


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


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

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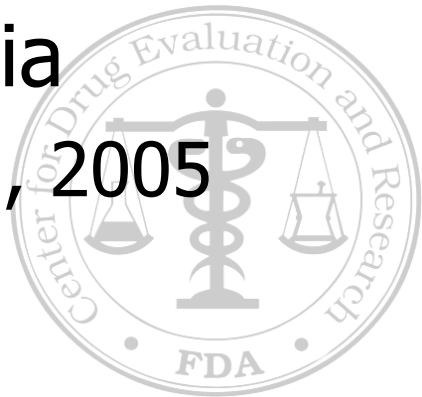
FDA/RPSGB Guidance Workshop
December 14, 2004

Guidance Workshops

- Brussels, Belgium
  - February 22, 2005
- Mumbai, India
  - February 25, 2005



The Course

- History of PAT
- Guidance Overview
  - What is PAT?
  - Principles and Tools
  - Strategy for Implementation
- Regulatory Approach
  - Who is involved?
- Where are we going with PAT?

The Genesis of PAT: A Proactive Initiative

- Began at ACPS Discussions in July, 2001
- FDA Science Board Meetings (11/01, 4/02)
  - Current state of Pharmaceutical Manufacturing
    - Industrial Practice
    - FDA Regulation
  - Science Board support for FDA's proposal to facilitate innovation

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

THE WALL STREET JOURNAL.

WEDNESDAY, SEPTEMBER 3, 2003 - VOL. CCXLII NO. 45 - ★★★★ $1.00

Factory Shift

New Prescription For Drug Makers: Update the Plants

After Years of Neglect, Industry Focuses on Manufacturing; FDA Acts as a Catalyst

The Three-Story Blender

By Leila Abboud
And Scott Hensley

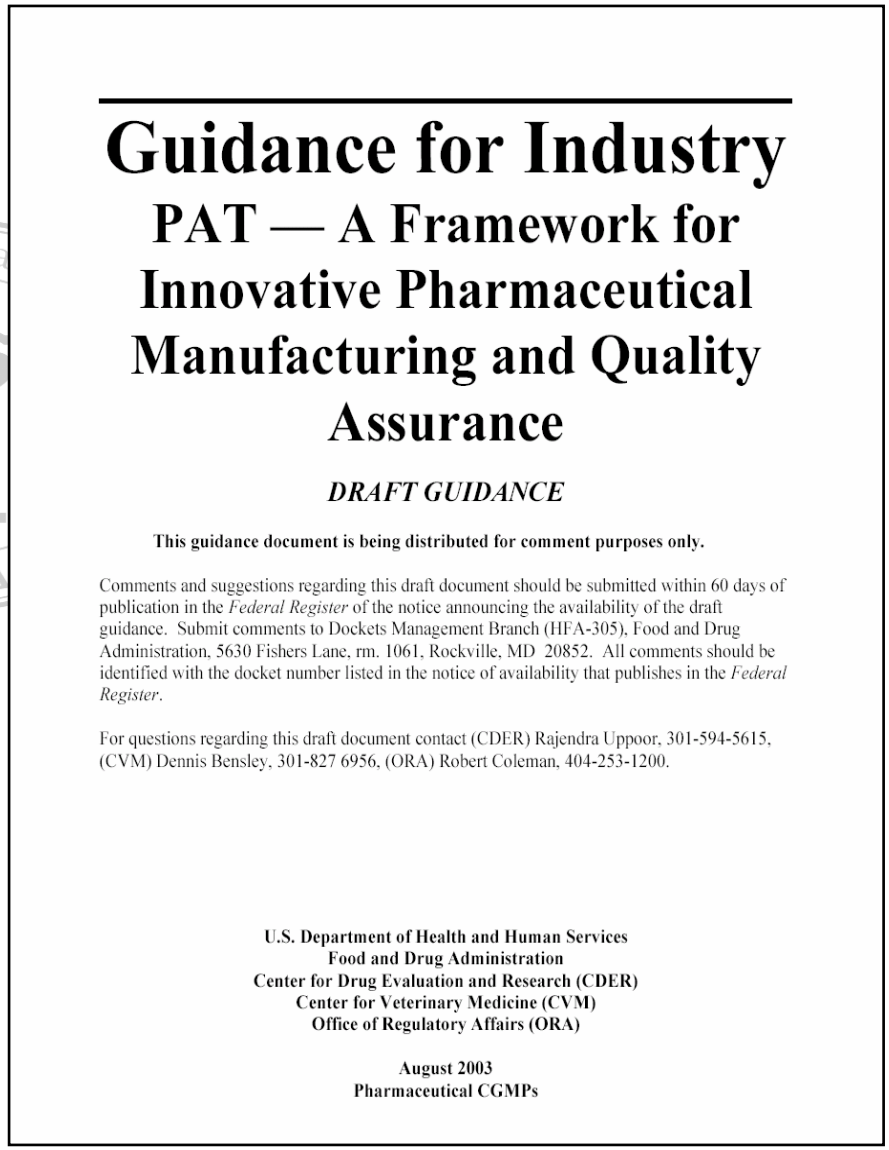
Main points from this:

