Advancing Industry 4.0 in Pharmaceutical Manufacturing: Integrating the Process Safety Perspective

G.V. Rex Reklaitis
P2SAC Meeting – Spring 2019
Science and risk based manufacturing for improved patient reach & healthcare supply chains

Real-time release testing in oral solid dose Continuous manufacturing systems

**Vision**

**Goal**

**Quality by Testing (Legacy)**
- End Testing
- Batch wise SQC charts
- Extensive DoE

**Quality by Design (mid 2000s Onwards)**
- Process Design & Process Qualification
- Flowsheet models, design space
- Measurement systems
- Real-time release

**Smart Manufacturing (Now)**
- Continued Process Verification
- Quality-by-Control paradigm
- Design for automation

**Continuous Manufacturing**

**Improved Batch Processes**

**Talk Agenda**

- QbD to Operational Excellence
- Process Automation
- Condition Based Maintenance
- Sensors & Systems Integration
Continuous OSD Manufacturing

Journey from QbD to Operational Excellence

- Material Characterization
  - Solid handling
  - Effect of unit operations

- Process Modeling
  - Mechanistic understanding
  - Quality by Design

- Pilot Plant Studies
  - Dry Granulation, Tablet Compaction
  - PAT measurements

- Integrated Systems
  - Product quality, process robustness
  - Real-time release strategies

- IIoT, Analytics & Control
  - Data-driven insights for strategizing operations for 6σ systems
Quality by Design & Real-Time Release Testing

Operational Excellence using Data, Models and Automation
Compaction Modeling for Material Tracking

\[ \bar{W} \sim \mathcal{N}(\mu_W, \sigma_W^2) \]

\[ \mu_W := \frac{\rho_b \pi D^2}{4} H_{\text{fill}} \left( 1 - \xi_1 \frac{n_T}{n_F} + \xi_2 \frac{H_{\text{fill}}}{D} \right) \]

\[ \sigma_W / \mu_W := s_{MCC} (1 - x_{\text{APAP}}) + s_{\text{APAP}} x_{\text{APAP}} \]

\[ \sigma_{\text{punch}} = \frac{4 F_{\text{punch}}}{\pi D^2} \]

\[ \bar{\rho}(x_{\text{APAP}}, H, W) := \frac{4W}{\pi D^2 H \rho_t} \]

Kawakita model\(^2\)

\[ \bar{\sigma}_{\text{punch}}(x_{\text{APAP}}, \rho_{\text{in-die}}) := \frac{\rho_{\text{in-die}} - \bar{\rho}_b}{[\rho_{\text{in-die}}(a - 1) + \bar{\rho}_b] b} \]

Elastic recovery

\[ \bar{\rho}_{\text{tablet}}(x_{\text{APAP}}, \rho_{\text{in-die}}) := \rho_{\text{in-die}} (1 - \epsilon_\rho) \]

\[ \epsilon_\rho = \epsilon_0 \frac{\rho_{\text{in-die}} - \rho_{c, \rho}}{1 - \rho_{c, \rho}} \]

Leuenberger model\(^1\)

\[ \bar{\sigma}_{t}(x_{\text{APAP}}, \rho_{\text{tablet}}) := \sigma_{t,0} \left[ 1 - \frac{1 - \rho_{\text{tablet}}}{1 - \rho_{c, \rho}} \right] \]
Monitoring Product Quality & Process Health

Data Sources

**Equipment**
- Process Parameters
  - Vibrations, lubrication frequency, Oil levels
  - Device alarms, electrical system status

**Analyzers**
- Quality Attributes
  - Device setup and operating conditions
  - Device life – light source intensity, white/dark references, calibration history

**Soft Sensors**
- Operational Data Analytics
  - Process & statistical models
  - Heuristics
Monitoring Product Quality & Process Health

*Data Sources*

**Equipment**

- Mass flow sensors
- Material analyzers

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*Images of various equipment and mass flow sensors.*
Process Control

Hierarchical control architecture

- Sensor accuracy, precision, sampling time
- Sensor location
- Control architecture reconfiguration
- Control method
- Controller tuning

Continuous improvement
- Process verification
- Formulation optimization
- Process reconfiguration

Risk levels & failure mode

Evaluation & regulatory filling
- T2P, M2P, MRI
- Risk levels & failure mode
- High, Medium, Low
- Evaluation & regulatory filling
- Fail, Good, Excellent

- T2P: Time to product
- M2P: Magnitude to product
- MRI: Morari’s resilience index

- e.g. GMP guidelines
- Design & qualification
**Complex System of Systems**

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<th>Product Quality</th>
<th>Process Safety</th>
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**Failures Impact Quality & Safety**
- Increased offline quality testing
- Diminished competitive advantage
- Limits & Questions use of technology

What if... these complex systems fail?

