


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


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

Ali Afnan, Ph.D.
Office of Pharmaceutical Science, CDER, FDA

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What is PAT?

An Enabling Framework

- **For innovation in development, manufacturing and quality assurance by**
  - **removing "regulatory fear/uncertainty"**
  - **utilizing science & risk-based approach to regulatory requirements and oversight**
  - **providing a flexible and less burdensome regulatory approach for well understood processes**
  - **creating an environment that facilitates rationale science, risk, and business decisions**

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**

The goal of PAT is to understand and control the manufacturing process

What is PAT?

Scientific principles and tools supporting innovation

- PAT Principles
  - Process Understanding
  - Risk-Based Approach
  - Regulatory Strategy to accommodate innovation
  - Real Time Release
- PAT Tools
  - Multivariate Tools for Design, Data Acquisition and Analysis
  - Process Analyzers
  - Process Control Tools
  - Continuous Improvement and Knowledge Management Tools

What is PAT?

- **Integrated Approach**
  - **PAT Team approach to Review *and* Inspection**
  - **Joint training and certification of staff**

PAT

- **Ensure appropriate control of all relevant critical attributes of in-process materials (e.g., using process endpoints) to allow the process to manage the inherent variability of material attributes that can impact the quality of the output**

PAT Framework

PAT goals are achieved through

- **Dynamic Processes that manage variability**
- **Using validated controls**

What is a PAT application?

- 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 (assessment and mitigation) acceptable?
  - Is the strategy for integrating systems acceptable?
  - Is the strategy for real time release acceptable?
- Is the proposed regulatory process acceptable?

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**

Process Understanding - Validation

- **Can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to achieve validation**
  - **process validation can be enhanced**
    - **possibly continuous quality assurance where a process is continually monitored, evaluated, and adjusted**
    - **using validated in-process measurements, tests, controls, and process endpoints**
  - **A process is controlled using validated controls**

FDA PAT guidance and Qualification

A focus on process understanding can reduce the burden for validating systems, providing more options for qualifying and justifying systems intended to measure and control biological, physical, and/or chemical attributes of materials.

FDA PAT guidance and Qualification

Risk-based approaches are suggested for validation of PAT software systems. The recommendations provided by other FDA guidances such as *General Principles of Software Validation* should be considered. Other useful information can be obtained from consensus standards, such as ASTM.

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

Real Time Release (RTR)

- Process understanding, control strategies, plus on-, in-, or at-line measurement of critical attributes
  - that relate to product quality
- provide a scientific risk-based approach to real time quality assurance.

Real Time Release (RTR)

- With real time quality assurance, the desired quality attributes
  - Are ensured through continuous assessment during manufacture.
- Data from production batches can serve to validate the process and reflect the total system design concept
  - supporting validation with each manufacturing batch.

Real Time Release (RTR)

