Process Analytical Technology:

Innovation supporting Right First Time in Pfizer Global Manufacturing

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Process Analytical Support Group
Integration of Q8,Q9,Q10 at Pfizer

- Pfizer now has a single global quality organisation. This facilitates a single Pfizer Quality system incorporating Development and Manufacturing.
- Pfizer uses a product lifecycle management approach to maximise the benefits of quality by design, quality risk management and quality systems.
- Pfizer is using a QbD approach for all new products.
- Two QbD submissions approved to date.
- CQV and RTR pilots underway.
Monitoring in Development & Co-Development

What to Monitor/Measure?

How to Measure?

Analyse Output

Outcome

Enhanced Product/Process Understanding

=> Establish critical product attributes and critical process parameters

=> Develop Design Space………..> filing

=> Develop Control Strategy for Manufacturing…….. >filing
Product/Process Monitoring in Manufacturing

What to Monitor/Measure?
- Ensure a state of control is maintained
- Identify areas for continual improvement
- Enhance Product/Process Understanding
- Increase Agility

How to Measure?
- Analyse Output
- Risk Assessment and Prioritization
- Lab investigations
- DOE/PAT Modelling
- Statistical Tools

Outcome
- Ensure a state of control is maintained
- Identify areas for continual improvement
- Enhance Product/Process Understanding
- Increase Agility
PAT – Innovation enabling RFT manufacturing

- PAT is a set of tools which can be applied to achieve a goal, not a goal in its own right
- The goal is to reduce variation in our processes – achieve Right First Time manufacturing
- PAT provides a window to enhance process understanding
- PAT is applied based on comprehensive process risk assessments as part of an overall strategy to enhance RFT manufacturing
- PAT can be used to enhance process safety
- PAT can enable a more cost effective and agile manufacturing operation
- PAT can help to monitor what matters
  - Development of knowledge space during development
  - Maintaining state of control during manufacturing
HOW PAT PROJECTS ARE IDENTIFIED AND PRIORITISED IN PGM

**Existing manufacturing processes**

- PAT requirements identified and prioritised by cross functional process experts/ process teams based on experience, process capability, process understanding requirements, safety and quality drivers

**New manufacturing processes**

**Comprehensive RFT risk assessment to identify PAT measurement needs**

1. Create a Process Flow Chart
2. Identify Quality Attributes and How Measured
3. Identify and Prioritize Process Parameters
4. ID experiments needed to understand CQA = f (CPP)
5. Risk Assessment: Prioritize Experiments
6. PAT Decision Analysis

- Risk based PAT projects priority list
- Focus on the voice of the customer
- Relentless focus on the process
- PAT applied where the need and benefit are greatest
- Focus on key quality attributes for new processes
- PAT enabling RFT manufacturing
KEY AREAS OF PAT APPLICATION (API)

- Crystallisation monitoring
- Dryer monitoring
- Reaction monitoring
- Cleaning optimisation
- High shear wet milling
- Dry milling
- Solvent recovery
- Raw material id
Application of PAT in Pfizer to support API manufacturing

At proof of concept

RAW MATERIAL RECEIPT

NIR, POU
Raman

REACTION STEPS

MIR/NIR, exhaust
FBRM
NIR, POU
UV, surface
NIR

Crystallisation /Filtration

DRYING

MILLING

Finished API

CLEANING VERIFICATION

SOLVENT RECOVERY

Global standard Applications

NIR
NIR
FBRM
NIR
FBRM
NIR
UV
GC

NIR
UV
MIR
PAT in action – API examples

- **NIR for Drying**
  - Cycle time reduction
  - Sampling removal

- **UV for cleaning**
  - Cleandown method development and optimisation
  - Reduced sampling

- **FBRM for crystallisation**
  - Crystallisation understanding
  - Crystallisation optimisation

- **MPA for raw material ID**
  - Rapid raw material release
  - Conformity testing
PAT in action – API examples

- ATTRIBUTE BASED ENDPOINT
- PROCESS OPTIMISATION

FBRM for wet milling

- ENDPOINT DETECTION
- SAMPLING REDUCTION
- PROCESS UNDERSTANDING

MIR FOR RXN MONITORING

- SAMPLING REDUCTION
- REAL TIME QUALITY CHECK

GC for solvent recovery
API case study

- New reaction route to API
- Level of reactant and impurities at RXN endpoint identified as key quality attributes
- Lab POC carried to demonstrate potential
- Qualitative model built on lab data
API case study

MIR probe installed via recirculation loop
API case study

- MIR probe installed via recirculation loop
API case study

- Endpoint determined by MIR – attribute based endpoint
- Key addition point to reduce impurity formation identified by MIR
- PAT for rxn monitoring offers significant potential for variability reduction
KEY AREAS OF PAT APPLICATION (DP)

- Raw material testing
- Blend monitoring
- Fluid bed dryer monitoring
- Granulation monitoring
- Content uniformity and hardness of tablets
- NIR ID on finished products
- Roller compaction monitoring
- Vial headspace integrity monitoring
- Milling monitoring
- Cleaning verification/optimisation
- Rapid micro testing
- Particle size distribution in suspensions
- Vial content uniformity
- Solution concentration monitoring
Application of PAT in Pfizer to support DP manufacturing

