PAT Regulatory Process: Review and Inspection

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Outline

- Introductory Remarks
- PAT System Implementation Options
- PAT Regulatory Process
- Team Approach: Review and Inspection
- PAT Submission Information
- Success Story: A PAT Submission Comparability Protocol
- Summary and Closing Remarks

Existing Process

- Manufacturing and associated regulatory practices (do) did not adequately support or facilitate innovation and continuous improvement
- An innovative regulatory process was necessary to transform pharmaceutical manufacturing to meet the current and future needs of the US public

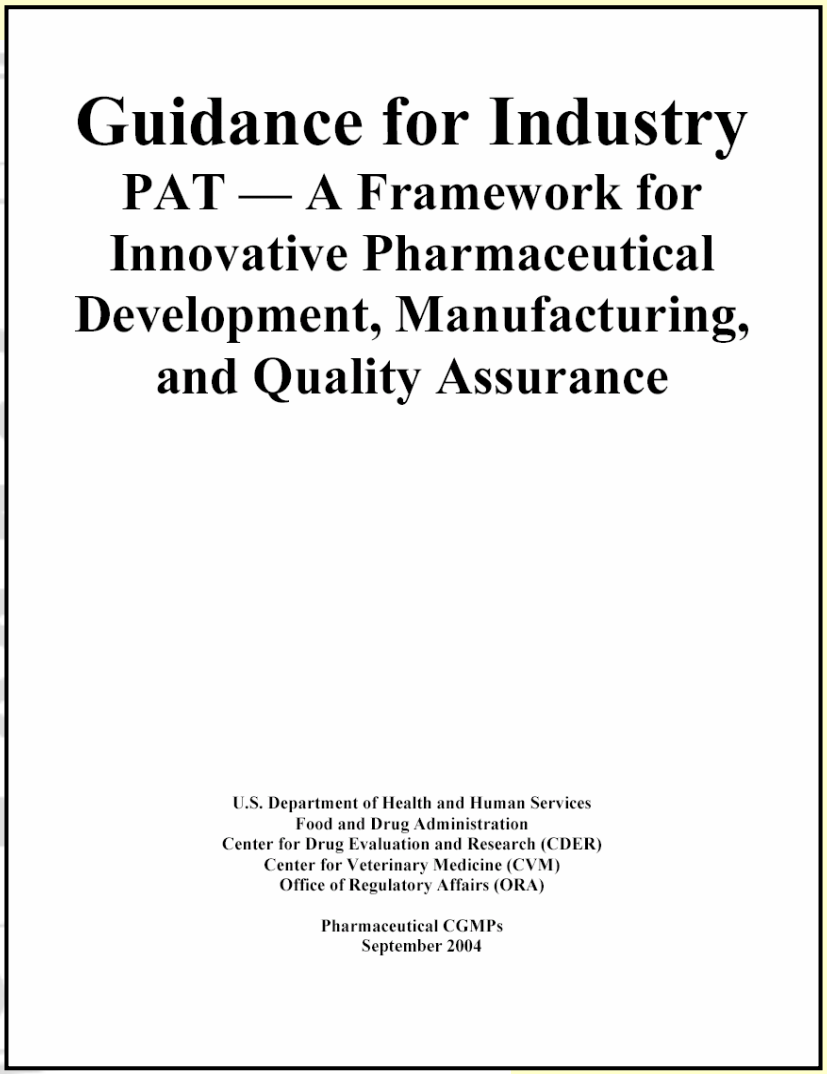
"Ajaz Hussain- FDA Science Board Meeting, November 05, 2004"

PAT Regulatory Milestones

- FDA Advisory Committee for Pharmaceutical Science-July 19, 2001
- PAT Subcommittee Meetings
  - February, July, October 2002
  - Draft PAT Guidance September 2003
  - Final PAT Guidance September 2004
  - PAT Team Certification completed September 2004

PAT Guidance

- **Incorporates flexible Regulatory Strategy accommodating *innovation* by**
  - **PAT Team approach to Review *and* Inspection**
  - **Jointly trained and certified staff**



Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

Pharmaceutical CGMPs
September 2004

PAT System Implementation Options

- **Under the facility's own Quality System**
  - Inspections by the PAT Team or PAT certified Investigator can precede or follow PAT implementation
- **Supplement Submission (PAS, CBE-0, CBE-30, AR, etc.) prior to implementation**
  - If necessary, an inspection can be performed by a PAT Team or PAT certified Investigator prior to implementation
- **Comparability protocol (CP) Submission**
  - Outlining PAT research, Validation and implementation strategies, and time lines

