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

The Future Lies Ahead – Achieving the Transition to the "Desired State"

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26 Oct 2007

Future

… design and develop well understood processes that will consistently ensure a predefined quality at the end of the manufacturing process.

Such procedures would be *consistent* with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency.

The PAT Guidance

The Desired State

- **Product quality and performance**
  - **ensured through design**
    - **Formulation, product and process**
  - **effective and efficient manufacturing processes**
- **Specifications: Product and process**
  - **based on a *mechanistic* understanding**
  - **how formulation and process factors affect product performance**
- **Continuous *real time* quality assurance**
- **Regulatory policies and procedures: Relevant**
  - **tailored to accommodate … scientific knowledge**

The Goal

- … is to design and develop well understood processes
  - that will consistently ensure a predefined quality at the end of the manufacturing process.
- Such procedures consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns
  - while improving efficiency
  - Allowing continuous improvement
    - ⇨ Process Optimization, Product Improvement

What does This Have to Do with PAT?

- Critical Path about accelerating pace of introduction of new science/technology into regulation and regulated industry
- PAT emblematic of new way of thinking about pharmaceutical manufacturing
- Move from empirically-derived trial-and-error methods to rigorous, mechanistically-based and statistically controlled processes

1. What is PAT ?

•Manufacturing Execution Systems

Process Models

Instruments

SOPs

Data Communications Infrastructure

Raw Materials Data

Predicted CQAs

Regulatory Approval

Control Models

Real-Time Data Management

Analysis tools

Mechanistic Models

Process Equipment Development

Process Control Systems

"PAT is considered to be a system for designing, analysing, and controlling manufacturing through timely measurements of critical quality attributes and performance attributes…….. with the goal of ensuring final product quality"

Author : Gawayne Mahboubian-Jones

1. What is PAT ?

"PAT is considered to be a system for designing, analysing, and controlling manufacturing through timely measurements of critical quality attributes and performance attributes…….. with the goal of ensuring final product quality"

The Manufacturing Process

 Author : Gawayne Mahboubian-Jones

1. What is PAT ?

"PAT is considered to be a system for designing, analysing, and controlling manufacturing through timely measurements of critical quality attributes and performance attributes…….. with the goal of ensuring final product quality"

The Condition of the Process Material

Measuring the Critical Quality Attributes during the process

 Author : Gawayne Mahboubian-Jones

1. What is PAT ?

"PAT is considered to be a system for designing, analysing, and controlling manufacturing through timely measurements of critical quality attributes and performance attributes…….. with the goal of ensuring final product quality"

The Trajectory of the Manufacturing Process

(to ensure we can and do achieve the desired final CQAs)

 Author : Gawayne Mahboubian-Jones

1. What is PAT ?

"PAT is considered to be a system for designing, analysing, and controlling manufacturing through timely measurements of critical quality attributes and performance attributes…….. with the goal of ensuring final product quality"

To implement PAT we must do all three

 Author : Gawayne Mahboubian-Jones

2. How do we apply PAT ?

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3. Why do we apply PAT ?

"PAT is considered to be a system for designing, analysing, and controlling manufacturing through timely measurements of critical quality attributes and performance attributes…….. with the goal of ensuring final product quality"

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PAT Antonyms

- **Measuring (not controlling) the finished product attribute**
- **Sophisticated analyzers for on-line monitoring finished product**
- **Fast end-product testing**

PAT: Process Understanding & Control

- **Process Understanding is the foundation**
- **Real time (or near real time) measurement**
  - **of Critical Attributes of materials (raw and in-process)**
- **AND Control of Attributes**
  - **Using the Process**
- **Process control aimed at reducing or eliminating variability**
- **The process understanding … will enable process control and optimization, address the limitation of the time-defined end points… and improve efficiency.**
- **Real Time Release (RTR) is an outcome**

