PAT: Opportunities for "Green" Quality and Control

Creating Business Value: Green Quality through Green Chemistry and Green Engineering in the Pharmaceutical Industry

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Silver Spring, MD

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What are the objectives?

Discussion Topics

- “Desired State”
- Integrated Process Control
  - Process Improvement/Optimization
- (R)Evolution of Agency Processes
  - PAT, DMF modernization, Rule change
- Real-Time Release and Evolution of “Specifications”
- Opportunities

FDA "Desired State"

Extensive Product Testing
Little Process Understanding

Increasing Desirability

High Process Understanding and Control

Obviated End Product Testing

Adapted from 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

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight". *Janet Woodcock*

Why PAT? Industry Perspective

Current Paradigm

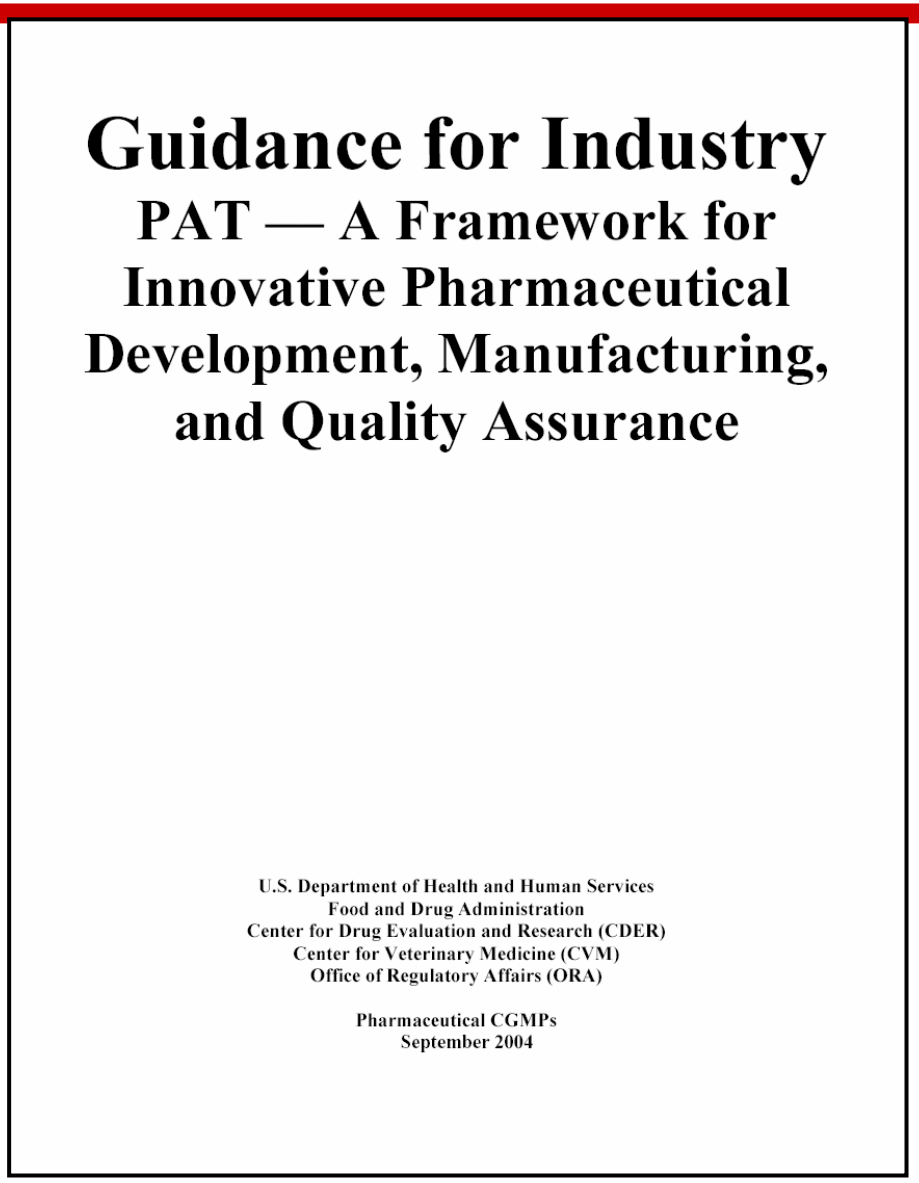
- Utilisation levels - 30% or less
- Scrap and rework - plan for 5-10%
- Time to effectiveness - takes years
  - Many supplements in first few years
- Hesitant to Innovate (Perceived Barriers)
  - Incentive?
  - "Don't ask/Don't tell"
- Manufacturing Costs: $90 Billion