Global standards

At proof of concept

NIR, POU
FBRM
MIR/NIR, exhaust
FBRM
NIR, roller compaction
UV surface
Blisters

Solution make up
Granulation
Drying
Milling
Blending
Compression Tabletting and Release
Cleaning
Packaging

RAW MATERIAL RECEIPT

NIR
NIR
UV
NIR
NIR
NIR
NIR
Tandem
UV
NIR
NIR
headspace

Particle size, Laser defraction

Application of PAT in Pfizer to support DP manufacturing
PAT in action – DP examples

NIR FOR FBD monitoring

• ENDPOINT DETERMINATION
• CYCLE TIME OPTIMISATION
• OFF TEST REPLACEMENT

NIR for blend monitoring

• BLEND PROCESS DEVELOPMENT
• BLEND PROCESS VALIDATION

MPA for raw material ID

• Rapid raw material release
• Conformity testing
PAT in action – DP examples

NIR for vial integrity

- QUALITY CHECK
- ROOT CAUSE ANALYSIS

Particle size by laser diffraction

- PROCESS OPTIMISATION
- PROCESS MONITOR

Tandem II – Content uniformity and hardness

- QUALITY CHECK
- OFF-LINE TEST REPLACEMENT (FUTURE)
Drug product case study

- NIR installed and qualified to track drying of finished product in fluid bed dryer
- Quantitative model build based on PLS correlation with off line samples
- Model validated through extensive testing
- Application submitted as part of EMEA worksharing review pilot

Slide courtesy of Rossanna Della Ventura, Ascoli
EMEA worksharing process

- A method to monitor the drying of a drug product real time using NIR was submitted as part of the EMEA ‘worksharing’ pilot.

- Pilot process used individual agencies to carry out a single review and provide recommendations for approval to other agencies. Aim is to significantly reduce review time.

- Classification (Type I vs Type II) debate illustrated difference of opinion between regulators on ‘novel’ status of NIR.

- Approval notification received April 2008
The role of PAT in PGM Bio API manufacturing

At proof of concept-

Global standards
PAT in action – Bio examples

NIR for raw material ID
- RAPID ID
- CONFORMITY TESTING

In-line HPLC
- FRACTION DETECTION
- ON LINE IMPURITY CHECK

In-line glucose FIA

In-line turbidity
• REAL TIME CELL CONCENTRATION MONITORING

Ultrasonic monitoring of distillation
• DISTILLATION MONITORING AND CONTROL

Pictures courtesy of Thomas Krumm, Frankfurt
Benefits and challenges of PAT

**Benefits**
- Real time window on process
- Root cause determination
- Increase in process knowledge and understanding
- Ability to reduce process variability
- Sampling, testing, product contact reduction
- Attribute based endpoints
- Process control
- More agile manufacturing operations

**Challenges**
- Technology robustness
- Cost
- New skill sets needed across functions
- Reluctance for change
- Perception of regulatory obstacles
Future direction for PAT at Pfizer

Process Effectiveness & Efficiency

- Continuous manufacturing
- Advanced Process Control
- Agile Manufacturing
  - CQV
  - RTR

Enabling RFT

Process Understanding

Increasing Analytical Efficiency

Analytical Efficiency

Chronology

Future direction of PAT at Pfizer

- A number of pilots are already underway focussing on new manufacturing paradigms
  - Continuous processing
  - Continuous quality verification
  - Real time release
  - Advanced process control

- PAT is an important enabler for these pilots

- Close interaction and discussion with regulators will be essential
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BACKUP
- **CQV**: An approach to process validation where the manufacturing process performance is continuously monitored, evaluated and adjusted (as necessary). A science based approach to verify that the process is capable and will consistently produce product meeting predetermined quality attributes.

- **RTR**: An outcome of a control strategy in which product quality is assured for batch release through a combination of process information and input or in-process material attribute measurements during manufacturing in lieu of traditional off-line, end product testing.
Support structure for PAT in PGM

- Global PAT support team
- Technology development and evaluation
- PAT implementation
- Innovative pilots
- Material characterisation
- Active sites have dedicated PAT leads/teams
- PASG works closely with site PAT leads
Application spread – Europe/Ireland-Singapore 2007

Application summary -
Europe-Ireland-Singapore  2007 active projects

Implementation

Development
Pfizer Quality System

Early Development
- Product/Process Development
- Technology Transfer
- Initial Scale-up & Commercial Manufacture

Manufacturing

Discontinuation

Research
- Phase I Clinical
- Phase II Clinical
- Phase III Clinical
- Product Filing

Market

Discontinue

Proof of Concept

Launch
Monitoring in Development and Co-Development

- Develop Design Space & Control Strategy (Risk Mitigation)
- Perform Experiments
- Risk Assessment Prioritize Experiments
- Experimentation
- Risk Assessment
- Prioritization
- Experimental Planning
- ID Experiments
- Understand CQA = f(CPP)
- Quality Risk Assessment
- Identify and Prioritize Process Parameters
- Identify Quality Attributes and How Measured
- DOE/PAT/Modelling