- High tech in R & D
- Relatively low tech in Manufacturing
- It matters
  - Big Pharma manufacturing costs are $ 90 Bn
  - Significantly more than R&D

Quality by Design: A Challenge to the Pharma Industry
(CAMP, R. Scherzer. FDA Sci. Board. 4/9/02)

Draft PAT Guidance

- Released September 3, 2003
- Public Comment through November 4, 2003 (http://www.fda.gov/ohrms/dockets)
- Involve FDA PAT Team
  - Review comments
  - CDER, ORA, CVM
  - Team Approach
  - Certification



Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to 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 listed in the notice of availability that publishes in the *Federal Register*.

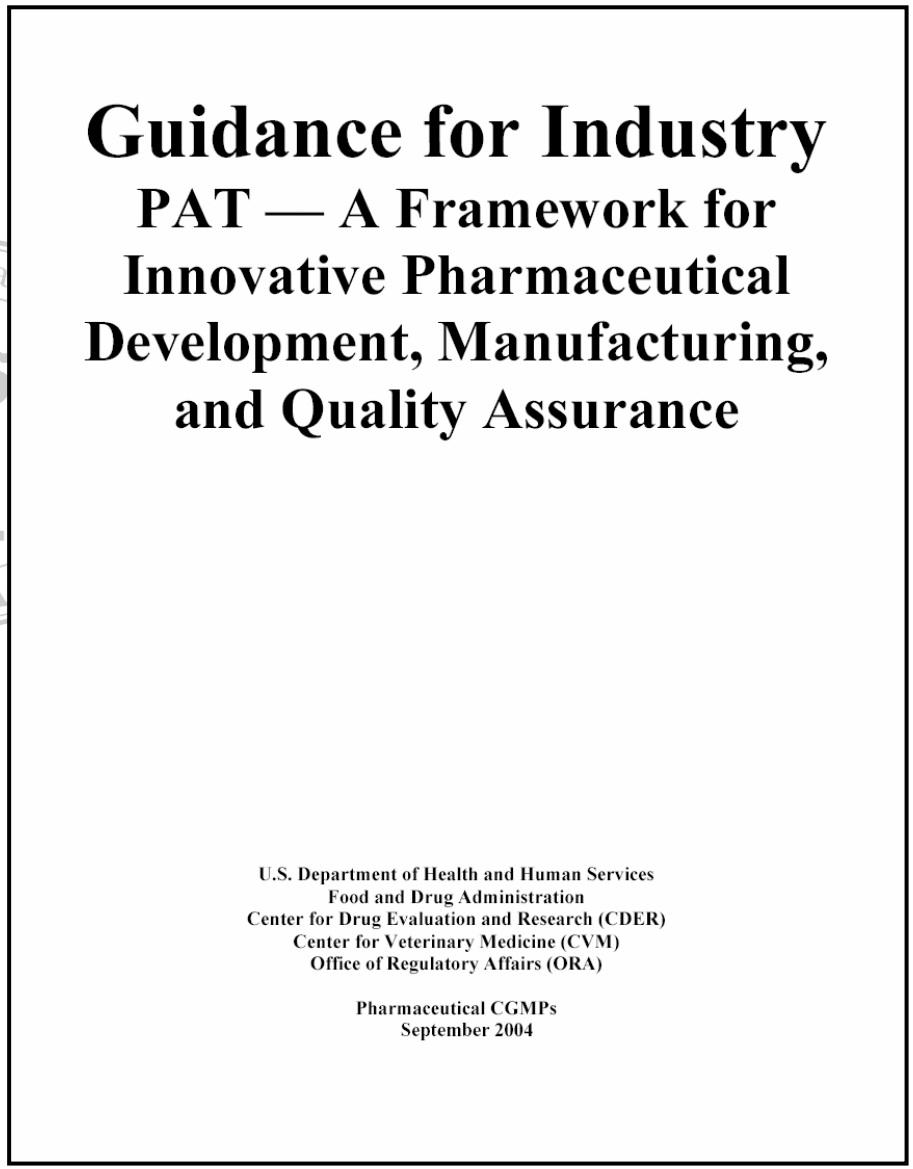
For questions regarding this draft document contact (CDER) Rajendra Uppoor, 301-594-5615, (CVM) Dennis Bensley, 301-827 6956, (ORA) Robert Coleman, 404-253-1200.

