QbD/PAT: Are we there yet?

Interphex
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Pedro E. Hernández, Ph.D.
PHPD Consulting Services
PAT : A Disjointed Product Approach or an Integrated Solution to Deliver Real Manufacturing Benefits?
Room: 1E12 ~ 2:00PM - 3:30PM (Wednesday, March 30, 2011)

“If you can't describe what you are doing as a process, you don't know what you're doing.”
W. Edwards Deming
Quality by Design

Moheb Nasr, Ph.D., FDA
Origins of PAT

Introduced in the 1940's under the acronym PAC in the following industries:
- Petrochemical
- Agriculture
- Fine Chemicals and polymers
- And later semi-conductors

Center for Process Analytical Chemistry (CPAC), established at the University of Washington in 1984:
- A consortium of Industrial, National Laboratory and Government Agency Sponsors addressing multidisciplinary challenges in Process Analytical Technology (PAT) and Process Control through fundamental and directed academic research.

http://www.cpac.washington.edu/

Food and Drug Administration (2004) Q8 (R2) (2009), Q9 (2006), ICH Q10 (2009), ICH Q11 (EWG)
FDA and EMA Will Launch Collaborative QbD Application Review Pilot

FDA and EMA will be conducting a pilot program for joint review of the quality-by-design component of new drug marketing applications – bringing the once-distant vision of a common review process closer to reality.

Q8(R2) Pharmaceutical Development, guidance for industry, November 2009.
Q9 Quality Risk Management, guidance for industry, June 2006.
Q10 Pharmaceutical Quality System, guidance for industry, April 2009.

Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) (EWG, 2012?)
Applications should include the following minimal elements delineated in the ICH Q8(R2) Annex:

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs) of the drug product
- CQAs of the drug substance and excipients
- Selection of an appropriate manufacturing process
- Control strategy

Furthermore, based on the ICH Q8(R2) all applications should contain the following:

- Information that conveys an understanding of the development of the drug product and its manufacturing process
- Identification of those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality that support the safety and efficacy of the drug product
- Justifications for the control strategy
Quality means doing it right when no one is looking.

Henry Ford
Process Analytical Technology

Process = Dynamic Environment

Fit For Purpose Development

cGMP

Implementation

Monitoring

In Process Application Development/Deployment

Continual Improvement and Process Control

Process Data gathering for statistical analysis

Method/Technology optimization

Feasibility

Proof of Concept for the Technology

Identify Critical Process Steps and PAT Technologies

Risk Analysis

Identify Critical Process Steps and PAT Technologies
Methods, SOPs and trainings are developed, verified and implemented with team inputs from R&D, TT, PPU, Quality, Regulatory, IT, Engineering and EHS support.
**Process Analytical Technology**

**Example of In-line, On-line and At-line vs. Off-line (lab) tools**

- **In-line** analysis means that the analyzer interface is located within the process itself, in-situ, by means of a probe or through a window.
- **On-line** means automated sampling off the process stream.
- **At-line** means manual sampling with transport to an analyzer located in the manufacturing area.

![Diagram of In-line, On-line, At-line, and Off-line tools](image)
QbD and PAT

Process Understanding

Design Space

Knowledge Space

Control Space

REDUCED

NOR

Input material attributes (Physical properties etc)

Output product (intermediate/final quality attributes)

CQA’s

Multi- or single unit operation

In-process parameters

Output

Reduced product variability and increased process capability

Design Space

Design Criteria

PAT

Input

Process

Output
Quality by Design

Traditional Manufacturing vs. QbD Manufacturing

**Traditional Manufacturing Process**
- Variable Starting Materials
- Fixed Manufacturing Process
- Variable Finished Product

**QbD Manufacturing Process**
- Variable Starting Materials
- Controllable Manufacturing Process
- Consistent Finished Product

**Process Understanding:**
- Critical sources of variability are identified and explained
- Variability is managed by the process: Control Strategy
- Product quality attributes can be accurately and reliably predicted over the design space
PAT is More Than Sensors

Tools for supporting the PAT/QbD principles*:

- Process Analyzers
- Process Control tools
- Data analysis & mining tools (Multivariate Data Analysis, …)
- Data collection, storage and retrieval tools
- Reporting tools
- Continuous improvement & knowledge management tools

All linked together into one PAT/QbD system architecture, easy to integrate with development & manufacturing infrastructures

* Ingrid Maes, Siemens AG (SiPAT)
1. SCADA control and data acquisition – all 5 feeders
2. Weighing cells to monitor blender load
3. Valve control of blender load
4. PAT Application for blend potency & homogeneity
5. Monitoring of tablet weight
6. Monitoring of tablet moisture content
Process Analytical Technology
From Science to Compliance

- Equipment Hardware / Software
- Data / Information
- SPC
- API / Excipients
- Manufacturing Process
- IS Infrastructure / Enterprise Software
- Method / Model / Macros Development
- Change Control
- Training
- Documentation
Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives.