Self-Driving Car Anatomy
Sensor Network Condition Based Maintenance

Process Data
- Real-time data
  - CPPs & CQAs
  - Device alarms
  - Equipment
  - PAT Tools

Condition Monitoring
- Sensor Network
  - SPC Analysis
  - Data reconciliation
- PAT Tool
  - Fault Diagnosis
    - Sensors flagged as gross errors

Maintenance Strategy
- Communication, fouling, orientation, device age
- Corrective, preventive, predictive?

Maintenance management
- PAT Tool qualification for inline/online use
  - ASTM Standards E2968, D6122, D6299

Primary Test Method
- At-line PAT Tool

S. Ganesh et al. Condition based maintenance for monitoring reliability in continuous tablet manufacturing (in preparation)
Utilizing Sensor Network Redundancy
Data Reconciliation and Gross Error Detection

- Contextualize direct measurements
- Flag faulty sensors
- Estimate unmeasured variables
- Validate model parameters

Model & a priori info.

Max likelihood estimate

Constrained least square optimization

\[
\min_{x,z} \quad v^T Q^{-1} v \\
s.t. \quad h(x, z, \theta) = 0 \quad \quad x^+ - x = v
\]

- \(x^+\) vector of measurements, \(\mathbb{R}^n\)
- \(x\) vector of reconciled values, \(\mathbb{R}^n\)
- \(v\) vector of errors, \(\mathbb{R}^n\)
- \(z\) vector of unmeasured states, \(\mathbb{R}^m\)
- \(Q\) covariance matrix, \(\mathbb{R}^{n\times n}\)
- \(\theta\) vector of system parameters, \(\mathbb{R}^p\)
- \(h\) algebraic equations, \(\mathbb{R}^{n+m+n} \rightarrow \mathbb{R}^k\)
Data redundancy for actionable insights

Gross error detection, parameter estimation, CQA validation in real-time


Q. Su, S. Ganesh et al., Data reconciliation in the Quality-by-Design (QbD) implementation of pharmaceutical continuous tablet manufacturing. Int. J. Pharm. (2019)
Operational Digital Twins

Data-driven & model-based insights for process health monitoring
Process Control Performance Monitoring and Improvement

Data historian
- Control performance monitoring
  - Oscillation, time delay, nonlinearity, minimum variance estimation
- Informative data region extraction
- Data compression & storage

Control system
- Manipulated variables
- Process model identification
  - Process model, tuning parameter
- Continuous improvement in process model, tuning parameter
- Continuous improvement in control continuous improvement
- Control performance degradation

Sensor system
- Continuous improvement
- Process variables

Actuator system
- Product quality track record
- Compliance metrics, Cp, Cpk, etc.

Manufacturing process
- Manipulated variables
- Product quality track record

Detection of model-plant mismatch
- Process dynamics changes

Pitops
- Process model identification
- Controller performance metrics

Continuous improvement verification
- Continuous improvement verification

Natoli NP400

**Model prediction horizon**

- **Tablet weight (mg)**
  - Set point (SP): 210.00 mg
  - Process variable (PV): 193.28 mg

- **Pre comp. force (kN)**
  - SP: 0.50 kN
  - PV: 0.91 kN

- **Main comp. force (kN)**
  - SP: 3.00 kN
  - PV: 2.28 kN

- **Production (kg/hr)**
  - SP: 7.00 kg/hr
  - PV: 4.53 kg/hr

**Historical prediction error**

- Twei Ek: -1.30 mg
- Pcom Ek: 0.01 kN
- Mcom Ek: 0.33 kN

**Abnormal prediction error**

- Prod Ek: -0.03 kg/hr
From Device Data to Actionable Insights

Individual equipment & sensors

Operations configuration & control using DeltaV

Industry 4.0/Smart Manufacturing/IoT

- Actionable insights
- Process Automation
- Product Understanding
- Integrated Systems
- Monitoring
  - Material
  - Unit Operations
Real-time operations mgmt. infrastructure

