The FDA’s Process Analytical Technology (PAT) Initiative

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Consortium for the Advancement of Manufacturing in Pharmaceuticals
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Dorado, Puerto Rico
Outline

• Background Information
  – What is PAT?

• Overview of the FDA’s PAT Initiative
  – PAT provides a “win-win” opportunity for both industry and public health

• Accomplishments
  – Building consensus and seeking information

• How?
  – Developing a regulatory framework for PAT
What is PAT?

• The term “PAT” is used here to describe optimal applications of process analytical chemistry tools, feedback process control strategies, information management tools and product/process optimization strategies to the manufacture of pharmaceuticals

• A platform for Continuous Process Verification (or Validation) and/or QA
An Manufacturing/QA Perspective

• PAT systems utilize appropriate on-line or at-line (physical and chemical) measurements, feedback controls, and documentation, during processing, to assure acceptable quality and performance attributes of in-process materials and formed/end product.
An Regulatory Perspective

• A platform for Continuous Process Verification (or Validation) and/or QA when, PAT based systems establish, during or at the end of the production cycle, documented evidence which provides a high degree of assurance that all critical processes were within established limits and produced a product that conformed to its predetermined specifications and quality characteristics. (draft - ver.3)
Few Examples

• Vibrational spectroscopy
  – NIR, Raman,..

• Acoustic and electroacoustic spectroscopy
  – for characterization of dispersions, emulsions, and microemulsions

• X-RAY Spectrometry

• Electrochemistry
  – pH, conductivity, potentiometry, dielectric measurements, chronoamperometry

• Chromatography
  – GC, LC, positive-displacement-driven, open tubular liquid chromatograph (OTLC)

• Soft Sensors

• Chemometrics

Why?
PAT for Pharmaceuticals: Why?

- Quality of products available to US public is generally good and adequate for the intended use

- The process by which we achieve this level of quality can be improved to provide significant benefits to both industry and public health (a “win-win” opportunity)
To address.....

• Low process capability
  – Scrap, Rework, or Recall
  – Protracted production cycle times and low capacity utilization
  – Resolution of process related problems slow and difficult
  – High cost of compliance

• Risk of
  – Drug shortages
  – Releasing a poor quality product
  – Recalls
  – Delay in approval of new drugs
  – Quality problems confounding clinical trial data

Note - Quality is the foundation for Safety & Efficacy decisions
PAT for Pharmaceuticals: Why?

- PAT a model for developing a “win win” approach for enhancing the science base and facilitating modernization of US manufacturing sector
- Provide high quality drugs to the US public in a timely manner by taking advantage of the many new drug development opportunities offered by advances in biology and chemistry
  - Ensure optimal utilization of public and private resources to meet the growing health care needs of the US public
- Minimize risks due to sub-optimal pharmaceutical process quality
Low manufacturing efficiency..

• Waste (time and resources), high cost of compliance, black-box,…
• Need for very high level of regulatory scrutiny (review and inspections)
  – High proportion of FDA resources needed to ensure adequate product quality
  – Recurring problems that do not seem to get resolved
  – Continued debates between FDA-industry, few permanent resolutions
Improve current processes. Why?

• The current manufacturing paradigm is skewed towards testing to document product quality and rejecting (or recalling) products of unacceptable quality
  – What is wrong with “testing to document quality”?
  – Under cGMP all processes need to be validated. Does this not assure quality was “built-in”? 
Pharma Manufacturing - Unmet Performance Expectations

- Utilisation levels - 15% or less *(but low levels masked).*
- Scrap and rework - we plan for 5-10% *(accepted as necessary).*
- Time to effectiveness - takes years *(not challenged).*
- Costs of quality - in excess of 20% *(that's the way it is).*
Protracted Production Cycle Times: Example
(Source: G. K. Raju, M.I.T.
FDA Science Board Meeting, November 16, 2001)

OVERALL CYCLE TIMES:
QC TESTING TIMES ARE SIGNIFICANT

Overall Cycle Time Components

TIME (Days)