William A. Foster
Agenda

- QbD/PAT Background
- Drug Substance to Drug Product
- Challenges
- Implementation Models

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Quality by Design: From DS to DP

DISCOVERY SYNTHESIS
- CAD
- QSAR
- LEAD
- 2nd Generation Lead

Meanwhile... Upstairs
- Patent Protection
- Formulation
- Market Share
- New Indications

Numerous Steps
- Linear Synthesis
- Expensive Reactants
- Cumbersome Reactions and Procedures
- Little Environmental and Safety Concerns
- Low Yields and Throughput
- Chromatography
Quality by Design: From DS to DP

PROCESS R&D

Rush & Deliver
- Timelines
- Supply
- Scale up

or

Research & Development
- Thermochemical Data
- Physical Properties
- Chemical Attributes

PROCESS KNOW-HOW → Define Process
Define the Chemistry and Formulation
Define the intermediates and attributes
Define the Process and Analytics
Define the milestones and timelines

PROCESS KNOW-WHO → Development Team
Chemist → Analyst
Toxicologist → Pharmacology
Regulatory → Engineer
Operator → Formulator, Others…

PROCESS KNOW-WHAT → Build a History
Risk Assessment
Critical Quality Attributes
Critical Process Parameters
Optimize yields, Maximize throughput
Streamline the process
Optimize analytical methods/PAT

PROCESS KNOW-WHEN → Transfer Knowledge
Technology Transfer Report
Analytical Package and PAT
Training Package
Environmental and industrial hygiene studies
Process Economic Analysis
Identify and Assign Resources
Quality by Design: From DS to DP

Research and Development → Technology Transfer → Manufacturing

Technology Development Innovation

Quality by Design → Process Robustness and Product Knowledge

PAT Enables Manufacturing Science & Continual Improvement
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Quality by Design/PAT

Challenges

R&D
Science and Expertise

Quality
Assurance & Compliance

Technology
Transfer and Engineering

Location!
Location!
Location!
Quality by Design/PAT

Challenges

R&D

It is in R&D where the product and process development starts and where the technical expertise in materials characterization, formulation and process development resides. But it is also where the issues material and equipment scale, engineering, sampling and cGMP compliance are not necessarily that well understood, perhaps because these issues are not always part of the mindset or requirements in the R&D environment.

Quality

By Quality here I am referring to the Compliance side. As a heavily regulated industry the pharmaceutical industry needs to ensure Compliance, which is non-negotiable. But in its zeal, it can encumber the initial studies at scale in a cGMP manufacturing environment by imposing “commercial” release level requirements on feasibility studies, even in cases when the product is not yet commercial. Even if the product is commercial, PAT involving non-contact monitoring, through a window in the process equipment, there should be no obstacles to its use.
In the case of new products, PAT should ideally be part of the overall technology transfer package and include the proper financial justification. This would enable PAT instrumentation acquisition and interface development, monitoring of the development batches and method optimization, validation at commercial scale and shop floor training.

At the end of the day, it is Operations where the PAT tool is going to show its value added, in the form of process knowledge, process control and continual quality improvement whether it is in a new product or an established product with its quality and financial rewards.

But it is Operations that sometimes is shortsighted when it comes too understanding the value added proposition. What will be the cost of modifying equipment, revalidating, training and sustainability?
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Implementation Models

New Products

- Early materials and process knowledge
- Proactive regulatory strategy
- Reduced development time cycles
- Advanced control strategy

Established Products

- Process and product prior knowledge
- Forensic Multi Varaite Data Analysis
- Historical Trending
- Prospective Modeling
Quality by Design/PAT

Implementation Models

Raw Materials

Why?

• Real Time Analysis of Raw Materials
• Portability from R&D to Manufacturing Site for Scale-Up Work
• Raman, FT-IR and NIR as Complementary Techniques
• Library Transferability for Seamless Method Transfer
Quality by Design/PAT

Implementation Models

**Traditional Laboratory Sample Analysis**

- Move Drum
- Open Drum
- Open liner
- Take sample
- Re-seal liner
- Send to Lab
- Material Cleared
- Move Drum
- Result logged
- Result sent to QC
- Lab analyzes

**Analysis in “Clean room” by NIR, FT-IR with probes**

- Move Drum
- Open Drum
- Open liner
- Make measurement
- Re-seal liner
- Material Cleared
- Move Drum
- Result logged
- Clean probe

**On-spot analysis by Handheld NIR**

- Open Drum
- Make measurement
- Result logged
- Material Cleared
Quality by Design/PAT

