


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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PittCon
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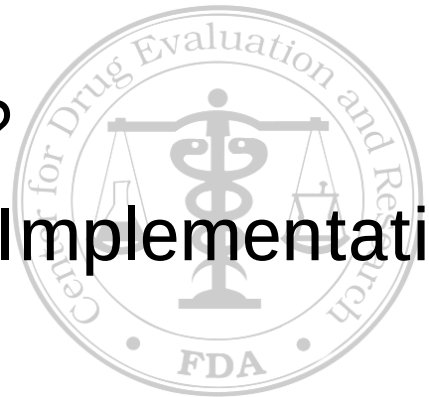
# The Course

- History of PAT
- Overview
  - What is PAT?
  - Strategy for Implementation
  - FAQs
- Regulatory Approach
  - Who is involved?
- Where are we going with PAT?
  - Next Steps



# 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.



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*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

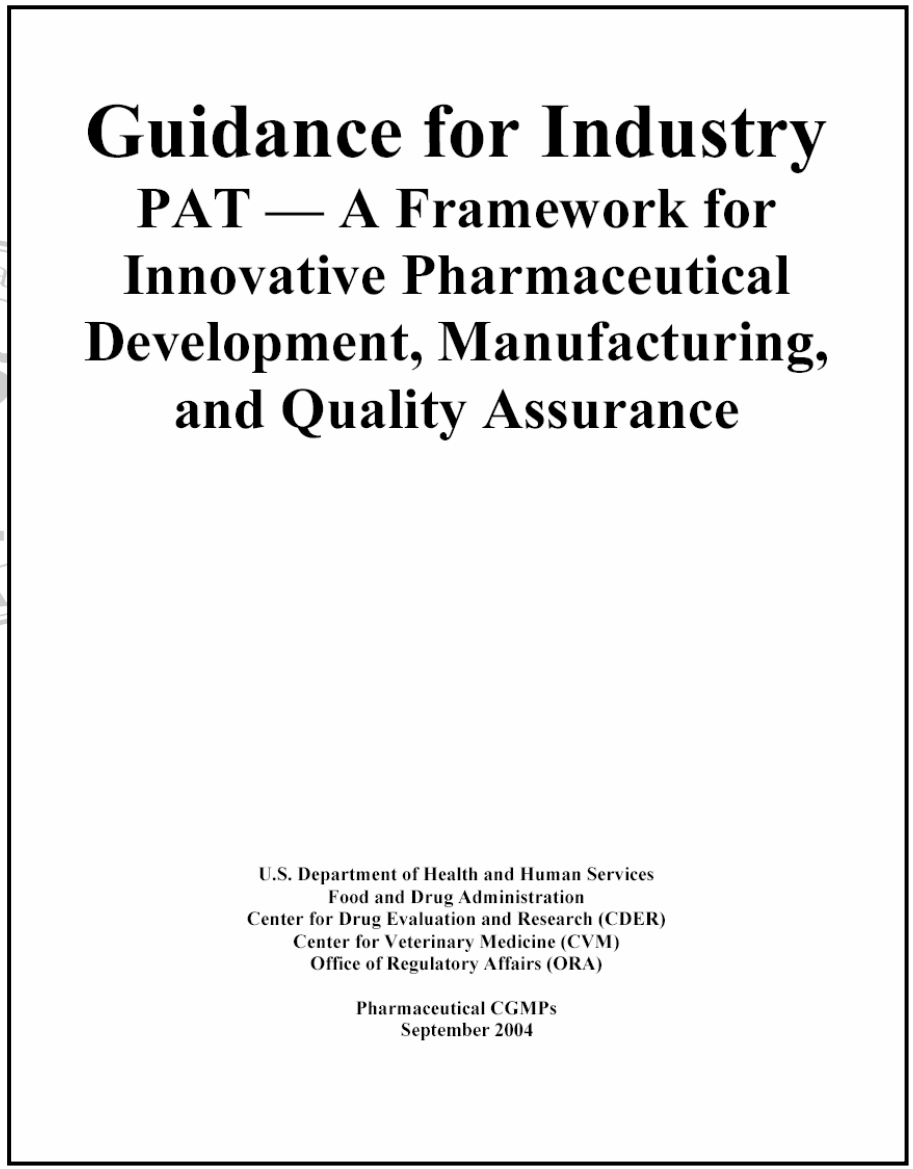
Main points from this:

- 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)

# PAT Guidance

- *Draft*, September 3, 2003
  - Comment through Nov 2003
- 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**

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

# 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

# FAQs

- New and abbreviated new drug application products and specified biologics regulated by CDER and CVM
  - non-application drug products
  - drug substance and drug product
- Voluntary
  - No need to extend to other products/facilities
- Transfer of laboratory methods to on-, in-, or at-line methods may not necessarily be PAT

# FAQs

- Research Data
  - Suitability of PAT tool production equipment
  - risk analysis determine impact on product quality (prior to implementation) - w/in facility's quality system
  - Data collected using an experimental tool should be considered research data
  - FDA does not intend to inspect research data
- Real Time Release
  - ability to evaluate and ensure the acceptable quality of in-process material and/or final product based on process data
  - includes a valid combination of assessed material attributes and process controls
  - RTR ≠ Parametric Release

# 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

# 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?

# 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

# The FDA PAT Team (ORA, CDER, CVM)

**PAT Steering Committee**

Doug Ellsworth, ORA/FDA
Dennis Bensley, CVM/FDA
Patricia Lefler, ORA/FDA
Joe Famulare, CDER/FDA
Keith Webber, CDER/FDA
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# Next Steps: Integrate System

- Incorporation of the PAT process under the FDA's Quality System
- Continued participation in ASTM Committee E55 and ICH
- Second PAT Team, teambuilding, training and certification
  - CBER and Team-Bio representative to join PAT Steering Committee

# Next Steps: Integrate System

- Expand the PAT program to *Product Specialists* and the *Pharmaceutical Inspectorate*
- Critical Path Initiative
  - to strengthen the internal and emerging external support infrastructure in the US for the desired state

# 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
- ASTM E55

# Contact

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  - wattsc@cder.fda.gov
- PAT on the Web:
  - http://www.fda.gov/cder/OPS/PAT.htm
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  - (301)-443-5197

# 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 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