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)

August 2003
Pharmaceutical CGMPs

PAT Guidance

- Released September 29, 2004
- Scientific principles and tools supporting innovation
  - Process Understanding
  - PAT Tools
  - Risk-Based Approach
  - Integrated Approach
- Regulatory Strategy accommodating *innovation*
  - PAT Team approach to Review *and* Inspection
  - Joint training and certification of staff



Guidance for Industry

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

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Pharmaceutical CGMPs
September 2004

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

Guidance Scope

- Framework founded on process understanding
  - facilitate innovation and risk-based regulatory decisions

- Two components:
  - Scientific principles and tools supporting innovation
  - Regulatory strategy to accommodate innovation
    - Team approach to review and inspection
    - Joint training and certification of PAT review and inspection staff

Guidance Scope

- Alleviate concern that innovation will result in regulatory impasse
- 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

PAT Framework

- The goal of PAT is to enhance understanding and control of the manufacturing process
- *quality cannot be tested into products; it should be built-in or should be by design*.
- allows more focus to be placed on relevant multi-factorial relationships
  - provides a basis for identifying and understanding relationships among various critical formulation and process factors and for developing effective risk mitigation strategies (e.g., product specifications, process controls, training)

PAT Framework: PAT = 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

PAT Framework: Process Understanding

- A focus on process understanding can reduce validation burden
  - providing more options for justifying and qualifying systems intended to monitor and control biological, physical, and/or chemical attributes of materials and processes
- Transfer of laboratory methods to on-, in-, or at-line methods may not necessarily be PAT
  - Existing regulatory guidance documents and compendial approaches on analytical method validation should be considered

Principles and Tools

- PAT Tools
- Risk Based Approach
- Integrated Systems Approach
- Real Time Release

PAT Tools

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

- An appropriate combination of some, or all, of these tools may be applicable to a single-unit operation, or to an entire manufacturing process and its quality assurance

PAT Tools: Multivariate Tools

- Products and processes are complex multi-factorial systems
  - physical, chemical, biological
- statistical design of experiments
  - one-factor-at-a-time experiments do not address interactions of product and process
  - ID critical product and process variables
- mathematical relationships
  - applicability and reliability of model predictions can be assessed by statistical evaluation

PAT Tools: Process Analyzers

- Evolution of Process Analyzers
  - univariate process measurements (pH, T, P) to
  - nondestructive measurement of biological, chemical, and physical attributes of material
- Need not be absolute values of attributes
- Flexible process to manage material variability
  - justified when differences in quality attributes used to control (e.g.,feed-forward and/or feed-back) the process

PAT Tools: Process Analyzers

- Comprehensive statistical and risk analyses of the process generally necessary
  - Assess the reliability of predictive mathematical relationships
  - Based on risk, a simple correlation function may need further support or justification (mechanistic explanation of causal links)
  - Installation on existing production equipment
- *Process signature* may be used for process control
  - when related to product and process quality

PAT Tools: Process Control Tools

- Monitor the state of a process and actively manipulate it to maintain a desired state
- Strategies accommodate
  - attributes of input materials
  - the ability and reliability of process analyzers to measure critical attributes
  - ahievement of process end points to ensure consistent quality
- End points = achievement of the desired material attribute (not process "t")
  - range of acceptable times likely to develop

PAT Tools: Process Control Tools

- Multivariate Statistical Process Control
  - can be feasible and valuable to realizing the full benefit of real time measurements
- Decisions based on process understanding
  - prediction and control of relevant (critical) process/product attributes
  - consistent with CGMP requirements, as such control procedures validate the performance of the manufacturing process - 21 CFR 211.110(a)

PAT Tools: Process Control Tools

- Alternative, effective mechanisms to demonstrate validation
  - high assurance of quality on every batch designed to ensure quality)
  - validation demonstrated through continuous quality assurance
    - process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process end points
- Software validation via risk-based approach
  - recommendations provided by other guidances
  - information from consensus standards (ASTM)