Implementation Models

Incoming Raw Material ID

- Inspection and regulatory documentation at point-of-receipt by receiving (non-lab) personnel
  - minimize delays in release, while increasing quality coverage
  - Aligned with inventory tracking by RM-ID numbers and batch/lot/internal reference numbers, ER’s automatically generated
  - Trending toward 100% incoming inspection
Quality by Design/PAT

Implementation Models

Fast, reliable, compliant real time results

In-coming  In-Process  In the lab
Quality by Design/PAT

Implementation Models

Raman
NIR
FT-IR in

On-line PAT

QC/QA Lab
Warehouse ID
At-line PAT
Dino-Lite Digital Microscope and Camera

• The AM413TL features enhanced working distance and is useful in many industrial and laboratory applications.
• Magnification: 10X, 20X-92X continuous
• Working Distance: 20X@5.7", 52X@2.5", 90X@2"
• Resolution: 1024 x 1280 pixels (SVGA)
• Built-in white-light LED illumination.
  8 each LEDs under software control
• Frame rate: up to 30fps
• Interface: USB 2.0
• Dimension: 10cm (Height) X 3.2CM (Dia.)
• Weight: 90g
• Capture picture, video and time-lapsed video with a mouse click.
• Compatible Windows 98SE/ME/2000/XP Vista and most MAC OS
Quality is not an act, it is a habit.
Aristotle
QbD/PAT
From Science to Compliance: Document Actions

- QbD Master Plan
  - Organizational
  - Site
  - Product
- Incorporated QbD/PAT elements into Master Batch Records
- Operators and supervisors trained on PAT elements in master batch records
- SOPs: Impact Assessment and Risk Analysis procedure
- Draft procedure for control strategy
- Recognized as a continuous improvement process
  - Failure Modes & Corrective actions
  - Decision trees
  - Documents (FMEA, SOP’s, MBR, etc.)
    - Progressive Elaboration (Software Engineering)
- Documents, training, and systems will mature with on going continual improvement.
Quality is the result of a carefully constructed cultural environment. It has to be the fabric of the organization, not part of the fabric.

Philip Crosby
QbD/PAT
From Science to Compliance

IS/IT Infrastructure / Enterprise Software

PAT Typical Configuration and Data Flow

PAT Instrument

PAT Validated Computer

Network (Enterprise/Process)

PAT Shared Folder Server

Open Lab, DART, Historians, Databases

Office PC

Network Printer (Any)

A) Spectral Data collected during process
B) Reports, PDF of Reports and Spectral Data
C) Storage of Reports, PDF and Spectral Data on file server, retrieval in other systems
D) Printing of reports, and PDF files
E) Retrieval of reports, PDF and Spectral Data for advanced analysis
F) Reports, PDF and Spectral Data transfer to reporting, and data historian systems

a b c d e f
Process Analytical Technology
From Science to Compliance

System Integration
- Process Understanding
- Monitoring @ commercial scale
- Data analysis / process variability
- Definition of process boundaries
- System integration
- Operation strategy
- Revise SOP
- Training strategy
- PAT development report
- Computer Systems Validation

Ownership Transition
- Technology to PPU/Quality
- Revise SOP’s / product spec as applicable for reduced testing and Update PBR/MES
- Define Data Custody Chain based on level of integration and compliance requirements
- Approve SOPs for Data Custody Chain
- Computer Systems Validation

Deployment
- Real Time Release Testing
- Continuous process monitoring
- Continual Improvement
- Define future integration on a need and ROI basis
Equipment Hardware / Software
- Failure Handling Decision Trees
  - Individual for each operation
    - Blending
    - Roller Compaction
    - Compression
  - Actions defined per process steps
    - Set up
    - Process
    - Assessment
    - Next steps
- Included in SOP
- Training
Process Analytical Technology
What is required?

An organizational transformation from a “Quality by Inspection” culture to one of “Quality by Design”

A cross-functional collaboration and a mixture of skills and efforts from various areas of expertise

Commitment and recognition that QbD and PAT and achieving continuous quality assurance is Everybody’s Responsibility
Rockhound: from Armageddon, the movie...

“You know we're sitting on four million pounds of fuel, one nuclear weapon and a thing that has 270,000 moving parts built by the lowest bidder. Makes you feel good, doesn't it?”
CULTURE CHANGE

The concepts of QbD, Design Space and PAT are inherently & fundamentally linked.

PAT is only a TOOL to be applied along with several others as part of a SYSTEM to assure manufacturing efficiency and product Quality.

It’s about culture and philosophy – not tools and technology.

“QbD + PAT = Real Time Release”

THE DESIRED STATE FOR QUALITY BY DESIGN MANUFACTURING
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Emil Ciurczak and John Carroll
Hesitating to act because the whole vision might not be achieved, or because others do not yet share it, is an attitude that only hinders progress.  

M. K. Gandhi