The Harmonized PAT Solution: Application of Risk-Based Tools & PAT Strategies in Pharmaceutical Product Manufacture

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Cubist Pharmaceuticals
Presentation Objectives

- Provide Overview of FDA’s PAT Initiative
- Provide Overview of Risk Management & Risk Assessment Tools
- Provide PAT Strategy for Pharma Industry
- Present Case Example on PAT Strategy

Take Home Message

PAT = Process Understanding + Risk Mitigation
PAT Elements

- Process Understanding
- Principles & Tools
  - PAT Tools
    - Multivariate Data Acquisition & Analysis tools
    - Process Analyzers
    - Process Control Systems
  - Risk-Based Approach
  - Integrated Systems Approach
  - Real Time Release

*PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, & Quality Assurance, Sept 2004*
**PAT Challenges**

- Technology
- Regulatory Driver
- Product Pipelines
- Automation
- Product Characterization

*Process Understanding, Variation, Specificity, Robustness, Technology, & Regulatory Uncertainty*
Risk, Risk Assessments & Risk Management
## Risk Assessment: Applications

<table>
<thead>
<tr>
<th>Risk Assessment Project Type</th>
<th>Risk Assessment Application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proactive Situation</strong></td>
<td><strong>Reactive Situation</strong></td>
</tr>
<tr>
<td>Regulatory</td>
<td>• Due Diligence</td>
</tr>
<tr>
<td></td>
<td>• GCP &amp; GMP Assessment</td>
</tr>
<tr>
<td></td>
<td>• New Product (Beginning of</td>
</tr>
<tr>
<td></td>
<td>Lifecycle)</td>
</tr>
<tr>
<td>Product (Patient Focus)</td>
<td>• Drug Development</td>
</tr>
<tr>
<td>Process</td>
<td>• Re-Engineering (Middle of</td>
</tr>
<tr>
<td></td>
<td>Development Lifecycle)</td>
</tr>
<tr>
<td>Financial</td>
<td>• Merger &amp; Acquisition</td>
</tr>
<tr>
<td></td>
<td>• Feasibility</td>
</tr>
</tbody>
</table>

PDA Boston – December, 2004
Quality System Applications & Risk Assessments

- Drug Development
- Product Traceability
- Purchasing Controls
- Acceptance Testing
- Production & Process Controls
- Change Control
- CAPA
- Root Cause Analysis
- Process Validation
- Complaints
- Process Design
- Environmental Control
Risk Analysis Approaches

- **Risk Matrixes**
  - Probability vs. Severity = High, Medium, or Low
- **“Risk” Definition & Categorization**
  - Level I = …
  - Level II = …
  - Level III = …
- **Pre-Defined Question & Decision Tree**
  - “If then, else...”

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td></td>
</tr>
<tr>
<td>Medium Risk</td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td></td>
</tr>
</tbody>
</table>

- Does control at this step eliminate or reduce the likely occurrence of a hazard to an acceptable level?
  - No
  - Yes

- Critical Control Point
  - Yes

- If a subsequent step eliminates the identified hazard(s) or reduces its likely occurrence to an acceptable level:
  - Not a CCP
  - CCP
Risk Assessment Tools

- **FMEA** - Failure Modes Effects Analysis
- **FMECA** - Failure Modes Effects & Criticality Analysis
- **FTA** - Fault Tree Analysis
- **HACCP** - Hazard Analysis Critical Control Points

And

- **Combination Methods** – *Tools & Approaches*
Combination Methods Overview

- Key Questions to Ask & Understand
  - What is the Risk Focus?
  - What are the Risk Requirements?
  - What are the Risk Metrics to be quantified & Measured?
  - What is the Outcome of the Exposure? As well as...
  - What is it you need?
  - How do you plan to do it?
  - What is the ultimate outcome?
  - What are the challenges?

