



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



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# Opportunities for “Green Quality” and Control

**Seize the Moment:  
Opportunities for Green Chemistry and  
Green Engineering in the Pharmaceutical Industry**

September 27, 2007, New York, NY

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## What are the objectives?

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### **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”

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Extensive Product Testing  
Little Process Understanding



High Process  
Understanding and Control

Increasing Desirability

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

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### 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

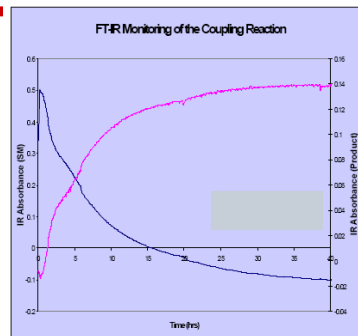
## PAT Tools: Process Control Tools

- **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*



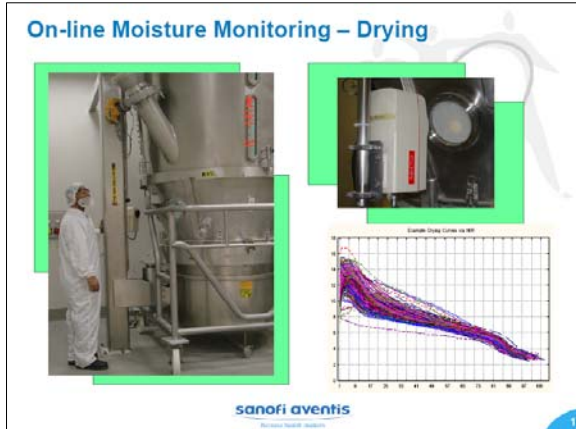
*San Kiang, BMS*

### 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

### On-line Moisture Monitoring – Drying



David Radspinner, Sanofi-Aventis  
PAT Guidance Workshop, December  
14, 2004, London, UK

Control Process

Increase Efficiency

On-line moisture measurement

Eliminate Solvent Use

No sampling and lab test

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)

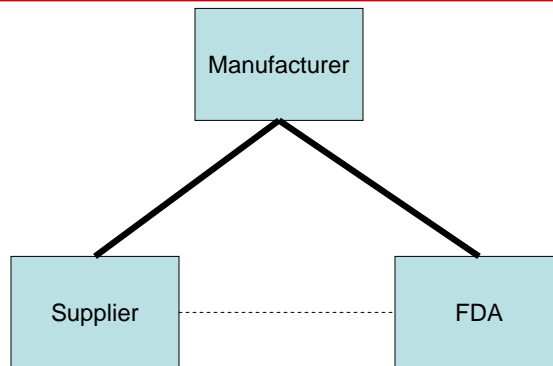
## Real Time Release – PAT Guidance

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- *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.

## Modernize DMF

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- Depend more on manufacturer/supplier quality systems
- Learn to use quality agreement to support product quality efforts
- Better identification/management of confidential/proprietary information

## How may this evolve?

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- 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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## **Acknowledgements**

Keith Webber, Deputy Director, OPS/CDER  
Jon E. Clark, Associate Director, OPS/CDER  
David Cummings, CQM, OPS/CDER  
Ali Afnan, Visiting Scientist, OPS/CDER

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