The role of PAT in Lean Manufacturing

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Presentation Outline

• How does PAT contribute to a Lean supply?
  • Flexible manufacturing
• API crystallization
  • Predictable outcomes!
• RTR testing of a Pfizer product
  • Future RTR measurement strategy
  • Potential for feed frame measurements
• What about the packaging?
  • Potential for PAT to smooth the supply chain
Technology Development Focus within Pfizer Global Supply

Supply Reliability

Quality / Compliance

Cost / Value Delivery

Supply Chain Objective – Take a $ billion out of PGS inventory

Design future analytics to support a transformed supply chain
Context - Three fundamentals for a modern lean and agile supply chain

• Synchronize production to demand
  – Pull not push supply chain

• Utterly reliable production
  – PAT applied to the API-DP interface
  – Condition monitoring and advanced control

• Flexibility
  – Product to product
  – Capacity utilization
  – Across the Network

Simon Chalk, BioPhorum Operations Group
Context - Where and how to build flexibility
API & DP Plants Technologies

- Small batch sizes
  - Reduce inventory and space investment
  - Reduce overall lead time
  - Increase complexity in the site (more orders to manage an approve)

- Quick changeovers
  - Reduce lead time
  - Increase equipment utilization (OEE)

- Reliable and predictable processes
  - Improve process robustness
  - Reduce defect rates – increase reliability
  - Improve planning process
  - Improve overall service

- Quick approval (release) times
  - Reduce Lead Time

Juan Fernando Forero, Pfizer Supply Chain
PAT Calibration Models & solubility/nucleation curves generated as part of an automated sequence using a concentrated solution that is sequentially diluted, equilibrated & measured using the PAT devices. FBRM data with mathematical and heuristic rules to define solubility & nucleation thresholds.
1. undersaturated
2. solution cools to saturation
3. enters metastable zone, nucleation begins
4. rapid nucleation
5. crystals form & grow; supersaturation decreases
6. crystal growth close to supersaturation
7. end of crystallisation

驾驶结晶化下降SS轨迹 
• 作用控制 
• 优化产率、批次时间和关键质量参数
Chantix Real Time Release and PAT

PAT:
1 = Identification
2 = Blend Uniformity
3 = Weight, Hardness, Disintegration, Potency, Content Uniformity
4 = Water Determination
Identity Testing

- Replacement of regulatory release test for API in tablet matrix proposed during dispensing
  - Closed manufacturing facility with single API

Threshold where first mismatch (false positive) would occur (i.e. threshold must be set higher)

Threshold where first failed valid identification (false negative) would occur (i.e. threshold must be set lower)
NIR Mounted on a rotating blender

NIR in enclosure

Rotation point
**NIR interfaced with Press**

Process Analyzers
- Measure condition of the process material in real time
- Collect more information about the batch

1. **10X Sampling Unit**
2. **NIR Process Analyzer**
3. **Report**
4. **Control Charts**
5. **MES-Systems**
Results from 18,000 tablets for a 5mg dose in a 200mg tablet

Histogram of Potency (mg/g) - Nominal 5 mg/g

Normal

Mean 4.958
StDev 0.1058
N 17547
Standard platform for RTR

- RTR has significant benefits to Pfizer
- To supply chain management
- Reduced testing in a laboratory
- Increased process understanding
- Whilst also increasing the level of Quality Assurance of the product
- Require an easy to implement, low cost, standard platform for the application of PAT
Schematic of Feed Frame PAT Installation

Full Tablet Dies

Direction of Tablet Die Movement

Right Paddle wheel direction of rotation

Empty Tablet Dies

Left Paddle Wheel direction of rotation

Powder Inlet Chute

Tablet Dies
Example Probe Installations

Manesty Unipress Diamond (USA) and Fette 2090 (Germany)

The design and engineering of the probe interface is completed.
Intelligent Compression and QbD

Powder density change

Norvasc formulation
+ 15% of nominal

Tablet Tensile Strength vs Time

Stop
Start
Poor compression predictability here

Time
Density

Reduction in Tablet Tensile Strength vs Time

Reduction in Tablet Tensile Strength vs Time

Raw spectral intensity @1100nm

- nomimal
- 15% of nominal
+ 15% of nominal

10 mins

Model Validation Trials

Tablet Tensile Strength (Mpa)

Time(min)
Potential Benefits

- Increased process understanding of blending and compression processes.
- Understand and monitor feed-frame function
- Ability to detect segregation during powder transfer from IBC to the tablet press
- Applicable to both Batch and Continuous Processes
- Integration of PAT signal and tablet press weight control signal into compression machine logic.
  - Advanced Process Control
- Opportunity to implement as part of RTRt paradigm
Packaging and supply chain

• Packaging can be a significant pinch-points in pharmaceutical supply chain
• Production errors are generally costly, as product in near the end of manufacturing cycle – added value of previous work
• Almost entirely relies on conventional visible wavelength light for inspection systems
Thermal Imaging can see through most packaging materials

Basis of significantly enhanced packaging inspection systems
Blister Integrity Testing

Blister Sealing and product present count monitoring

Open end of blister
Bottle content inspection
Through plastic bottles!!!!

Opaque Bottle Content Monitoring

Tablet content inspection
Desiccants count and inspection
Liquid content inspection
Testing in Pfizer facility

- Torn / Broken Liner Challenge
  - Detected

- Skewed Caps Challenge
  - Detected

- Overheated Seals Challenge
  - Detected
Typical Bottle Failure Modes

- Bent or damaged Foil
- Missing Foil
- Overheating
- Under-heating
- Untorqued Cap
- Harmed Cap border
- Crooked Cap
- Bottle miss position
Bottle defects under the cap

Cap with intact teeth

Cap with damaged tooth

Good sealing

Bad sealing
Summary

- PAT is making a significant contribution to a Lean supply chain
- Predictable processes – advanced control
- RTR as a concept is now well established. New strategies for using sensors on-line provides bigger supply chain benefits
- Thermal imaging is opening the door to better sensors, condition monitoring and optimization of packaging operations
- PAT has an important role to play as an enabler of a modern supply chain
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