Balance RA Tools vs. RA Approaches

- Format
- Content
- Context
- Intent
- Implementation
- Integration
- Effectiveness
# Risk Management: Applications

<table>
<thead>
<tr>
<th>Risk Assessment Categories <em>(Project Type)</em></th>
<th>Risk Assessment Application</th>
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<tr>
<td>Regulatory</td>
<td></td>
</tr>
<tr>
<td>- Due Diligence</td>
<td>- Crisis Management</td>
</tr>
<tr>
<td>- <strong>GMP Assessment</strong></td>
<td>- Regulatory Issues</td>
</tr>
<tr>
<td>- New Product (Beginning of Lifecycle)</td>
<td>- Consent Decree</td>
</tr>
<tr>
<td></td>
<td>- Warning Letter</td>
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<td></td>
<td>- <strong>FDA-483</strong></td>
</tr>
<tr>
<td>Product</td>
<td></td>
</tr>
<tr>
<td>- Product Development</td>
<td>- Design Control (Middle of</td>
</tr>
<tr>
<td></td>
<td>Design Lifecycle or After</td>
</tr>
<tr>
<td></td>
<td>Development)</td>
</tr>
<tr>
<td>Process</td>
<td></td>
</tr>
<tr>
<td>- Re-Engineering (Middle of Development)</td>
<td>- Mature Process – Risk Mitigation</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial</td>
<td></td>
</tr>
<tr>
<td>- M&amp;A</td>
<td>- Crisis Management</td>
</tr>
<tr>
<td>- Feasibility</td>
<td></td>
</tr>
</tbody>
</table>

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**How do I relate these to one another?**

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Risk Management Concept

ICH Q9: Quality Risk Management

Risk Assessment

Risk Analysis

Risk Evaluation

Risk Control

Monitoring & Performance Measurement

Risk Management Planning

ISO 14971
The Harmonized PAT Solution
The “Simplified” Process Model

- Regulators
- Organization
- Customer

- Metrics
- Measurement
- Monitoring

Requirements → DRIVE → Performance

PDA Boston – December, 2004
Process Understanding Concept: 
*Process Variation*
## Harmonized PAT

<table>
<thead>
<tr>
<th>PAT Elements</th>
<th>PAT Strategy</th>
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<tbody>
<tr>
<td></td>
<td>Risk Management</td>
</tr>
<tr>
<td></td>
<td>Process Understanding</td>
</tr>
<tr>
<td></td>
<td>Process Analysis</td>
</tr>
<tr>
<td></td>
<td>Process Optimization</td>
</tr>
<tr>
<td>PAT Tools</td>
<td></td>
</tr>
<tr>
<td>• Multivariate Data</td>
<td>• Provide Risk Based Decision Processes</td>
</tr>
<tr>
<td>Acquisition &amp; Analysis Tools</td>
<td>• Identify critical attributes</td>
</tr>
<tr>
<td>• Modern Process Analyzers</td>
<td>• Identify automation attributes</td>
</tr>
<tr>
<td>/ process analytical tools</td>
<td>• Identify monitoring &amp; control elements</td>
</tr>
<tr>
<td>• Process &amp; Endpoint</td>
<td>• Obtain Knowledge of product &amp; process</td>
</tr>
<tr>
<td>monitoring &amp; control tools</td>
<td>specifications &amp; requirements</td>
</tr>
<tr>
<td>• Continuous Improvement &amp;</td>
<td>• Provide Framework to facilitate Process</td>
</tr>
<tr>
<td>KM</td>
<td>Understanding &amp; Decision Making Process</td>
</tr>
<tr>
<td>Process Understanding</td>
<td>• Provide Framework to execute Risk-based</td>
</tr>
<tr>
<td>Risk-Based Approach</td>
<td>strategies</td>
</tr>
<tr>
<td>Integrated Systems Approach</td>
<td>• Analyze risk at product, process, &amp; quality</td>
</tr>
<tr>
<td>Real Time Release</td>
<td>systems perspective</td>
</tr>
<tr>
<td></td>
<td>• Define Mitigation Strategy</td>
</tr>
<tr>
<td></td>
<td>• Implement test strategies</td>
</tr>
<tr>
<td></td>
<td>• Optimize Process</td>
</tr>
<tr>
<td></td>
<td>• Implement Optimization points</td>
</tr>
<tr>
<td></td>
<td>• Apply Technology</td>
</tr>
</tbody>
</table>
PAT Application Example