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**

PAT: Towards the Desired State

Process End Points

- **Currently, most pharmaceutical processes are based on time-defined end points**
  - **time-defined end points do not consider (or manage) physical differences in raw materials**
  - **Even though materials meet pharmacopeial specifications (generally identity and chemical purity)**
- **A process end point should *not* be a fixed time;**
  - **it is the achievement of the desired material attribute**

Control Strategies

Ability to evaluate and ensure product quality based on performance parameters and product attributes in real time allowing feedback, feed forward, and potentially real time release

Real Time Release (RTR)

- **The ability to evaluate and ensure the acceptable quality of in-process and/or final product based on**
  - **Valid combination of**
    - ⇨ **material attributes**
      - – **assessed using direct and/or indirect process measurements.**
    - ⇨ **& process controls**
  - **serves as the basis for real time release of the final product**
- **demonstrating each batch conforms to quality attributes**

PAT & Specifications

- **Release specifications set to critical quality attributes based on knowledge of the relationship between the product attribute and clinical performance - i.e. not empirically derived from quality attributes of clinical batches or process capability**
- **End product testing is limited because:**
  - **non critical attributes are not specified**
  - **critical attributes are monitored in real time during manufacturing**
  - **the attribute is well-controlled by the process**
- **Unnecessary stability studies are eliminated based on knowledge and sound risk assessments**

PAT: Towards the Desired State

The Team Concept

- **Commitment to support innovation**
  - **Team approach to**
    - ⇨ **chemistry, manufacturing and control (CMC) review**
    - ⇨ **current good manufacturing practice (CGMP) inspections**
    - ⇨ **joint training and certification of PAT review and inspection staff.**
  - **Systems approach to provide flexibility, in manufacturing and regulation**
    - ⇨ **taking advantage of our team approach**
  - **Address areas of regulatory uncertainty and fear**

PAT Regulatory Interaction: What to Communicate

Process Understanding, Process Control

- **Effective innovation in development, manufacturing and quality assurance would be expected to better answer questions such as the following:**
  - **What are the mechanisms of degradation, drug release, and absorption?**
  - **What are the effects of product components on quality?**
  - **What sources of variability are critical?**
  - **How does the process manage variability?**

What to Communicate

Managing Manufacturing Processes

- **Effective processes for managing physical & chemical attributes of raw and in-process materials requires**
  - **fundamental understanding of attributes that are critical to product quality**
  - **And controlling those attributes**
    - **Off-line sampling for identification and control of critical attributes may not be efficient**

PAT: How to Deliver The Desired State

Design Know-How

- **Define "Product Quality" & Design a Quality Product**
  - **Clinical investigation**
  - **QbD**
- **Identify and measure critical material and process attributes relating to product quality**
- **Design a process measurement system to allow real time or near real time monitoring of all critical attributes**
- **Design process controls that provide adjustments to ensure control of all critical attributes**
- **Develop mathematical relationships between product quality attributes and measurements of critical material and process attributes**

How to Deliver The Desired State

Know How: Process Optimization

- ***Pro-actively*** **identify common cause variables**
- **and measure critical material and process attributes relating to product quality**
- **Design and implement a control strategy and risk management initiative to enable Control of the process**
- **Demonstrate process Understanding**

Moving Forward

- Major future opportunity will be better linkage between clinical performance and quality parameters
- This will inform what to measure (and what not to measure)
- Important concept for “Quality by Design”—have to understand parameters of quality