PAT Tools: Continuous Improvement and Knowledge Management

- Continuous learning through data collection and analysis over the life cycle of a product
  - contribute to justifying proposals for postapproval changes
- Within products and processes
- Across products and processes

PAT: Risk-Managed Approach to Regulatory Scrutiny

- 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 can facilitate risk-managed regulatory decisions and innovation

Integrated Systems Approach

- Necessary for evaluation and timely application of systems
- Across disciplines and organizations
  - upper management support critical

Real Time Release

- *Real time release* is the ability to evaluate and ensure the acceptable quality of in-process material and/or final product based on process data.
- Typically, the PAT component of *real time release* includes a valid combination of assessed material attributes and process controls.
- The combined process measurements and other test data gathered during the manufacturing process can serve as the basis for *real time release* of the final product and would demonstrate that each batch conforms to established regulatory quality attributes.

Research Data

- Suitability of PAT tool production equipment
  - risk analysis determine impact on product quality (prior to implementation)
  - within the facility's quality system without prior notification to the Agency
- Data collected using an experimental tool should be considered research data
  - intrinsic data trends may be observed
  - scientifically evaluate to determine affect on quality and implementation of PAT

Research Data

- FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental process analyzer or other PAT tool

Regulatory Implementation Strategy

- Flexibility, coordination, and communication critical to enable successful implementation of PAT
- Agency's regulatory strategy
  - A PAT team approach for CMC review and CGMP inspections
  - Joint training and certification of PAT review, inspection, and compliance staff
  - Scientific and technical support for the PAT review, inspection, and compliance staff
  - The recommendations provided in this guidance

PAT Regulatory Approach

- Tailor the regulatory scrutiny to meet the needs of PAT-based innovations that
  - improve the scientific basis for establishing regulatory specifications
  - promote continuous improvement
  - improve manufacturing efficiency while maintaining or improving the current level of product quality
- Goal is to facilitate a consistent scientific regulatory assessment involving multiple Agency offices with varied responsibilities

PAT Regulatory Approach

- Any questions contact PAT Team at PAT@cder.fda.gov
- All written correspondence clearly identified as PROCESS ANALYTICAL TECHNOLOGY or PAT.
- All marketing applications, amendments, or supplements to an application should be submitted to the appropriate CDER or CVM division in the usual manner

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

PAT Approach: Quality by Design

Focus on Process Understanding

- What parameters are critical to Product Quality?
  - Experimental Design
- How do we analyze these parameters?
  - K.I.S.
- How do we control these parameters throughout the process?
  - Feed-back/-forward

The FDA PAT Team (ORA, CDER, CVM)

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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?

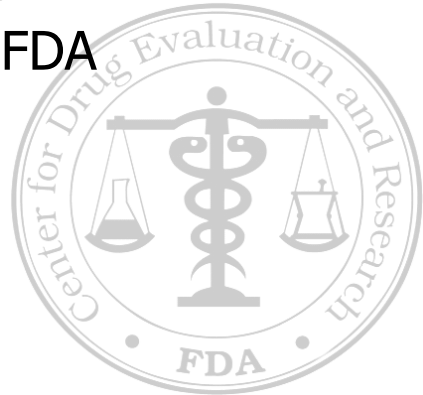
PAT and CGMP Initiative

- FDA CGMP Initiative
  - Risk-based regulation
  - "Non-impeding" regulation
  - Consistent regulation
- Success based on Broad Cooperation
  - Industry
  - Academia
  - FDA

    http://www.fda.gov/bbs/topics/NEWS/2002/NEW00829.html

ASTM Technical Committee E55

- Technical Committee E55: The Pharmaceutical Application of Process Analytical Technology
  - Consensus Standards
  - Industry, Academia, FDA
  - Balanced
- ASTM International
  - Global
  - ANSI accredited
  - > 100 years experience
- Committee Organization
  - E55.01: PAT System Management
  - E55.02: PAT System Implementation and Practice
  - E55.90: Executive Committee
  - E55.91: Terminology
- NTTAA



Summary

- Not just analyzers
  - System for design, analysis, and control
  - Focus on Process Understanding
- Voluntary
- Several Options for Implementation
  - Existing Products and Processes
    - Research Data
  - New Products and Processes
  - Proposed by firm
- Team Approach to Regulation
  - Joint Training and Certification
  - Continued Training of FDA Staff