Doug Dean, FDA Science Board, Nov 16, 2001

Ray Scherzer, FDA Science Board, Apr 2, 2002

PAT Guidance

- 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
- Not “How-to”



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

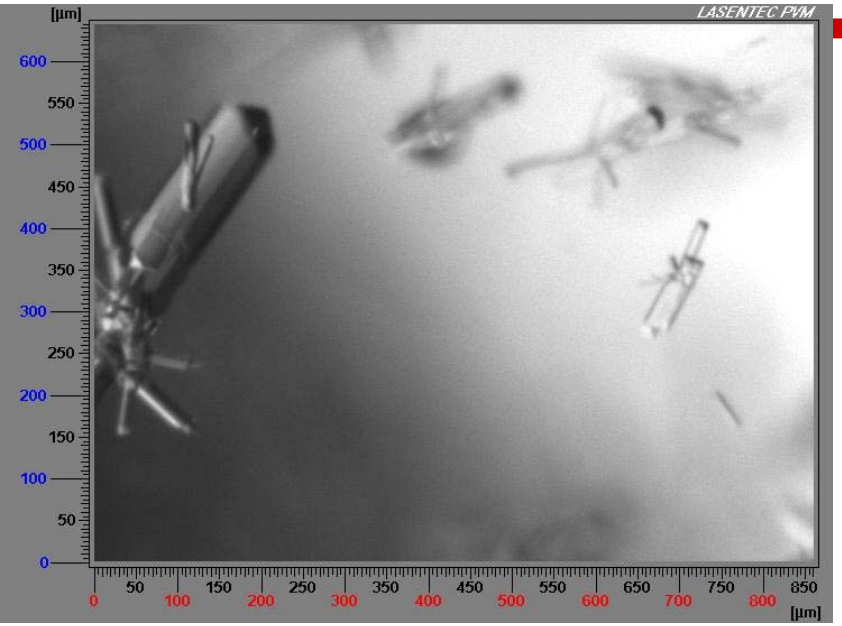
What is PAT?

- A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality.
- Focus of PAT is Understanding and Controlling the manufacturing Process

PAT Tools: Process Control Tools

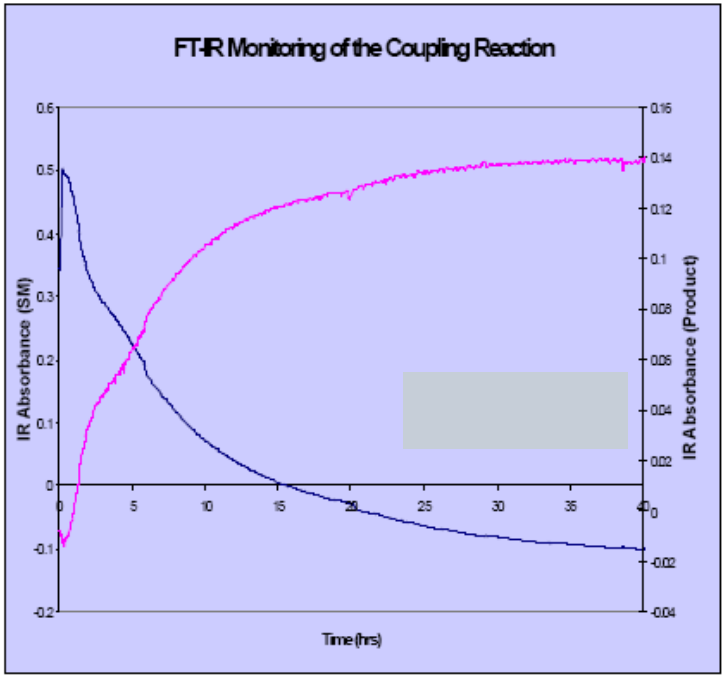
- Monitor the state of a process and actively manipulate it to maintain a desired state
- Strategies accommodate
  - attributes of input materials
  - the ability and reliability of process analyzers to measure critical attributes
  - achievement of process end points to ensure consistent quality
- End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

