U.S. Department of Health and Human Services
Food and Drug Administration

Process Analytical Technology (PAT) – FDA Update

D. Christopher Watts, Ph.D.
Team Leader, Standards & Technology
Office of Pharmaceutical Science, CDER, FDA

Concept Heidelberg
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What are the objectives?

Discussion Topics

- Background and History of PAT
- Regulatory Expectations
- Impact of PAT for Pharmaceutical Industry
- Future Challenges and Opportunities for PAT

Model for Science-Based Manufacturing

Questions to Answer

- Why PAT Initiative?
- What is PAT?
- What has the FDA done?
- What's Next?
- What will be different?
- How may things evolve?

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Why PAT?
The Genesis of the Initiative

- Public dialogue
  - ACPS discussions (July 2001)
  - FDA Science Board Meetings (November 2001, April 2002)
- Current state of Pharmaceutical Manufacturing
  - Industrial Practice
  - FDA Regulation

http://www.fda.gov/cder/OPS/PAT.htm#scienceboard

Why PAT?
FDA Perspective

- An increasing burden on FDA resources:
  - ~ 4,000 manufacturing supplements annually
  - Unable to meet statutory biennial GMP inspection requirement
  - Lower scrutiny of non-domestic industry
- Recalls
  - Public Health impact

Dr. Janet Woodcock,FDA Science Board

Industry Perspective

- Time to effectiveness - takes years
  - Many supplements in first few years
- Hesitant to Innovate
  - Incentive?
  - "Don't ask/Don't tell"
- encourage innovation in pharmaceutical development, manufacturing, and quality assurance
  - Science Board and ACPS support

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What is PAT?

A system for:

- designing, analyzing, and controlling manufacturing
- timely measurements (i.e., during processing)
- critical quality and performance attributes
- raw and in-process materials
- processes

"Analytical" includes:

- integrated chemical, physical, microbiological, mathematical, and risk analysis

Focus of PAT is Understanding and Controlling the manufacturing Process

Process Understanding

- A process is well understood when:
  - all critical sources of variability are identified and explained
  - variability is managed by the process
  - product quality attributes can be accurately and reliably predicted
- Accurate and Reliable predictions reflect process understanding
- Process Understanding inversely proportional to risk
- Flexible Regulatory Approach
  - Change Management (Decrease Supplements)

PAT Tools

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

- Combination of some, or all
  - single-unit operation, or to an entire manufacturing process and its quality assurance

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FDA and Process Analytical Technology (PAT)

- FDA-wide Initiative
  - Initially CDER, CVM, and ORA
  - CBER now active participant
- Final Guidance Issued September 2004
  - Global Workshops (Participation from Regulatory Authorities in Europe, Japan, and India)
- PAT Team Training and Certification
  - Initial training and certification program complete (~15)
  - Second program began January 2006 (~45) (CBER, CDER, CVM, ORA)
- Standards for PAT

PAT Guidance

- Released September 29, 2004
- Scientific principles and tools supporting innovation
  - Process Understanding
  - PAT Tools
  - Risk-Based Approach
  - Integrated Approach
- Regulatory Strategy facilitating *innovation*
  - PAT Team approach to Review *and* Inspection
  - Joint training and certification of staff
- Changes
  - Not “How-to”
  - Expand to OBP

Guidance Scope

- Framework founded on process understanding
  - Facilitate innovation and risk-based regulatory decisions
  - Alleviate concern that innovation will result in regulatory impasse
- Two components:
  - Scientific principles and tools supporting innovation
  - Regulatory strategy to accommodate innovation
- New and abbreviated new (human and veterinary) drug application products and specified biologics regulated by CDER and CVM, as well as nonapplication drug products
- Voluntary
- PAT system implementation for particular products, no need to extended to other products

What has been done? Training and Certification

- Training Curriculum
  - PAT-Subcommittee of ACPS
- Academic Institutions
- Didactic and Practical Sessions
- Evaluate and Address Guidance Comments

Expectations: Implementation Options

- Under the facility's own quality system
  - Inspections by the PAT Team or PAT certified Investigator can precede or follow PAT implementation.
- A supplement (PAS, CBE, etc) can be submitted prior to implementation
  - if necessary, an inspection can be performed by a PAT Team or PAT certified Investigator before implementation.
- A comparability protocol can be submitted
  - Following approval of this comparability protocol by the Agency, one or a combination of the above regulatory pathways can be adopted for implementation
- To facilitate adoption or approval, a preoperational review of a PAT manufacturing facility and process may be requested

Expectations: Questions to Consider

- Is this a PAT submission?
- PAT principles and tools:
  - Are the systems for design, measurement, control, continuous improvement and knowledge management acceptable?
  - Is the approach to risk management acceptable?
  - Is the strategy for integrating systems acceptable?
  - Is the strategy for real time release acceptable?
- Is the proposed regulatory process acceptable?