QbD, PAT, CMC

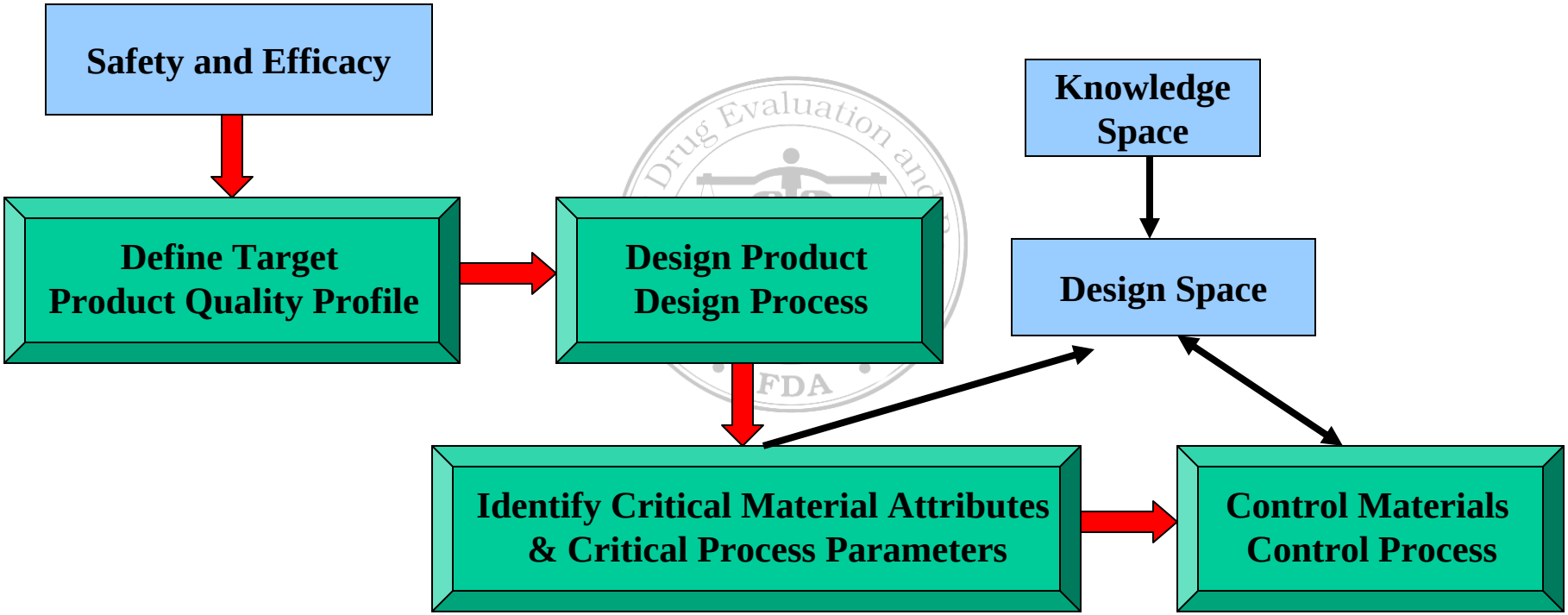
The Linkage?

What is QbD?

Quality by Design **"means that product and process performance characteristics are scientifically designed to meet specific objectives... To achieve QbD objectives, product and process characteristics important to desired performance must be derived from a combination of prior knowledge and experimental assessment during product development."**

J. Woodcock, *Am. Pharm. Rev.*, 2004

Overview of QbD



TARGET → **DESIGN** → **IMPLEMENTATION**

Quality by Design

- **Quality by Design means**
  - **designing and developing formulations and manufacturing processes to ensure a predefined quality**
- **Quality by Design requires**
  - **understanding how formulation and manufacturing process variables influence product quality**

Quality Product

- **Defining target product quality profile**
  - **The performance needed to get clinical benefit and meet consumer expectation**
- **Knowledge how formulation impacts product quality**
- **Designing product and processes to meet target product quality profile**
- **Identifying critical material attributes, process parameters, and sources of variability**
- **Controlling materials and manufacturing processes to manage variability and to produce consistent quality over time**

Regulatory Process
Delivering The Desired State

CMC

- **Consider the *Formulation***
  - **Is it suitable to deliver the function on the product**
  - **Is it suitable to manage the variability of the components (excipients, API, packaging, etc)**
  - **Determine relevant specifications based on mechanistic understanding**
  - **Manufacturer: Communicate this *knowledge***
  - **Regulator (Review): Risk assess the Formulation- is it suitable for the proposed manufacturing process?**

