Continuous manufacturing & robust process control for safe pharmaceutical manufacturing

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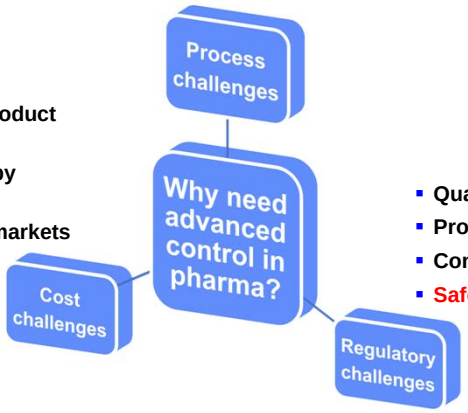
Purdue Process Safety and Assurance Center (P2SAC)

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

- Lack of real-time measurements
- Lack of models
- Lack of actuators



- Large variations in product pipeline
- Downward pressure by healthcare providers
- Growth in emerging markets

- Quality assurance
- Process validation
- Continuous verification
- Safety

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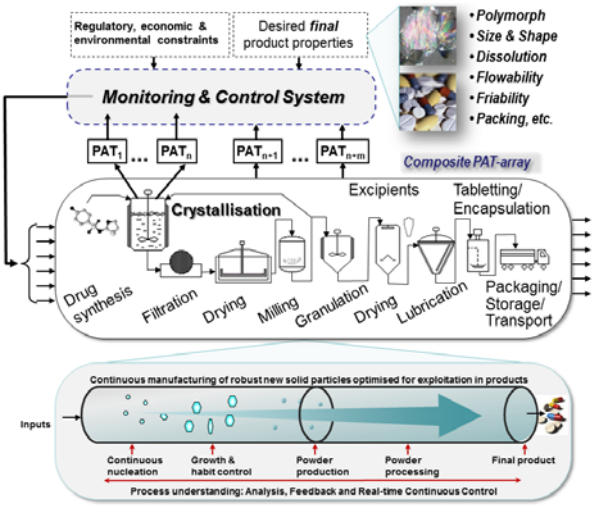
Holistic systems view of Integrated & Continuous Manufacturing of Pharmaceuticals



- **Integrated**
- **Intensified**
- **Monitored**
- **Controlled**
- **Safer**

Advanced control enables a new generation of integrated, intensified & intelligent manufacturing systems with drastically improved flexibility, predictability, stability, controllability & safety

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Nagy&Braatz, Handbook of Ind. Cryst., 2013; Nagy&Braatz, Annu. Rev. Chem. Biomol. Eng., 2012

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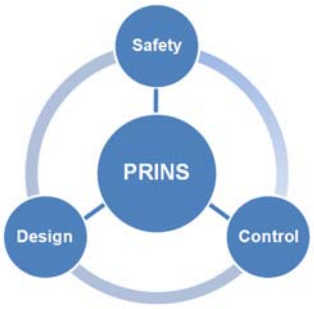
Overall Project Objectives

- 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



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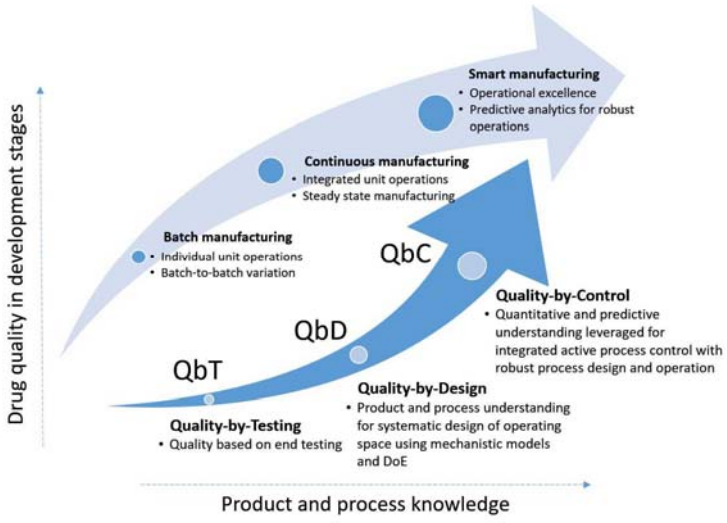
Quality-by-Control (QbC) paradigm



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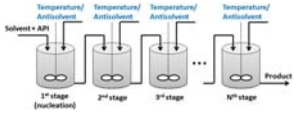
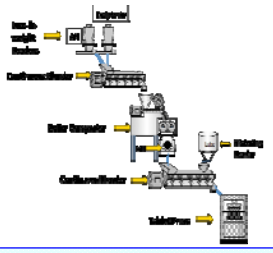
Past and Present Target Processes for Implementation

