sources of variability during manufacturing

Next Steps: Role of Review Process

- What is the objective of the CMC review?
- To what extent does the process accomplish the objectives?

Active Areas

- International Harmonization
- Implementation of Internal Quality System
- Procedures for rapid public dissemination of agency decisions/guidance
- Part 11

Active Areas: cGMPs

- Clarification of terms: e.g., “process validation”
- Plans for additional guidances

Active Areas:

- CMC Review: Evaluation of risk-based approaches
- Definition of quality for a pharmaceutical product; definition of risk
- PAT: Reviewing submissions
- PI: Establishing training

Early Results

- Part 11 Guidance: Saving millions of dollars on IT Systems
- PAT: Number of submissions for new technology
- Harmonized aseptic guidance will provide savings

Summary

- Initiative should be "win-win" for public, industry, regulators
- Contingent on work continuing at a rapid pace over next year
- FDA has an ambitious plan for completion of project