PAT System Implementation Options

- Following the approval of the comparability protocol by the Agency, one or a combination of the above regulatory pathways can be adopted for implementation of the PAT system

- Additionally, a pre-Operational Review of a PAT manufacturing facility and process(es) by the PAT Team may be requested by the manufacturer to facilitate adoption or approval of a PAT System(s)

PAT Regulatory Process

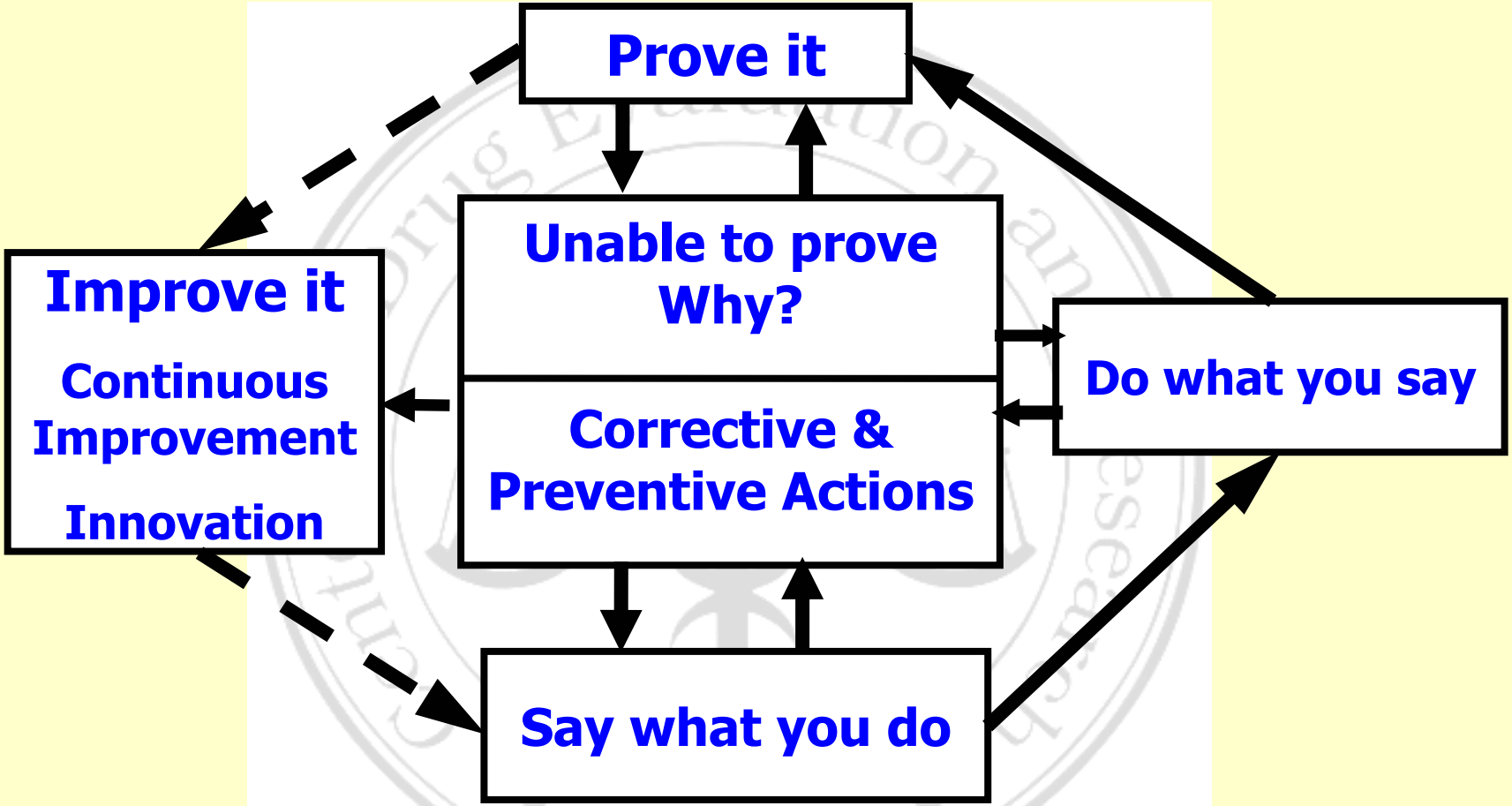
- A flexible regulatory approach
- May be initiated by an applicant with a scientific proposal to IND/NDA/ANDA, followed by discussions with PAT Team to ensure clear understating of scientific principles and the type of information and knowledge necessary to support the proposed PAT system
- Regulatory submission (e.g., supplement, CP), if needed per mutual discussions with PAT Team
- Evaluation of the regulatory submission by a team approach for ensuring all aspects of product quality and product reliability and followed by a team based inspection