- **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**



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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

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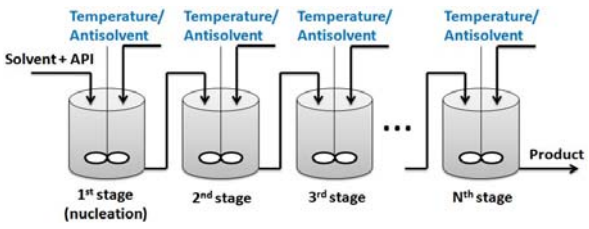
Cascade MSMPR system



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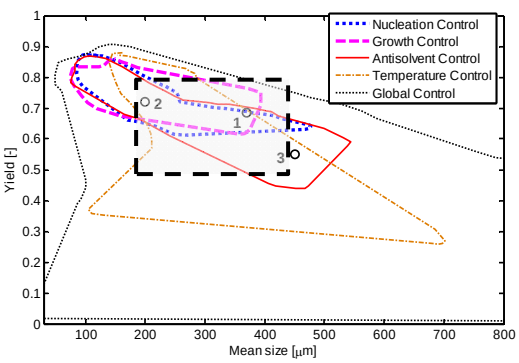
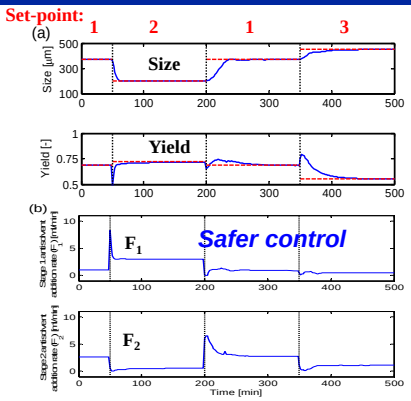
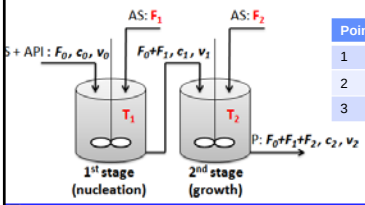
NMPC – attainable regions for control for safety







Point	Yield	Size
1	Medium	Medium
2	High	Small
3	Low	Large

- Attainable region depends on control approach
- **Depending on safety constraints change of control structure needed**
- Robust fault-tolerant control

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Continuous plug flow crystallization systems

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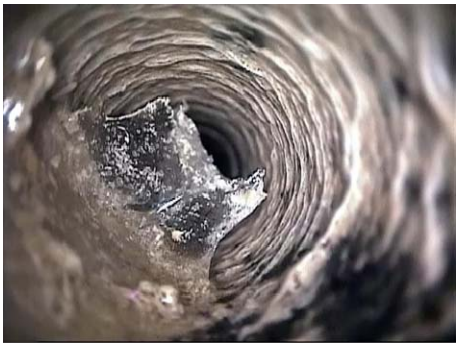
Fouling or encrustation

- 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**.



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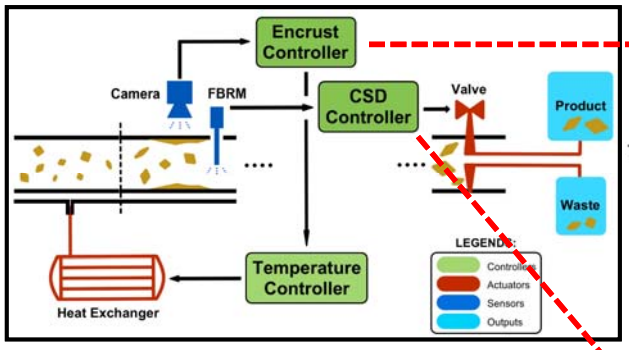
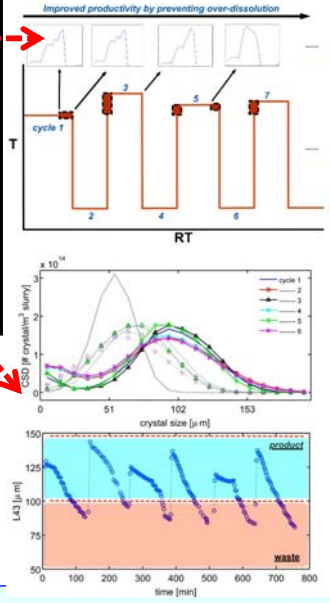
On-Off Fault-tolerant Feedback Control