What has been done?

- PAT "Approvals"
  - Branded Products
  - Generic Products
  - Regulatory approaches range from Comparability Protocols to Annual Reports
- Current Discussions with Industry
  - Biotech, Generic, New Drug, OTC

Standards for PAT

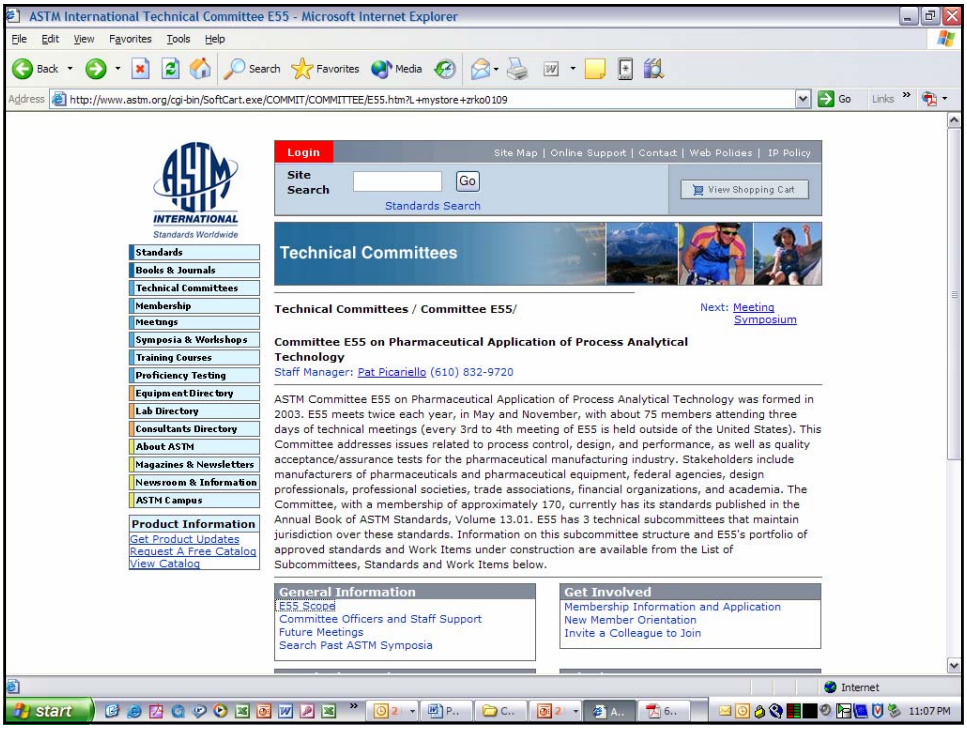
- Process focused
- Different from market standards
  - Market standards are not suitable for process control
- Consensus standards
- Facilitate optimization/continuous improvement
- ASTM Technical Committee E55
  - "Pharmaceutical Application of PAT"
  - Voluntary Consensus Process
- ASTM International
  - Global
  - ANSI accredited
  - > 100 years experience

Consensus Standards

- NTTAA (The National Technology Transfer And Advancement Act – Public Law 104-113)
  - use of voluntary consensus standards in place of Government unique standards
- OMB Circular A119 (Address Resources)
  - "...intended to reduce to a minimum the reliance by agencies on government-unique standards."
- 21 CFR 10.95
- Voluntary Consensus Standards
  - Involvement of all interested parties
  - Balanced discussion
  - Due process

§ 10.95 Participation in outside standard-setting activities.

(a) *General.* This section applies to participation by FDA employees in standard-setting activities outside the agency. Standard-setting activities include matters such as the development of performance characteristics, testing methodology, manufacturing practices, product standards, scientific protocols, compliance criteria, ingredient specifications, labeling, or other technical or policy criteria. FDA encourages employee participation in outside standard-setting activities that are in the public interest.