PAT Implementation: Under firm's Quality System

- "Organizations with robust QS may be able to reduce supplement submission
- Procedures designed to ensure that the drug products have identity strength, quality and purity
- Concept of Product Lifecycle
- Identification and control of critical variables"

"FDA Draft Guidance Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations-September 2004"

Modern Quality System



http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf

PAT Implementation: Robust Quality System

- Quality
- Quality by Design and Product Development
- Risk Assessment and Risk Management
- CAPA (Corrective and Preventative Actions)
- Change Control
- The Quality Unit
- Six System Inspection Model

"FDA Draft Guidance Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations-September 2004"

FDA Organization for PAT

Team Approach
A
Catalytic Engine
For
Success

FDA Organization for PAT

- Team members from Review, Inspection and Compliance
- PAT Policy, Consultant, Support
- PAT Training Coordinators
- PAT Steering Committee

The FDA PAT Team: ORA, CDER, CVM

Steering Committee:
Doug Ellsworth (ORA)
Patricia Lefler (ORA)
Dennis Bensley (CVM)
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PAT Team Building

PAT Team Building

December 2002

PAT Training

- **Training Curriculum**
  - **Selected by PAT-Subcommittee of Advisory Committee for Pharmaceutical Science**
  - **Two in-house didactic sessions and three practicum sessions at the following three Universities**
- **Three Universities (National Science Foundation Centers)**
  - **University of Purdue – Pharmacy (Center for Pharmaceutical Processing Research)**
  - **University of Washington - Chemistry (Center for Process Analytical Chemistry)**
  - **University of Tennessee – Chemical Engineering (Measurement and Control Engineering Center)**

PAT Training Certification

- PAT team members trained together
- Assignments:
  - Written Take-Home exam on the didactic sessions
  - Practicum Reports for 2/3 University sites
  - Team approach (Review, Inspection, Compliance) to evaluate merits of Public comments received for the PAT draft guidance, to submit a written report and presentation to the PAT steering committee
- Certification: September 2004

PAT Submission Information: Example

Information to support a PAT system implementation may include:

- **Process description, analytical properties, Testing and rationale, risk assessment**
- **PAT system and sampling description**
  - Type of measurement technology (e.g., NIR, spectral region), sampling system (e.g., fibers, if any, sample location, sample/product interface), sampling plan
  - Risk management, including identification of system failure and strategy for managing system failure
- **Experimental design protocol, including table of experiments with justification, and references to documents (experimental design and conclusions)**
- **Factors identified as critical, factors chosen as critical and chosen for control justification, References to experimental design**
- **Modeling strategy, and criteria for management of outliers**
- **Change control strategy for model maintenance**
- **Performance verification, calibration**
- **Process monitoring and control strategy**
  - Acceptance criteria

What PAT Tools are used?

- Multivariate tools for design, data acquisition and analysis
- Modern process analyzers
- Process control tools
- Continuous improvement and knowledge management tools

Process Understanding?

- Is the process well understood?
  - Are all critical sources of variability identified and explained ?
  - Is variability managed by the process
  - Are product quality attributes predicted accurately and reliably?
- True process understanding reflects accurate and reliable predictions
- Process understanding inversely proportional to risk

Critical Parameters & Process Controls Identification

Focus on process understanding

- **What parameters are critical to product quality?**
  - **Experimental Design**
- **How are these parameters controlled throughout the process?**
  - **Feed-back/-forward**

Process Understanding and Control of identified critical parameters can…

- Assure the quality of in-process materials and/or drug products
- Continuously validate the performance of the manufacturing process
- Allow the process to manage variability
- Assure product quality in real time or near real time

PAT Regulatory Risk-Management

- Expect an inverse relationship between the level of process understanding and the risk of producing a poor quality product
- Well understood process → less restrictive regulatory approaches to manage change
- Focus on process understanding and the facilities quality system can facilitate risk-managed regulatory decisions and innovation

Regulatory Tools By FDA & ICH

- **Provided by FDA & ICH include:**
  - **PAT Guidance, PAT Team, ASTM Standards, and support infrastructure**
  - **Compliance Policy Guide 7132c.08**
  - **Draft Guidance* on "Comparability Protocol"**
  - **Draft Guidance on "Quality Systems Approach to Pharmaceutical CGMP Regulations - Sept 2004**
  - **ICH Q8, Q9, and proposed Q10 will expand the international scope**