PROCESS CASE STUDY

MIT PHARMACEUTICAL MANUFACTURING INITIATIVE (PHARMI)
Protracted Production Cycle Times: Example
(Source: G. K. Raju, M.I.T.
FDA Science Board Meeting, November 16, 2001)

PROCESS D WITH QC TESTS:
Cycle Times including BULK ACTIVE

QC1
BLEND 2:
PRE-BLEND
CHEMICAL
WEIGHING
PROCESSING
BLEND 1:
COMPRESS
BOTTLE
PACKAGING
GRANULATE
PREP

QC2
QC3
15 DAYS
10 DAYS
15 DAYS
20 DAYS

21-90 DAYS
60 DAYS

MIT PHARMACEUTICAL MANUFACTURING INITIATIVE (PHARMI)
OOS or Exceptions Further Increase Cycle Times  
(Source: G. K. Raju, M.I.T.  
FDA Science Board Meeting, November 16, 2001)

**Pharmaceutical Manufacturing: Impact of Exceptions**  
*(Detailed Analysis of 2 Products)*

<table>
<thead>
<tr>
<th>PERFORMANCE MEASURE</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Cycle time</td>
<td>95 days</td>
</tr>
<tr>
<td>Std dev(Cycle time)</td>
<td>&gt; 100 days</td>
</tr>
<tr>
<td>Exceptions increase cycle time by</td>
<td>&gt; 50 %</td>
</tr>
<tr>
<td>Exceptions increase variability by</td>
<td>&gt; 100%</td>
</tr>
<tr>
<td>Capacity Utilization of “System”</td>
<td>LOW</td>
</tr>
</tbody>
</table>

**NEED FOR FUNDAMENTAL TECHNOLOGY**
Resolution of process problems slow/difficult: Tendency to “live” with the approved “validated” process (Source: G. K. Raju, M.I.T. FDA Science Board Meeting, November 16, 2001)

**PHARMACEUTICAL MANUFACTURING:**

*LOOKING BEYOND THE “AVERAGE”*

**NEED FOR FUNDAMENTAL TECHNOLOGY**
OOS result investigations cited as a key problem area on almost half of warning letters issued
(The Gold Sheets: Vol. 34, No. 4, April 2000)

- Reasons for deficient failure investigations (Marsha Major GMP conference sponsored by the University of Rhode Island/Pharma Conferences in September 1999)
  - Various independent groups involved …. without unified responsibility and ownership
  - Investigators lacked the proper expertise and/or training
  - Other higher priority work takes precedence ...
  - Investigators do not have the authority to request or seek information from other areas
  - The investigation SOP is not used.
Reasons for deficient failure investigations (Contd.)

- Insufficient time or resources given …the investigation
- The investigation identifies the problem and never discusses it or how to correct it.
- The investigation never identifies the problem because the tough questions weren’t asked
- No follow through to correct problem and prevent recurrence
- Investigators write what they think their managers want to hear
Low Process Capability: Drug Shortages

• American Society of Health-System Pharmacists (http://www.ashp.org/shortage/mgtguideline.pdf)
  – “.. have been a challenge to pharmacy managers for many years. Nevertheless, these drug product shortages have been increasing in frequency and severity since the late 1990s.”
  – “Managing drug product shortages has become routine, forcing health care organizations to expend more personnel time and other resources identifying, tracking, and resolving shortage problems.”
  – “Manufacturing difficulties have been the leading cause of injectable drug product shortages,…”
Factors that contribute to disruptions in availability of drug products include the following (http://www.ashp.org/shortage/mgtguideline.pdf):

- Raw and Bulk Material Unavailability
- Manufacturing Difficulties
- Voluntary Recalls
- Manufacturer Production Decisions
- Orphan Drug Products
- Restricted Drug Product Distribution
- Industry Consolidations
- Market Shifts
- Unexpected Increases in Demand
- Non-Traditional Distributors
- Natural Disasters
Current Drug Shortage Listing + Products Experiencing Limited Distribution

Low Process Capability: Risk of Recalls

Mike Verdi. DMPQ/OC/CDER
Defect Discovery: Who?