Regulatory Process
Delivering The Desired State

CMC

- **Consider the *Manufacturing* Process**
  - **Is it suitable to deliver the formulation**
  - **Is there understanding of the relationship between the formulation and the process**
  - **Can the process manage variability**
  - **What are the critical steps? And are they being managed?**
  - **Manufacturer: Communicate this *knowledge* & correlate to the formulation and the controls**
  - **Regulator (review): Risk assess the Manufacturing process- is it capable of managing the formulation & is it suitable for the controls?**

Regulatory Process
Delivering The Desired State

CMC

- **Consider the *Controls***
  - **Are they suitable to deliver the manufacturing process**
  - **Is there understanding of the relationship between the process and the controls**
  - **Will the controls manage the manufacturing process**
  - **Manufacturer: Communicate this *knowledge***
  - **Regulator (review): Risk assess the Controls- are they suitable for the proposed formulation and the manufacturing process?**

Regulatory Process (Inspection) Delivering The Desired State

- **Consider the *Controls***
  - **Can and do the controls manage the manufacturing process?**
  - **Can this be demonstrated with manufacturing batches?**
- **Is the Manufacturing Process capable of handling the formulation?**
  - **Are the specification meaningful?**
  - **Are the specifications adequate?**
  - **Is the combination of Controls, Manufacturing and the Formulation (Chemistry) capable, and is this being demonstrated through executed batches that are being release to the market?**
  - **Is there evidence of increase of process understanding**
  - **Is the process optimized?**

Consensus Standards

The Way Ahead

The Desired State

A Mutual Goal of Industry, Society and Regulators:

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

Dr. Janet Woodcock - October 5, 2005

Delivering the Desired State

Standards: Laws & Directives

- **Congress: National Technology Transfer and Advancement Act (NTTAA); 1995**
- **Office of Management and Budget (OMB): Circular A-119; 1998 (original in 1993)**
- **http://standards.gov/standards_gov/index.cfm**

Delivering the Desired State

Standards: The Mandate…

- **OMB Circular A-119**
  - **"…this Circular directs agencies to use voluntary consensus standards in lieu of government-unique standards except where inconsistent with law or otherwise impractical."**
  - **"This circular applies to all agencies…"**
  - **"All federal agencies must use voluntary consensus standards in lieu of government-unique standards in their procurement and regulatory activities…"**

Delivering the Desired State

"Use voluntary Consensus Standards…"

- **"To determine whether established regulatory limits or targets have been met"**
- **"Test methods"**
- **"Sampling procedures"**
- **"Protocols"**

Delivering the Desired State

FDA Standards Activities

- **Standards and Technology Team created within OPS**
  - **Coordinates CDER interaction with CSOs and the USP/NF**
  - **Advises applicants and DMF holders about implementation of standards**
- **Standards Working Group (SWG)**
  - **Build consensus across FDA for official position on standards-related issues**

Some Standards

- **E2474-06: Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology**
- **E 2500 – 07 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment**
- **E 178 – 02: Standard Practice for Dealing With Outlying Observations**
- **D 4855:Standard Practice for Comparing Test Methods**
- **E 2281 – 03 Standard Practice for Process and Measurement Capability Indices**
- **D 6708 – 01 Standard Practice for Statistical Assessment and Improvement of the Expected Agreement Between Two Test Methods that Purport to Measure the Same Property of a Material**

Some Standards

- **D6299-18408: Standard Practice for Applying Statistical Quality Assurance Techniques to Evaluate Analytical Measurement System Performance**
- **E691-9800 Standard Practice for Conducting an Interlaboratory Study to Determine the Precision of a Test Method**
- **D 6617 – 00 Standard Practice for Laboratory Bias Detection Using Single Test Result from Standard Material**
- **1325 Standard Terminology Relating to Design of Experiments**

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