- 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

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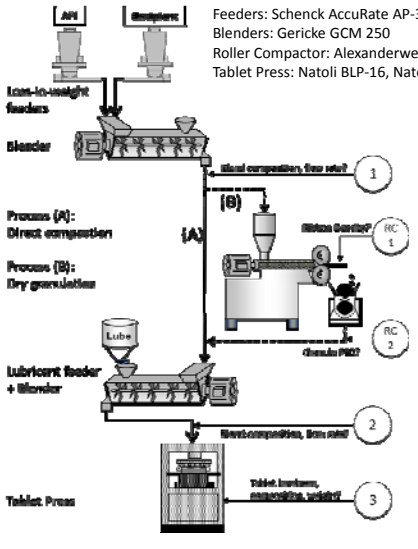
Purdue Continuous Tableting Pilot Plant

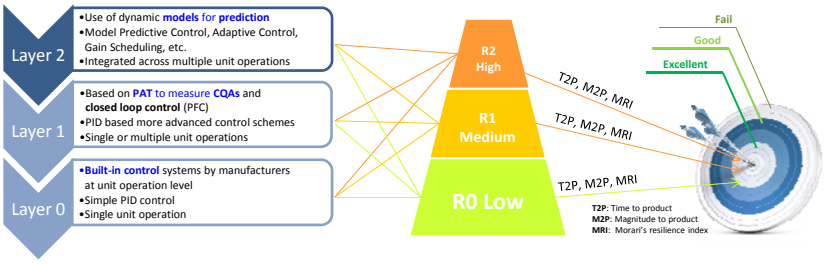
Hierarchical Control System Development and Analysis

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



Hierarchical control architecture | **Risk levels & failure mode** | **Evaluation & regulatory filling**

Continuous improvement

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

- Formulation optimization
- Process reconfiguration

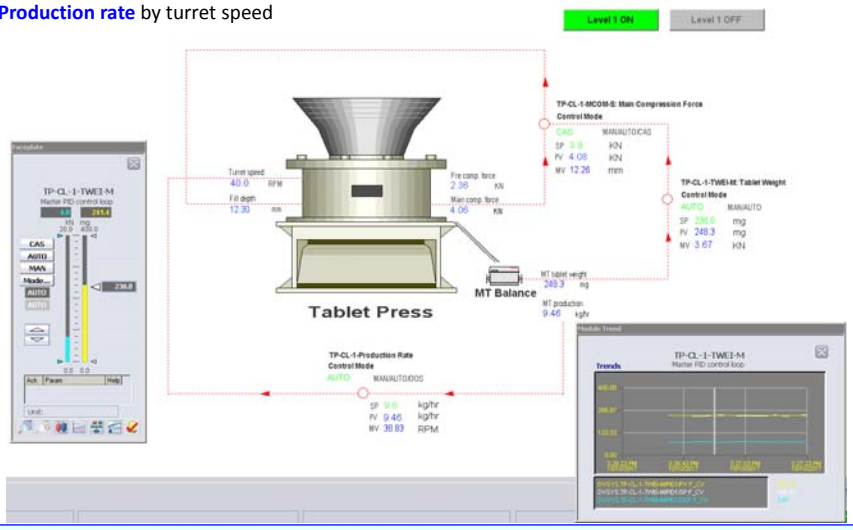
e.g. Good Manufacturing Practices (GMP) guidelines

- Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.
- Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary.

[1] *Su Q*, Moreno M, Giridhar A, Reklaitis GV, Nagy ZK. *Journal of Pharmaceutical Innovation*. 2017;12: 327-346.

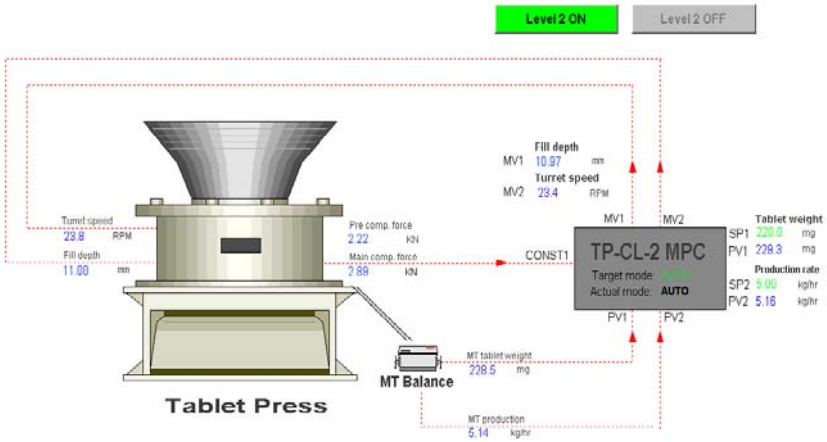
Level 1 PID control scheme for Natoli Tablet Press