Mike Verdi. DMPQ/OC/CDER
Top 10 Reasons for Recall

• GMP Deviations
• Sub potency
• Stability data did not support expiration date
• NDA/ANDA Discrepancies
• Dissolution failure
• Label mix-ups

• Content uniformity failure
• Presence of foreign substances
• pH failures
• Microbial contamination
• …
Process Validation

• Yes, process validation is required prior to marketing and many products are in good state of control
  – Scrap or rejection less than 10%
  – Timely resolution of Out-of-Specification (OOS) findings?

• However, manufacturing problems are (often) encountered during routine production (post validation). Why?
Minimum Regulatory “Sigma” Level for Drugs?

Under cGMP when failures/recalls exceeds 10% - no longer “validated.”
The minimum regulatory "Sigma” ~ 1.65?

<table>
<thead>
<tr>
<th>CP</th>
<th>SIGMA</th>
<th>DEFECTS</th>
<th>COST</th>
<th>CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.67</td>
<td>± 2σ</td>
<td>5%</td>
<td>25-35%</td>
<td>Not Capable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Competitive</td>
</tr>
<tr>
<td>1.0</td>
<td>± 3σ</td>
<td>0.13%</td>
<td>20-25%</td>
<td>Average</td>
</tr>
<tr>
<td>1.33</td>
<td>± 4σ</td>
<td>60 ppm</td>
<td>12-18%</td>
<td>Healthy</td>
</tr>
<tr>
<td>1.66</td>
<td>± 5σ</td>
<td>1 ppm</td>
<td>4-8%</td>
<td>Superior</td>
</tr>
<tr>
<td>2.0</td>
<td>± 6σ</td>
<td>2 ppb</td>
<td>1-3%</td>
<td>World Class</td>
</tr>
</tbody>
</table>

Pharmaceuticals

Semiconductor

FDA Science Board 11/16/01: PricewaterhouseCooper Presentation (Modified by AH)
A Multi-Factorial Disconnect Between “Spirit” of CGMP and Practicality of Process Validation

  - “....well-rehearsed demonstration that manufacturing formula can work three successive times.”
  - “It is authors’ experience that ... validation exercise precedes a trouble-free time period in the manufacturing area only to be followed by many hours (possibly days or weeks) of troubleshooting and experimental work after a batch or two of product fails to meet specifications. This becomes a never-ending task.”
Reasons for the Disconnect?

- Pharmaceuticals are complex, multivariate, physico-chemical systems
  - Treated (during development) as a univariate system (one-factor-at-a-time, trial and error experimentation (use of DOE <5%)
  - Materials not well characterized (physical)
  - Equipment selection – tradition
  - Process factors – not well understood
Vision for PAT

• PAT provides an opportunity to move from the current “testing to document quality” paradigm to a “Continuous Quality Assurance” paradigm that improves our ability to assure quality was “built-in” or was “by design” - ultimate realization of the true spirit of cGMP!

– Three examples (visions) of “Continuous Quality Assurance”
  • Norman Winskill and Steve Hammond, Pfizer. FDA Science Board Meeting, 11/16/01, Rockville, MD
  • David Rudd, GlaxoSmithKline. FDA’s PAT-Subcommittee meeting, 2/25/02, Gaithersburg, MD.
  • Robert S Chisholm, AstraZeneca. FDA’s PAT-Subcommittee meeting, 2/25/02, Gaithersburg, MD.
Shift the Manufacturing Paradigm

Process Control Philosophy - Paradigm Shift

Conventional approach - lab based

End of phase testing of quality, to reduce the risk in moving to the next stage

- Obtain raw materials
- Mix active and excipients
- Press tablets
- Package

P.A.T approach - process based, at-line or on-line

Continuously or more frequently test quality during each phase, to remove the risk in moving to the next stage

- Obtain raw materials
- Mix active and excipients
- Press tablets
- Package
Current control philosophy

- Process control
- Closed loop control (process parameters only)
- Policing function
  - Off-line (lab-based) review of product quality parameters