* **FDA Guidance For Industry, Comparability Protocols - Chemistry, Manufacturing, and Controls Information, February 2003, Once finalized, it will represent the Agency's current thinking on this topic.**

Success Story

Team Approach
An Assessment of
A PAT Submission:
Comparability Protocol

Success Story: PAT CP

- **Highlights of the CP and Regulatory Process**
  - Existing approved and marketed high volume DP-Tablet
  - Focus on monitoring and controlling the entire Manufacturing Process: Drug substance and the Drug Product
  - Open, frank and science based dialogue building trust and mutual understanding with the Agency from beginning of the project through development and final submission of CP
  - Firm's commitment to share the knowledge as learned
  - Team approach for pre-operational visit (POV) prior to submission of the CP: Drug substance and drug Product manufacturing sites, an invaluable learning process
  - Team assessment of the CP

Success Story: PAT CP

- **Objectives of POV for the proposed PAT system implementation:**
  - **Team assessment: Review, Inspection and Compliance discipline members**
  - **Understand the scientific rationale of the approaches taken**
  - **Evaluate robust process understanding pertaining to Process (prediction, monitoring, control strategies) and continuous improvement concepts for process outputs**
  - **Understand the risk management approaches**
  - **Understand the concept of real time release and progress made towards that goal**
  - **Most importantly sharing Firm's knowledge**

Success Story: PAT CP Assessment

- Team assessment of the CP
- Does it follow the concepts of the PAT Guidance?
  - A system for:
    - designing, analyzing, and controlling manufacturing processes
    - timely measurements (i.e., during processing)
    - critical quality and performance attributes
    - raw and in-process materials
- What PAT principles and tools are incorporated?
- Are the PAT systems proposed for design, measurement, and control (prediction) acceptable?

Success Story: PAT CP Assessment

- Are the approaches to risk management (assessment, prevention & mitigation) acceptable?
- Are the concepts of continuous improvement and knowledge management through life-cycle of the product under Firm's own quality system acceptable?
- Is the plan for integrating systems acceptable?
- Is the plan for real time release acceptable?
- Is the proposed regulatory process acceptable?
- What are the critical aspects that may need to be assessed during future site visits/cGMP inspections?

Success Story: Results

- The CP incorporated key elements of the process understanding (prediction and control strategies for entire manufacturing process, from DS => DP), risk management and real time release
- Demonstrated that Agency's PAT Guidance can be successfully used for a regulatory submission: e.g., Comparability Protocol (CP).
- Approval of a first complete PAT Comparability Protocol, which truly incorporates the principles embodied in the Agency's PAT Guidance.

Next Steps

- Anchoring changes in the corporate/organization culture
- Incorporation of the PAT process under the FDA's Quality System
- Continued participation in ICH and ASTM E55 Committee
- Training and certification of second PAT team
  - CBER and Team-Bio representative to join PAT Steering Committee

Next Steps

- **Expand the PAT program to include *Product Specialists* and *Pharmaceutical Inspectorate***
- **Critical Path Initiative**
  - **Embedding the PAT programs into this initiative for progress toward the desired state**

Summary

- **Agency's PAT initiative is a science and risk-based flexible regulatory framework:**
  - **Assures Team approach to review and inspection with supportive training, certification, expert consultant and research support**
  - **Offers integrated systems approach to provide flexibility in validation of new technology for its intended application**
  - **Addresses areas of "regulatory" uncertainty and fear of "delayed" approval**

Summary

- With the Team assessment approach, the organizational and communication barriers that existed at the beginning of the PAT initiative are fading away……
- The team members committed to function as a team to achieve common goals of ensuring product quality and reliability on the basis of risk-based scientific evaluation
- The integrated quality system orientation afforded a flexible regulatory approach for implementation of PAT

Summary

- Team approach to pre-operational review-inspection visit and to submission evaluation has proved to be one of the invaluable tools and could serve as a model for a complete assessment of a PAT system implementation
- Approval of a PAT CP proposing implementation of PAT systems both for the drug substance and the drug product with prospective intention of real time release of the drug product
- A tripartite Win-Win-Win situation for Public, Agency and Industry

Forthcoming PAT Guidance Workshops

- USA (Arlington, VA)
  - November 16, 2004
- Japan (Tokyo)
  - December 8, 2004
- UK (London)
  - December 14, 2004
- **Europe (Brussels, Belgium)**
  - **February 22, 2005**
- **India (Mumbai)**
  - **February 22, 2005**

Thanks