- **Is the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data.**

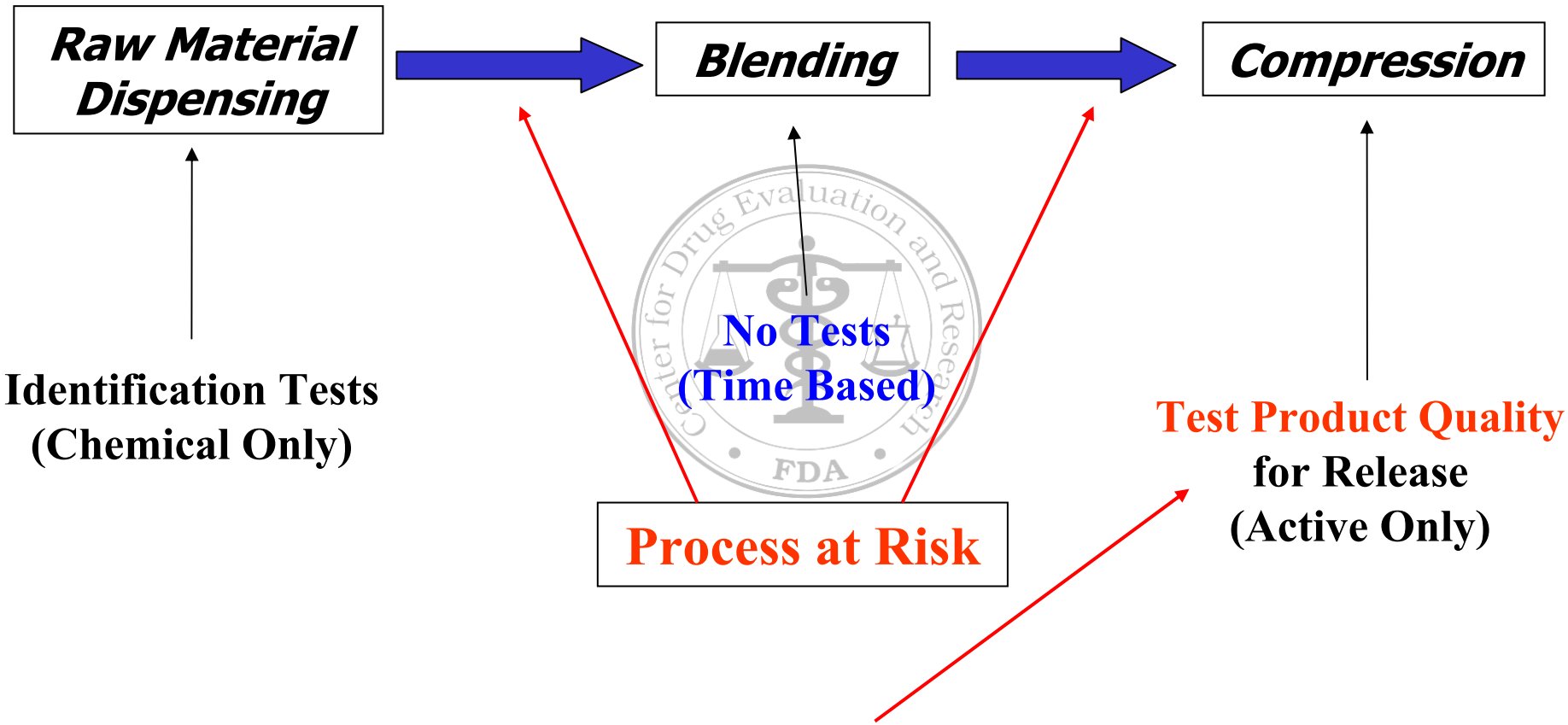
Real Time Release

- Typically, a valid combination of
  - material attributes
    - assessed using direct and/or indirect process measurements.
  - process controls
- serve as the basis for real time release of the final product
- demonstrating each batch conforms to established regulatory quality attributes.

PAT Regulatory Process

- A flexible process
  - generally starts with a scientific proposal by a sponsor followed by discussions with PAT team
  - to ensure clear understating of scientific principles and the type of information and knowledge necessary to support the proposed application
- This discussion may lead to a regulatory submission (e.g., a supplement or a comparability protocol)
  - the guidance provides for other flexible options
- Evaluation/assessment of the submission and a team approach for ensuring all aspects are addressed and followed by a team based inspection