Technology Transfer & Process Validation
Process Understanding

- Identify product requirements
- Define how they were derived
- Quantify robustness & adequacy
- Correlate Attributes to Interfaces
  - Process
  - System
  - Component

<table>
<thead>
<tr>
<th>Activity</th>
<th>Key Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Specification Identification</td>
<td>Identify Each Process Step</td>
</tr>
<tr>
<td>Process Map</td>
<td>Identify Elements for Variation: Equipment, Measurement, Personnel, Methods, Materials, Environment, Controls &amp; Monitoring</td>
</tr>
<tr>
<td>Process Flow Process</td>
<td>Identify Process Step Outcome</td>
</tr>
<tr>
<td>Map Key Inputs: Data / Information and Procedures / guidance</td>
<td>Map Process Outputs &amp; Deliverables</td>
</tr>
<tr>
<td></td>
<td>Identify Quality System Interfaces, Performance Measures, &amp; Milestones</td>
</tr>
</tbody>
</table>
## Process Understanding

### Process Identification Deliverable

- **Matrix of those Elements of Variation**

<table>
<thead>
<tr>
<th>Process Step: &lt;Description&gt;</th>
</tr>
</thead>
</table>

Each Process Step is described by:

**Equipment Table**
- Equipment
- Computer
- Computer Interface
- Instruments
- Utilities

**Personnel Table**
- Department
- Function
- Skills

**Methods Table**
- Procedure No.
- Process Instruction No.
- Process Parameter
- Process Attribute
- Process Variable

**Measurement Elements Table**
- Procedure No.
- Method Type
- Personnel
- Equipment
- Verification Element
- Specifications / Metrics

**Environment Table**
- Element
- Requirements Description

**Materials Table**
- Component
- In-Process Product
- Consumables
- Specifications
- Attributes

**Controls & Monitoring Table**
- Quality System Interface
- Procedure No.
- Personnel
- Method
- Requirements
Key Inputs

- Personnels

Key Outputs

- Personnel

Data / Information

- Documents to be developed

Process Step

- Determine Services
- Obtain Approval to proceed for:
  - Quality System Interfaces:
    - KM - Facilitate process
      - Red-lines
      - CS Group "QA" Review & SMEs
    - EO - Internal Training
    - KM - Facilitate Process
      - CS Group Author & Mgmt - process
      - KMI Review Team - Cross-Functional Management Review Team (Principal / Senior Consultant) to review, provide feedback & approval
      - CS Group Review
      - Technical Content
      - Preliminary Map
      - Document Review & Approval
      - Conformance to approved scheduled
      - Draft & Develop
      - Conformance to template standard
      - CS Group Input / Feedback on Technical Content
      - Documents
      - Preliminary Document
      - Conformance to Technical Content
      - KM - Facilitate process
      - CS Group "QA" Review & SMEs
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      - Documents
      - Preliminary Document
      - Conformance to Technical Content

Key Outputs

- Personnel

Performance Measures & CSF's

- To be determined

Specifications

- Procedures
- Environment
- Materials
- Measurement
- Equipment / Systems
- Personnel

Process Workflow

- Flow diagram of processes & activities

Process Outcome

- Per each level

Key Inputs

- Date & Information into the Process
- Procedures & Guidance that Drive Process

Key Outputs

- Deliverables Result for Process
- Activities Result from Process

Quality System Interfaces

- Quality Program Linkage Points

Performance Measurement

- Metrics to measure performance
Process Analysis

- Define Product Risks
- Identify Process Risks
- Identify Quality System Risk Areas
- Correlate Risks to Mitigation Strategies
Process Analysis