Business case for improvement

- Guaranteed product quality
- Avoidance of delay
- Optimal utilization of resource
- Minimization or elimination of waste
- Movement towards continuous processing
THE TRADITIONAL APPROACH

• Processes Validated at Life cycle commencement
• Operated/Controlled by Standard Operating Procedures (SOPs)
• Quality Assurance based on off-line testing of a sample of product at the end of each batch

THE PAT BASED APPROACH

• On or at line Analysis for real time quality control of each unit operation process control throughout the batch
• Real time statistically based quality assurance throughout the batch
• Increased statistically based testing regimes provide the potential for release of product without further off-line testing
Accomplishments

• History
  – FIP’s Millennium Congress, New Technology Forum of the Royal Pharmaceutical Society, PhRMA Technical Conclave, ...

• 19 July 2001, ACPS Meeting
• 16 November 2001, FDA Science Board Meeting
• 28 November 2001, ACPS Meeting
• 25-26 February 2002, PAT-Subcommittee Meeting
Need for FDA to Facilitate Introduction of PAT

• Industry is hesitant to introduce PAT in US
  – Regulatory uncertainty/risk leads to “Don’t Tell” or “Don’t Use” practice
    • New Technology = New Questions
      – Method suitability, chemometrics and validation
    • Old products + New technology = New Regulatory Concerns
      – Problems not visible under the current system
  – Mindset: Why change?
    • PAT application will add to current regulatory requirements
How does FDA plan to facilitate introduction of PAT?

- Eliminate regulatory uncertainty
  - #1. FDA will accept PAT applications that are based on “good” science
  - Develop standards for PAT
    - Method suitability and validation
    - Multivariate statistical/computer pattern recognition
    - Critical process control points and specifications
    - Changes, OOS…..
  - #2. Current system “adequate for intended use”
  - #3. Introduction of PAT not a requirement
How does FDA plan to facilitate introduction of PAT?

• Eliminate regulatory uncertainty
  – #4. Define conditions under which PAT may replace current “end product release testing”
  – #5. Process for addressing existing “invisible” problems in marketed products
  – #6. Review and inspection practices
  – #7. International harmonization
How does FDA plan to facilitate introduction of PAT?: Two Tracks

• **General Guidance on PAT**
  – **Information source:** ACPS Subcommittee on PAT and working groups
    • Meeting #1 2/25-26/02
    • Meeting #2 (6/02?)
      – Draft Guidance

• **Implementation**
  – CDER-ORA Team

• **Invite companies to propose submissions**
  – Expect to receive proposals for submissions (~3 by 4q 02)
  – Review-Inspection plans and teams for these submissions
    • Plan for concurrent development -review-inspection
General (principles) Guidance on PAT

• Proposed Goals and Objectives
  – General principles and terminology
    • Bring the community on the “same page”
  – Address issues related to “regulatory uncertainties”
  – Clarify the regulatory process
    • Review and inspection
  – Other tangible benefits
    • Serve as a tool for building within-company consensus
    • Promote research and development activities in the pharmaceutical PAT area
Options for Introducing PAT

A. Currently marketed “robust” products. PAT to improve efficiency (minimal improvement in quality assurance)

B. Currently marketed products that need improvement. Step wise PAT approach - first improve quality and then improve the efficiency

C. New products. PAT utilized throughout development and scale-up. Lab based tests to ensure shelf-life and/or for establishing “public standards.”
Guidance Development Process

• PAT Steering Committee
  – CDER (OPS/OC) and ORA
    • Douglas Ellsworth, Mike Olson/Diane Obrien, Joe Famulare, Frank Holcomb, Moheb Nasr, Yuan Yuan Chiu, Ajaz Hussain (Chair)

• Guidance writer: Raj Uppoor

• Project management: Chris Cole

• Communication tools - Web based and electronic tools (PAT@CDER.FDA.GOV)
How can you help?

- Identify “holes” in our arguments
- Share data on current process efficiencies
- Good science
  - Case studies – proof of concept
- Training programs
- Collaborate
- Recruit Champions