How can PAT help?
Example: Current Tablet Production



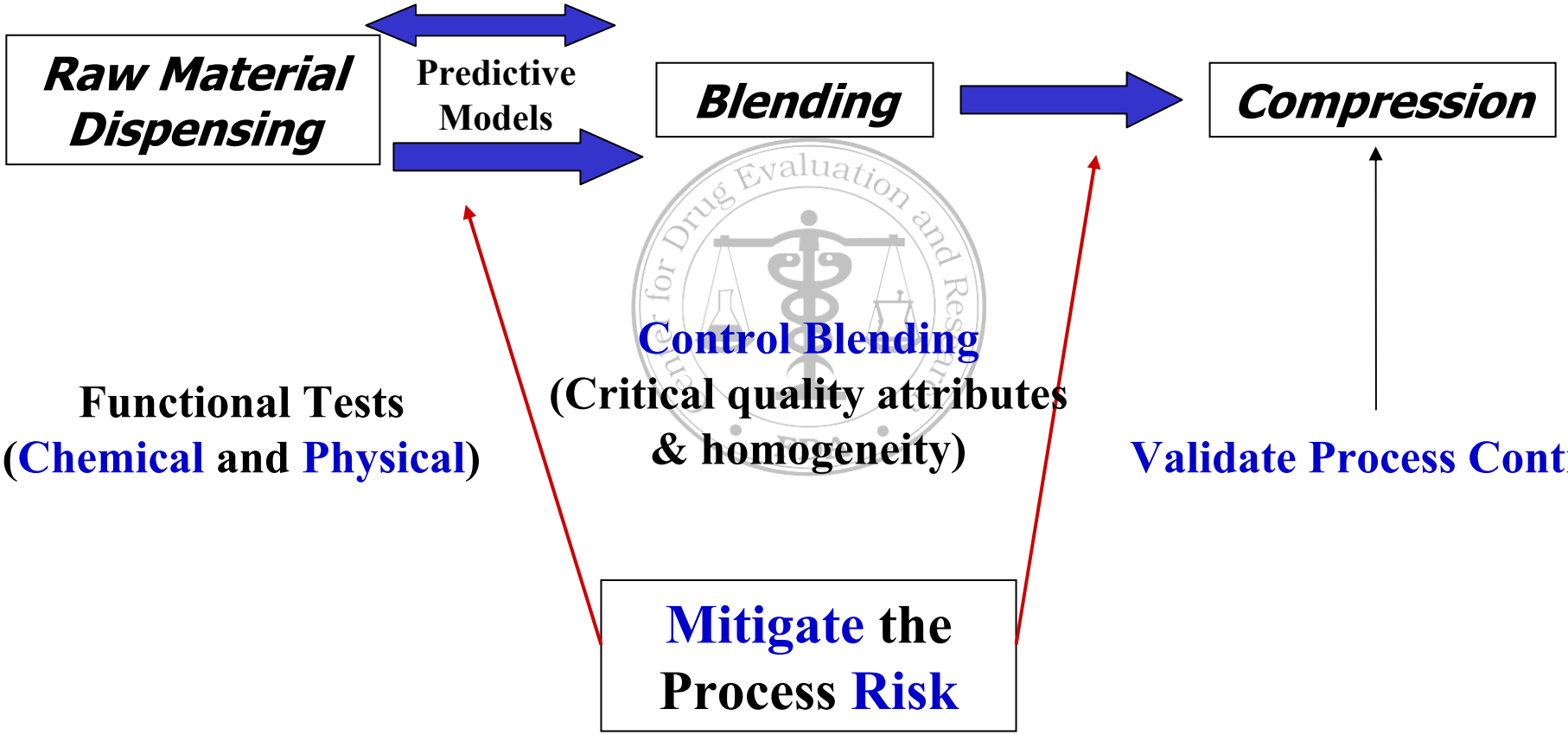
Current Tablet Production: Testing to Document Quality

- **What is the Product Test?**
  - **Typically 30 Tablets/batch (1,000,000)**
- **What process Information does this provide?**
  - **None. Testing is Product focused.**
- **Will we see "failures"?**
  - **Expect number of "failing" tablets/batch, even though 30 tablets/batch "pass"**
  - **4% of batches may fail, even though not different from a "passing" batch**
- **Does this facilitate process understanding and control?**
  - **No**

"Novel Technology" Approach: Still Testing to Document Quality

- **What is the Product Test?**
  - Test every tablet (all 1,000,000)
- **What process Information does this provide?**
  - None. Testing is still Product focused.
  - Better estimate of Variability in Final Product
- **Why the variability?**
  - ?
  - Change acceptance criteria?
    - ⇨ Allow some outside 75%-125%
- **Facilitate process understanding and control?**
  - No

PAT Approach Example: Tablet Production



Process Focused

PAT Approach: Quality by Design

Focus on Process Understanding

- What parameters are critical to Product Quality?
  - Experimental Design
- How do we measure/ monitor these parameters?
  - Appropriate Instrumentation
- How do we control these parameters throughout the process?

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Forthcoming Guidance Workshops

Brussels, Belgium

February 22, 2005

Mumbai, India

February 25, 2005

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