Process Risk Assessment

Process Fault Tree Analysis

Failure of Sterility

Fermentation Process

Sampling Process

QC Test Equip 1149 Failure

QC Test Eq 1149 out of Calibration
Process Analysis
Process HACCP Deliverables

Hazard Identification
Hazard Analysis
Critical Control Points
HACCP Plan

Level of Detail & Effort

Focus is on those Critical Elements of the Process!
## Process Analysis
### Quality System Risk Quantification

<table>
<thead>
<tr>
<th></th>
<th>System Design</th>
<th>System Performance</th>
<th>Business Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events</td>
<td>9.0</td>
<td>8.1</td>
<td>7.6</td>
</tr>
<tr>
<td>Annual Product Review</td>
<td>2.0</td>
<td>2.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Audit</td>
<td>2.9</td>
<td>4.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Change Control</td>
<td>8.5</td>
<td>8.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Deviation / CAPA</td>
<td>8.2</td>
<td>9.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Document and Records Management *</td>
<td>9.0</td>
<td>6.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Environmental Control</td>
<td>2.5</td>
<td>8.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Equipment System</td>
<td>2.9</td>
<td>2.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Facilities System</td>
<td>2.9</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Lot Release</td>
<td>8.5</td>
<td>8.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Management Controls</td>
<td>4.7</td>
<td>10.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Materials Management</td>
<td>2.9</td>
<td>4.7</td>
<td>9.2</td>
</tr>
<tr>
<td>Out of Specification</td>
<td>6.0</td>
<td>6.8</td>
<td>7.2</td>
</tr>
<tr>
<td>Packaging &amp; Labeling</td>
<td>3.0</td>
<td>2.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Production</td>
<td>3.9</td>
<td>2.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Regulatory Agency Submissions</td>
<td>5.5</td>
<td>2.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Stability Testing</td>
<td>3.0</td>
<td>2.9</td>
<td>7.6</td>
</tr>
<tr>
<td>Technical Complaints</td>
<td>2.9</td>
<td>6.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Testing</td>
<td>6.5</td>
<td>4.1</td>
<td>9.6</td>
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<tr>
<td>Training</td>
<td>9.0</td>
<td>6.8</td>
<td>8.0</td>
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<tr>
<td>Validation</td>
<td>9.0</td>
<td>6.9</td>
<td>9.2</td>
</tr>
</tbody>
</table>

**Scale**
- **Low:** 0 to 3.9
- **Medium:** 4.0 to 7.9
- **High:** 8.0 to 10
Process Optimization

- Define Analysis Areas
- Implement Corrective Action Plan
- Execute Optimization Strategies
- Implement Technology & Solutions
Create a Change Implementation Plan

- If appropriate, establish a method for determining the effectiveness of the change

Is the Change Implementation Plan approved?
- Proceed with plan and provide progress updates according to schedule
- Complete Change Implementation Plan
- Submit documentation of completed implementation to Change Control Manager

Is change effectiveness monitoring required?
- No
- Yes

Has implementation been completed?
- No
- Yes

Collect & evaluate effectiveness data

Was change effective?
- No
- Yes

Submit CRF to CCM for MCF closure

Close MCF

End

Prepare for senior management periodic summary reports.

MFG Process

- Process Flow Diagram
- Process Map
- Deviation Management
- Out of Specifications
- Change Control
- Systems-Based Model & Top-Down Approach
  - Integrated Quality Systems
  - Pre-Planned Linkages for Risk Management & Performance Measurement
- MFG Process

Cross-Functional Implications

Systems-Based Model & Top-Down Approach

- Integrated Quality Systems
- Pre-Planned Linkages for Risk Management & Performance Measurement
Implementation

- Measure
- Control & Monitor
- Analyze
  - Review
  - Refine
  - Revise

Again...

