Why do we need to use advanced control techniques in the pharmaceutical industries?

- Lack of real-time measurements
- Lack of models
- Lack of actuators
- Quality assurance
- Process validation
- Continuous verification
- Safety
- Large variations in product pipeline
- Downward pressure by healthcare providers
- Growth in emerging markets
Advanced control enables a new generation of integrated, intensified & intelligent manufacturing systems with drastically improved flexibility, predictability, stability, controllability & safety

Overall Project Objectives

- Develop a methodology for integrated Design-Control-Safety (DCS) platform for pharmaceutical processes

- **Safety by control**: Fault tolerant control (FTC) for safe plant operation
  - risk-based control system design and validation

- **Safety by design**: Improve inherent process performance and safety via adoption of continuous manufacturing of pharmaceuticals
Quality-by-Control (QbC) paradigm

Past and Present
Target Processes for Implementation

- **Continuous crystallization**
  - MSMPR (cascade of MSMPRs)
    - **Advantages**: equipment in place, easier use of PAT
    - **Disadvantage**: similar to batch processes (large residence time distribution, low heat transfer area/volume ratio)
  - Plug flow crystallizers (PFC) – different technologies
    - **Advantages**: faster, smaller volume, higher product consistency
    - **Disadvantage**: need for new equipment, difficulty of using PAT

- **Continuous tablet manufacturing**
Continuous Crystallization

- Two main technologies:
  - **MSMPR** (cascade of MSMPRs) – stirred tank or dynamic baffled
    - **Advantages**: equipment in place, easier use of PAT
    - **Disadvantage**: similar to batch processes (large residence time distribution, low heat transfer area/volume ratio)
  - **Plug flow crystallizers (PFC)** – different technologies
    - **Advantages**: faster, smaller volume, higher product consistency
    - **Disadvantage**: need for new equipment, difficulty of using PAT

- Typical problems:
  - Optimal operation
  - Control of CQAs
  - Startup
  - Fouling

Cascade MSMPR system
Continuous plug flow crystallization systems

- Attainable region depends on control approach
- Depending on safety constraints change of control structure needed
- Robust fault-tolerant control
Encrustation is a process by which solute (API) deposits on to the crystallizer surface.

- Encrust reduces heat transfer, and subsequently product quality and yield.
- Causes non-steady state process and leads to blockage.

On-Off Fault-tolerant Feedback Control

- The Encrust and CSD controller assures state of control.
- The CSD feedback controller detects the upper and lower bounds and trigger the point of collection (blue).
- Example of level-1 control, in which an active process control system is used to monitor CQAs in real-time.
- Process will work indefinitely due to QbC approach despite fault due to encrustation.
Purdue Continuous Tableting Pilot Plant

Hierarchical Control System Development and Analysis

Pharmaceutical continuous manufacturing pilot plant at Purdue

Feeders: Schenck AccuRate AP-300, DP-4
Blenders: Gericke GCM 250
Roller Compactor: Alexanderwerk WP120
Tablet Press: Natoli BLP-16, Natoli NP-400
Risk-based systematic design and analysis of feedback control strategies for continuous manufacturing processes

Layer 2
- Use of dynamic models for prediction
- Model Predictive Control, Adaptive Control, Gain Scheduling, etc.
- Integrated across multiple unit operations

Layer 1
- Based on PAT to measure CQAs and closed loop control (CPC)
- PID based more advanced control schemes
- Single or multiple unit operations

Layer 0
- Built-in control systems by manufacturers at unit operation level
- Simple PID control
- Single unit operation

Hierarchical control architecture

Risk levels & failure mode
- Evaluation & regulatory filling

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

- Formulation optimization
- Process reconfiguration

Continuous improvement

Level 1 PID control scheme for Natoli Tablet Press
- Cascade control: Tablet weight master loop (by main compression force), dosing slave loop (by dosing level)
- Production rate by turret speed

Level 2 MPC control scheme for Natoli Tablet Press

A linear MPC control of 2 by 2 with an additional constraint variable of main compression force was implemented in DeltaV platform, controlling the tablet weight and production rate by manipulating the fill depth and turret speed.

Data reconciliation - the power to combine knowledge, speed, accuracy, and precision of sensors

* Feb 19, 2018, API% = 10.0, MCC% = 89.8%, SiO₂% = 0.2
### Comparison of Level 1 PID and Level 2 MPC control performance (with Level 2 DR)

**Level 1 control** vs **Level 2 control**

- **Effect weight (mg)**
- **Takeoff flow (kg/h)**
- **Critical density

#### Data reconciliation reinitialized

**June 15, 2018, API% = 10, MCC% = 89.8, SO₂% = 0.2**

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### Risk analysis and assessment

A risk mapping, from the perspective of process control, will be designed based on scores of severity and probability of risks during continuous manufacturing, upon which the proposed real-time release control strategies will be evaluated to give corresponding controllability scores for each risk.

<table>
<thead>
<tr>
<th>Rate</th>
<th>Severity</th>
<th>Probability</th>
<th>Controllability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No effect</td>
<td>None</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 1 occurrence during the continuous production in 5 years (e.g., control instrument failure)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No patient effect</td>
<td>Low</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Process performance decreasing (e.g., divert of non-conforming product)</td>
<td>1 occurrence during the continuous production in 1 to 2 years (e.g., calibration errors)</td>
<td>Most of the applicable measurements &amp; controls are in place</td>
</tr>
<tr>
<td>5</td>
<td>No patient effect</td>
<td>Medium</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>Process performance decreasing (e.g., large amount of non-conforming product, process shut-down)</td>
<td>&lt; 1 occurrence during a single continuous production campaign (e.g., variance in raw material properties)</td>
<td>Some of the applicable measurements &amp; controls are in place</td>
</tr>
<tr>
<td>7</td>
<td>Potential patient effect</td>
<td>High</td>
<td>Frequent/No information</td>
</tr>
<tr>
<td></td>
<td>(e.g., large variance in critical quality attributes)</td>
<td>&gt; 1 occurrence during a single continuous production campaign (e.g., raw material reloading)</td>
<td>Few of the applicable measurements &amp; controls are in place</td>
</tr>
<tr>
<td>9</td>
<td>Significant patient effect</td>
<td>Very High</td>
<td>High frequent</td>
</tr>
<tr>
<td></td>
<td>(e.g., large variance in target product quality profile, loss of clinical performance)</td>
<td>At any time during the continuous operation (e.g., machinery vibration)</td>
<td>None of the applicable measurements &amp; controls are in place</td>
</tr>
</tbody>
</table>

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Level 0 control risk analysis in tablet press

Severity

1. Always under control
2. Remote credibility of under control
3. High credibility of under control
4. Moderate credibility of under control
5. No control

Level 1 control risk analysis in tablet press

Severity

1. Always under control
2. Remote credibility of under control
3. High credibility of under control
4. Moderate credibility of under control
5. No control
Conclusions

- Improved safety via better control and use of CM
- Continuous pharmaceutical manufacturing enhances safety of manufacturing processes
- Developed systematic hierarchical control structure
- Quality-by-control (QbC) - new paradigm for risk-based control system development for safer plant operation
- Exemplified for continuous crystallization & tablet manufacturing