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What's next? FDA Programs

- Training (began January 2006)
  - Build on Initial Program (n = 45)
  - Expand to Biotech and CBER
  - Duquesne and Delaware Universities
- Continuing Education (Agency-wide)
  - Seminars/Workshops
  - Lecture Series
- Incorporate in FDA's Quality System

What's next? FDA Programs

Pharmaceutical Quality Standards Working Group

- Broad Representation
  - CBER, CDER, CVM, OC, ORA
- CDRH Process
  - http://www.cdrh.fda.gov/science/standards/constand.htm
- Develop Positions/Processes
  - Adoption/recognition of standards
    - Communicate (internal, external)
  - Use of Standards
  - Participation of Agency Personnel

What's next? FDA Programs

- **Interaction Working Group**
  - Objective is to improve interaction between CMC Reviewers and CGMP Investigators
  - Broad Representation (ORA, CDER, CVM)
- **Pharmaceutical Inspectorate**
  - Level III Certified
  - Advanced training in technology, risk management, quality systems
  - Classroom Training, Details to Centers, Inspection Audits
  - Training includes Center personnel

Other FDA Activities to Develop Regulation in the 21st Century

- ICH Q8, Q9, Q10 – Evolution to QbD
- Validation
  - Revision of Compliance Policy Guide
  - Guidance being revised
- Risk-Based Site selection Model for CGMP Inspections
- Office of New Drug Quality Assessment (ONDQA)
  - Pharmaceutical Quality Assessment System
  - CMC Pilot
- Question Based Review (OGD)

CDER Conference on CMC: http://www.pharmaconference.com

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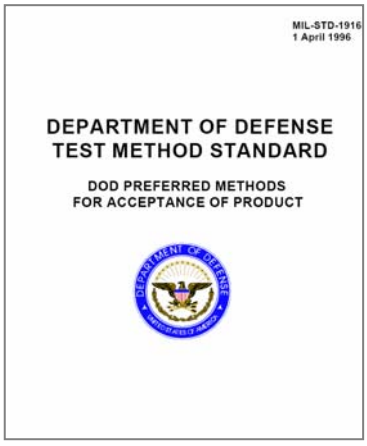
How do we get there? Can we learn from others?

- World's single largest purchaser
- Long history of good and bad experiences
- Lives depend on the quality of products
- Moved away from a focus on sampling and inspection of finished material
- Moved toward defining measurement and control of desired attributes during processing

Standards

- Sampling
  - MIL STD 105E (ANSI/ASQ)
  - No longer supported ('95)
- Process focused Standard
  - MIL-STD-1916



MIL-STD-1916 (April 1996)

3. DoD procurement practices encourage industry innovation and provide flexibility to achieve the benefits of continuous improvement.

4. There is an evolving industrial product quality philosophy that recognizes the need for quality policy changes that will provide defense contractors with opportunities and incentives toward improvement of product quality and cooperative relationships between the contractor and the Government.

5. Process controls and statistical control methods are the preferable means of preventing nonconformances, controlling quality, and generating information for improvement. An effective process control system may also be used to provide information to assess the quality of deliverables submitted for acceptance. Suppliers are encouraged to use process control and statistical control procedures for their internal control and to submit effective process control procedures in lieu of prescribed sampling requirements to the Government for approval.

6. Sampling inspection by itself is an inefficient industrial practice for demonstrating conformance to the requirements of a contract and its technical data package. The application of sampling plans for acceptance involves both consumer and producer risks; and increased sampling is one way of reducing these risks, but it also increases costs. Suppliers can reduce risks by employing efficient processes with appropriate process controls. To the extent that such practices are employed and are effective, risk is controlled and, consequently, inspection and testing can be reduced.

FDA "Desired State"

Extensive Product Testing
Little Process Understanding

→

High Process Understanding and Control

Obviated End Product Testing

Increasing Desirability

Jon E. Clark, Associate Director, OPS

Processes controlled

- well, and with high capability
- lot acceptance via sampling and inspection of the product is redundant and unnecessary

What is possible...

- Timely measurements of relevant characteristics (physical and/or chemical)
  - provide a means to understand, evaluate, and directly control the evolution of product quality during processing
  - foundation for real-time release
- Multi-variate/-dimensional measurements
  - used for process control
  - also provide a more comprehensive evaluation of product quality
  - establish relationships to product performance
- "Specifications"
  - compilation of information from throughout the manufacturing process
  - complex, but more complete, representation of product quality
- The FDA has evaluated and approved such approaches to assessing and controlling product quality

How may this evolve?

- Innovations in *Critical Path* research
  - advanced techniques for the predictability of safety and efficacy
  - mechanisms for the direct evaluation and control of clinical performance
  - integrated into process control strategies
- Associated "specifications"
  - formal means to convey implications of product and process changes
  - minimal uncertainty
  - minimal risk to the patient

What will Processes look like?

Summary

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Clarifications

- Voluntary ("FDA requires...")
  - No need to extend to other products/facilities
- Implementation
  - Many options/Incremental
- Control
  - Automation ≠ Control
  - Develop Strategy; Optimize/Refine Manufacturing
- Research Data
- FDA Approval
  - "We provide an FDA approved PAT..."

Contact

- chris.watts@fda.hhs.gov
- (301)-796-1625