Process Data
- Facility X
- Equipment instrumentation
- In-line & on-line process analyzers
- At-line sensors – primary test methods
- Characterization Lab

Supervisory Control
- Profibus Ethernet IP
- PI ICU for OPC

Product & Process Safety
- SmartFactoryRx
- OSIsoft
- PI Vision
- Knowledge provenance management (HUBzero)

Networked following ISA-95

UVA & MVA
Visualization
Digital Twin
Maintenance
Knowledge
Training
Improvements
OSIsoft PI System

Purdue University Center for Particulate Products and Processes (CP3)
Process analytics research and education using PI System in OSD CM & solids processing pilot plant

**CHALLENGE**
- Systems Integration & Operational reliability for real-time release in OSD CM systems
  - Product quality tracking & release
  - Manage systemic risks – sensor & equipment failure, cybersecurity

**SOLUTION**
- PI System commissioned for data integration & enabling advanced analytics
  - ICU, Manual Logger, Vision, Asset Analytics, Event Frames, DataLink
  - AF SDK used to interface with Matlab, AMAT SmartFactory Rx™

**RESULTS**
- Insights for predictive analytics - supervisory control, release strategies, maintenance etc.
  - Advancing pharmaceutical manufacturing
  - Data science research & education using real-world examples

- Process data integration, time-series historian & contextualization
- Enables data-driven analytics for process and business decisions
- Focus: Real time decision support
- Linkage with AMAT Smart Factory tools

OSIsoft PI World Presentations - [https://www.osisoft.com/about-osisoft/presentations/](https://www.osisoft.com/about-osisoft/presentations/)
Applied SmartFactory Rx

- Information workflows for data-driven & model-based analytics
- Maintenance management
- Data life cycle management
- Visualization
  - Annotate & manage faults, events
  - Track lots & process states, product quality
  - Configure release strategies

J. Moyne et al., A software-defined framework for the integrated management of smart manufacturing systems, Manufacturing Letters 2018
Safety by Design in OSD CM

Product & Material
- Traceability
- Contamination
- Containment

Process & Facility Safety
- Equipment hazards – moving parts, compaction, temperature
- Dust handling
- Leaks, blockage, overflows

The Human Factor
- Operator HMI
- Alarm Management
- Training and preparedness

Cybersecurity
- Smart sensors, PLCs, DCS, MES, LIMS, ELN, Reporting systems
- Computer literate operators
- Malicious intent

Design & Operational Safety

Risk assessment
- Sensor networks
- Automation
- Information systems
- Operational digital twins
- Culture & Education
Integrated approach to safety...

*of products, processes and people*

**Collaborative Approach**

- Develop conceptual designs for coupling RTPM & safety systems
- Identify relevant incidents, implement case studies, assess effectiveness

**Integrated Process Operations Management**

- Product quality *and* process safety focused regulatory & supervisory control
- Asset health monitoring & condition based maintenance
- Systems integration for Safety & Quality by Design
Teamwork makes the dream work...

- **Purdue Team**
  - Sudarshan Ganesh, Dr. Qinglin Su, Yasasvi Bommireddy, Yan-Shu Huang, Sumit Kumar
  - UG RAs (2018-19) – Ben Rentz, Dan Vo Bao Lee, Nolan Pepka, Alessandra Lewis
  - Faculty – Profs Rex Reklaitis, Zoltan Nagy, Marcial Gonzalez
  - Purdue CP3 – Dr. Dhananjay Pai, Prof. Carl Wassgren
  - Former group members – Dr. Mariana Moreno, Dr. Jianfeng Liu, Yash Shah

- **Purdue Engineering Computer Network** – Joshua Harley, Shawn Whitaker, Sundee Rao

- **Rutgers Team**

<ins>& the community interactions ...</ins>
Thank You! Questions?