Requirements

DRIVE

Performance
Risk Management

- Define
  - Scope
  - Approach
  - Interfaces
  - Outcome
Risk Management & Drug Development Lifecycle

Product Lifecycle:

Discovery

Development

Manufacturing

Distribution

Basic Research

Pre-Clinical

Clinical

Product Launch

Production

Marketing and Sales

Bottoms-Up Approach

- Risk Management & Drug Development
Risk Management & Drug Development Lifecycle

Product Lifecycle:

- Discovery
  - Basic Research
  - Pre-Clinical
- Development
  - Clinical I II III III B IV
- Manufacturing
  - Product Launch
- Distribution
  - Production
  - Marketing and Sales

Top Down Approach
  - Risk Management & Product Lifecycle
Risk Management “System”

Inputs
- Protocol Failure: Validation, Stability, Action Implementation
- OOS Results
- Deviations From Procedure
- Clinical Study Failures
- Adverse Events
- Audit Observations
- Product Design
- N...

Observation Records & Preliminary Investigation
- Deviation Mgmt / NCMR
  - Data observed of Exception
  - Preliminary evaluation & Investigation

Formal Investigation & Action Identification
- Action analysis team review for level III & optional Level II Review
- Formal Investigation, action identification & authorization for

Action Implementation
- Action implementation Planning Protocol Creation & Implementation

Action Database & Follow-up
- Action Database Audits Effectiveness Assessment Follow-up

Level I
- Level II
- Level II/III


← Bottoms-Up Approach
# Risk Management “System”

## Inputs

- Protocol Failure, Validation, Stability, Action Implementation
- OOS Results
- Deviations From Procedure
- Clinical Study Failures
- Complaints
- Adverse Events
- Audit Observations
- Product Design

## Observation Records & Preliminary Investigation

- Deviation Mgmt / NCNR
  - Data observed of Exception
  - Preliminary evaluation & Investigation

- CAPA
  - Adverse Trends in data
  - Data exceptions
  - Preliminary evaluation & Investigation

## Formal Investigation & Action Identification

- Action analysis team review for level III & optional Level II Review

## Action Implementation

- Level II

## Action Database & Follow-up

- Action Database Audits Effectiveness Assessment Follow-up

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**Deviations Management Top Down Approach**

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# Outcomes

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<tr>
<th>PAT Elements</th>
<th>PAT Strategy</th>
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<tbody>
<tr>
<td><strong>PAT Tools</strong></td>
<td>Risk Management</td>
</tr>
</tbody>
</table>
| Multivariate Data Acquisition & Analysis Tools | • Risk Management Program
|                                    |   - Program Plan & Document                                                   |
| Modern Process Analyzers / process analytical chemistry tools | • Risk Management System
|                                    |   - Methodology                                                               |
|                                    |   - Guideline                                                                |
|                                    |   - Procedures                                                               |
|                                    |   - Templates                                                                |
| Process & Endpoint monitoring & control tools | • Projects
|                                    |   - Top Down                                                                 |
| Continuous Improvement & KM        | • Bottom’s Up                                                                |
| **Process Understanding**          | Process Specification Identification |
|                                    | • Process Maps                                                               |
| **Risk-Based Approach**            | Process FTA                                                                  |
|                                    | Process HACCP                                                                |
| Integrated Systems Approach        | Quality System Assessment                                                    |
| **Real Time Release**              | Project Plan                                                                 |
|                                    | • Development Testing                                                       |
|                                    | • DOE                                                                        |
|                                    | • QS Optimization                                                           |
|                                    | • Technology Integration                                                    |
PAT Application

Project Outcomes

- Improved Product Quality
- Optimization of Processes & Interfaces
- Reduction in Production Cycle Time
- Variation Mitigation
- Process Epiphany: The “Ah Ha!” Factor
- Cost Savings & Optimized Resources
  - Technology
  - Personnel
  - ROI

→ Defendable Compliance vs. Minimal Compliance
The Harmonized PAT Solution:
Application of Risk-Based Tools & PAT Strategies in Pharmaceutical Product Manufacture

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