- Cascade control: **Tablet weight** master loop (by main compression force), dosing slave loop (by dosing level)
- **Production rate** by turret speed

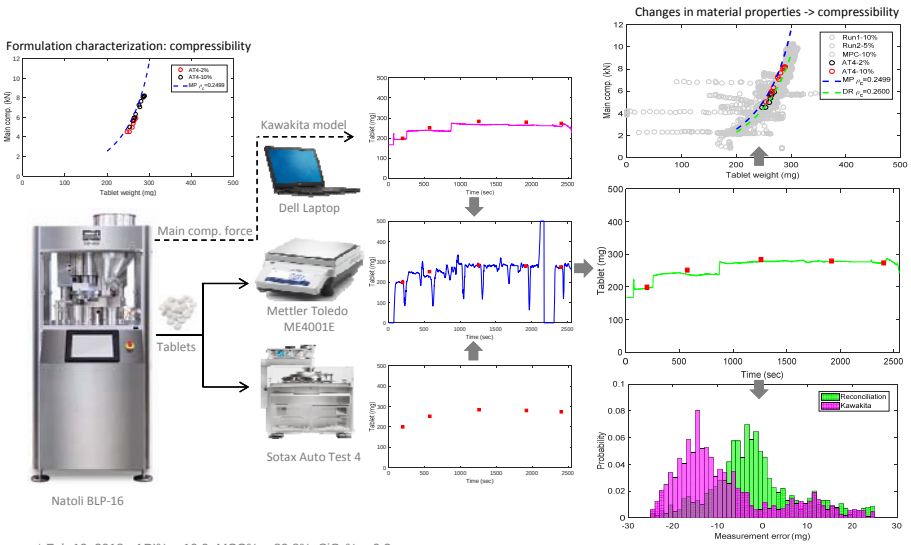


Level 2 MPC control scheme for Natoli Tablet Press

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**.

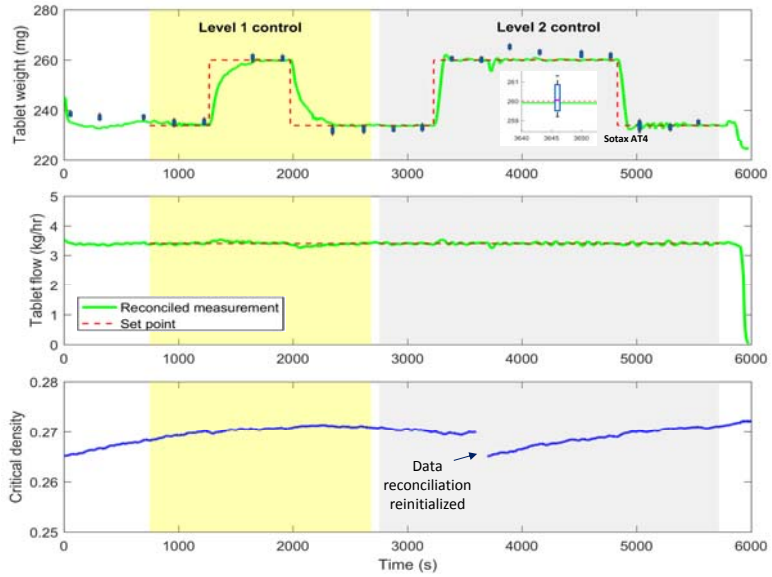


Data reconciliation - the power to combine knowledge, speed, accuracy, and precision of sensors



* Feb 19, 2018, API% = 10.0, MCC% = 89.8%, SiO_2% = 0.2

Comparison of Level 1 PID and Level 2 MPC control performance (with Level 2 DR)