Flexible Process: Based on Material Measurement(s)



Martin Warman, Pfizer,

IFPAC 2003

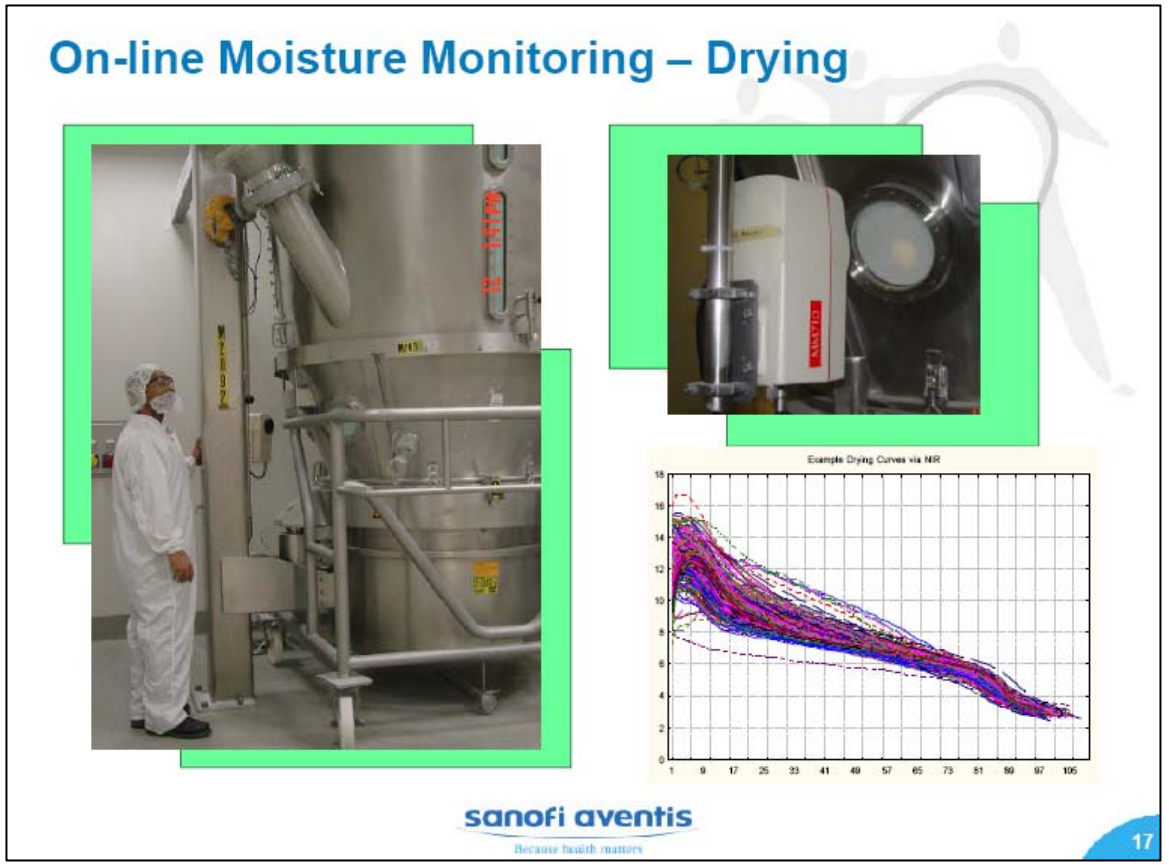


San Kiang, BMS

Understand and Control Raw Material Process

- Non-destructive on-/in-line material measurement
- Engineer Feed-back control for desired Physical and Chemical attributes
- Feed-forward control for other processes

PAT: Design, Analyze, and Control



David Radspinner, Sanofi-Aventis

PAT Guidance Workshop, December 14, 2004, London, UK

Control Process

On-line moisture measurement

No sampling and lab test

Increase Efficiency

Eliminate Solvent Use

Decrease Energy Use

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
- Processes Understood and Controlled (measure of material attributes)
  - Flexible Regulatory Approach to Change Management (Decrease Supplements)

Real Time Release – PAT Guidance

- *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.

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 happen?

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