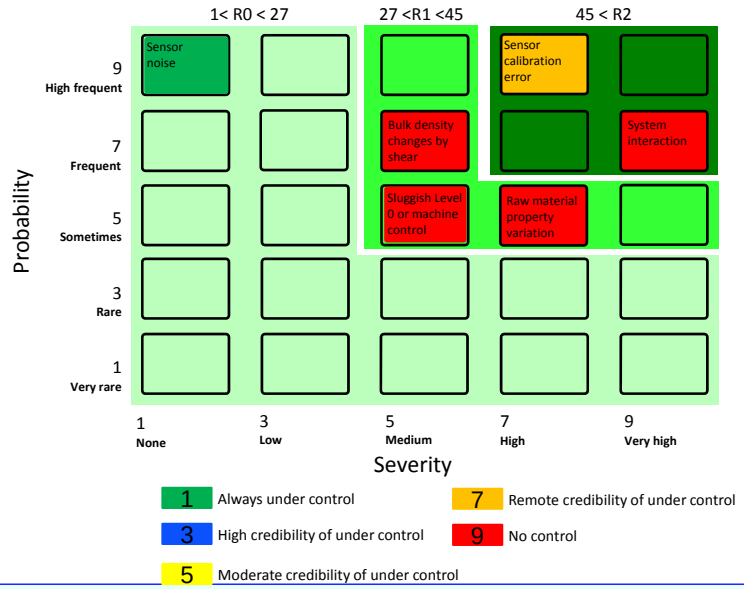
Risk analysis and assessment

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.

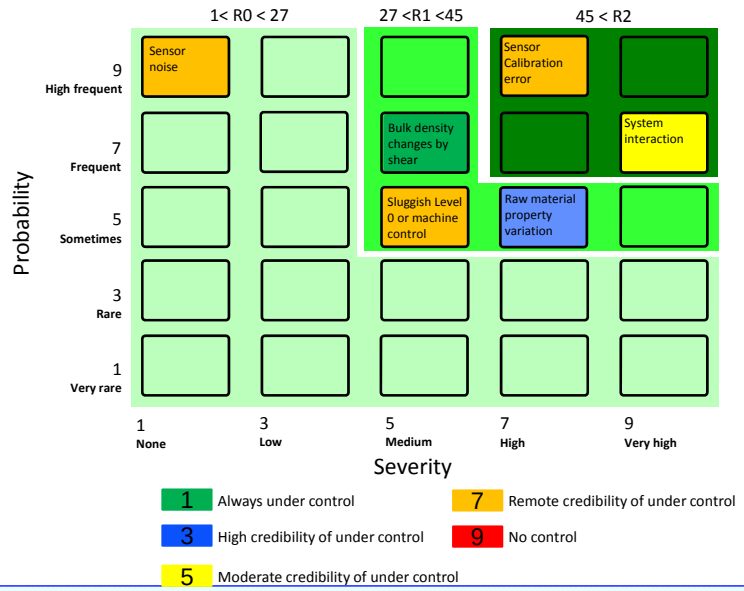
Rate	Severity		Probability		Controllability	
1	No effect	None	< 1 occurrence during the continuous production in 5 years (e.g., control instrument failure)	Very rare	All the applicable measurements & controls are in place	Always under control
3	No patient effect Process performance decreasing (e.g.,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

[1] Potter C. PQLI application of science- and risk-based approaches (ICH Q8, Q9, and Q10) to existing products. Journal of Pharmaceutical Innovation. 2009;4(1):4-23.

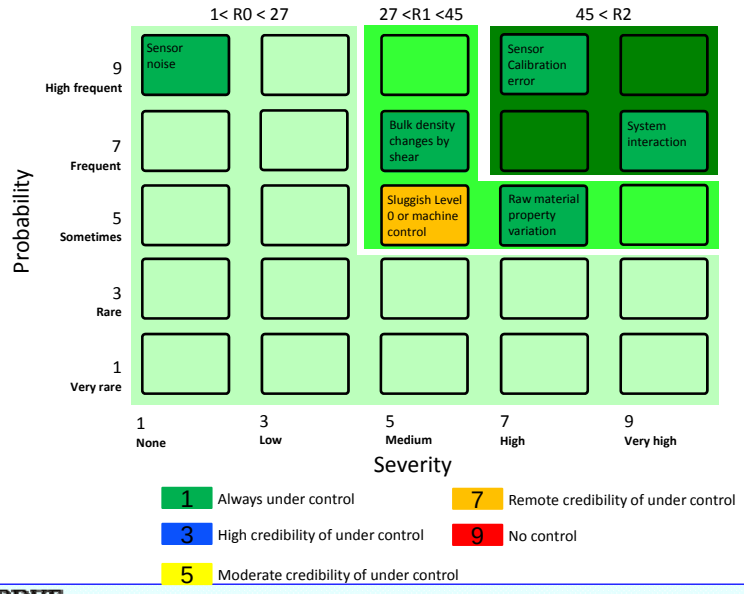
Level 0 control risk analysis in tablet press



Level 1 control risk analysis in tablet press



Level 2 control risk analysis in tablet press



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