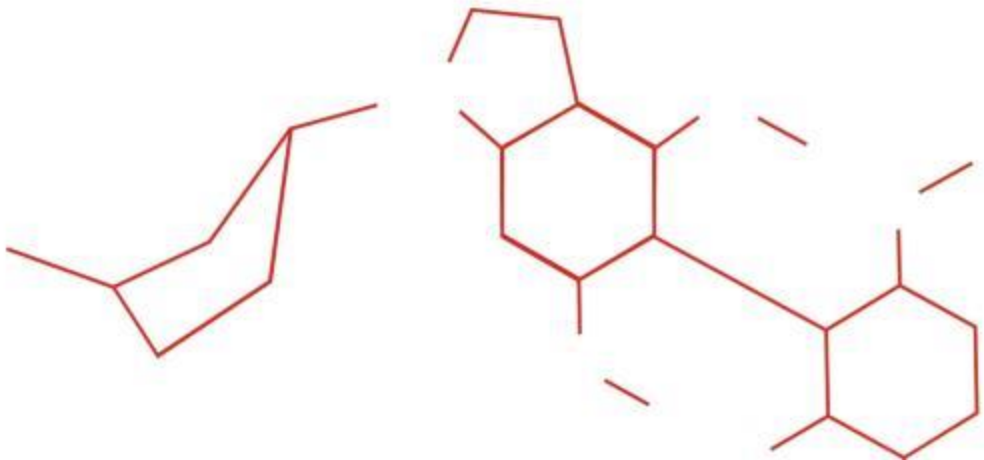
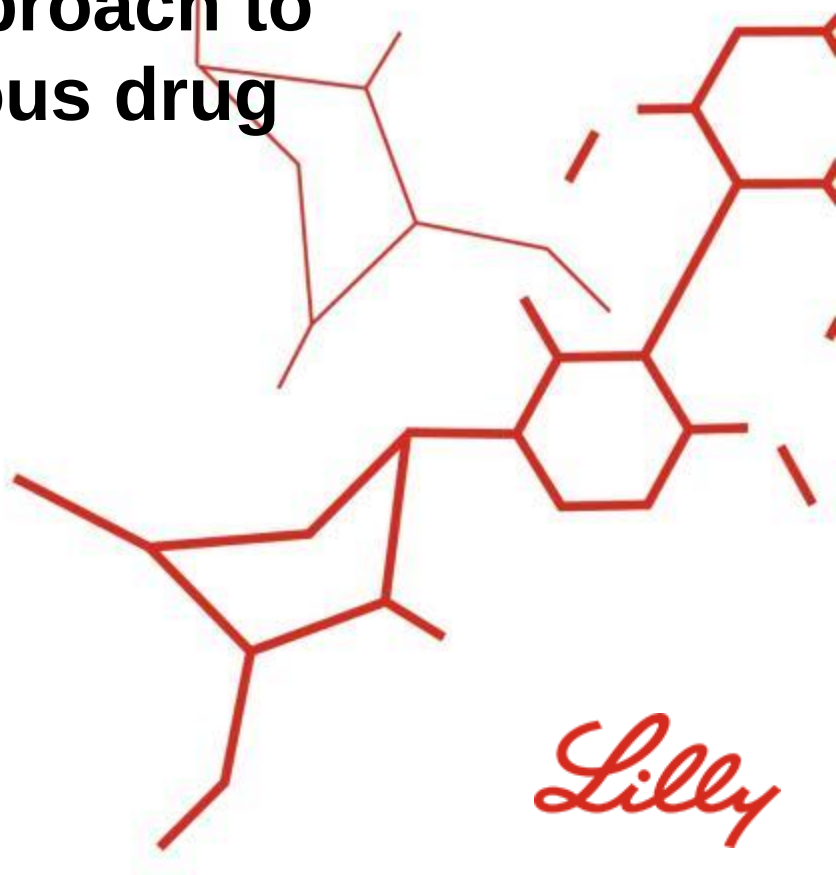


An integrated multi-layer approach to control strategy for continuous drug product manufacture

Ahmad Almaya, Ph.D.
Eli Lilly and Company
February 2016



Lilly's Journey with DP CM

2010
Business Case

2011
Simple Prototype

2012
Construct Development Facility in Indianapolis

2013
POC - confirm CDC replaces Batch RC
(multiple APIs)

Focus on Implementation in Development

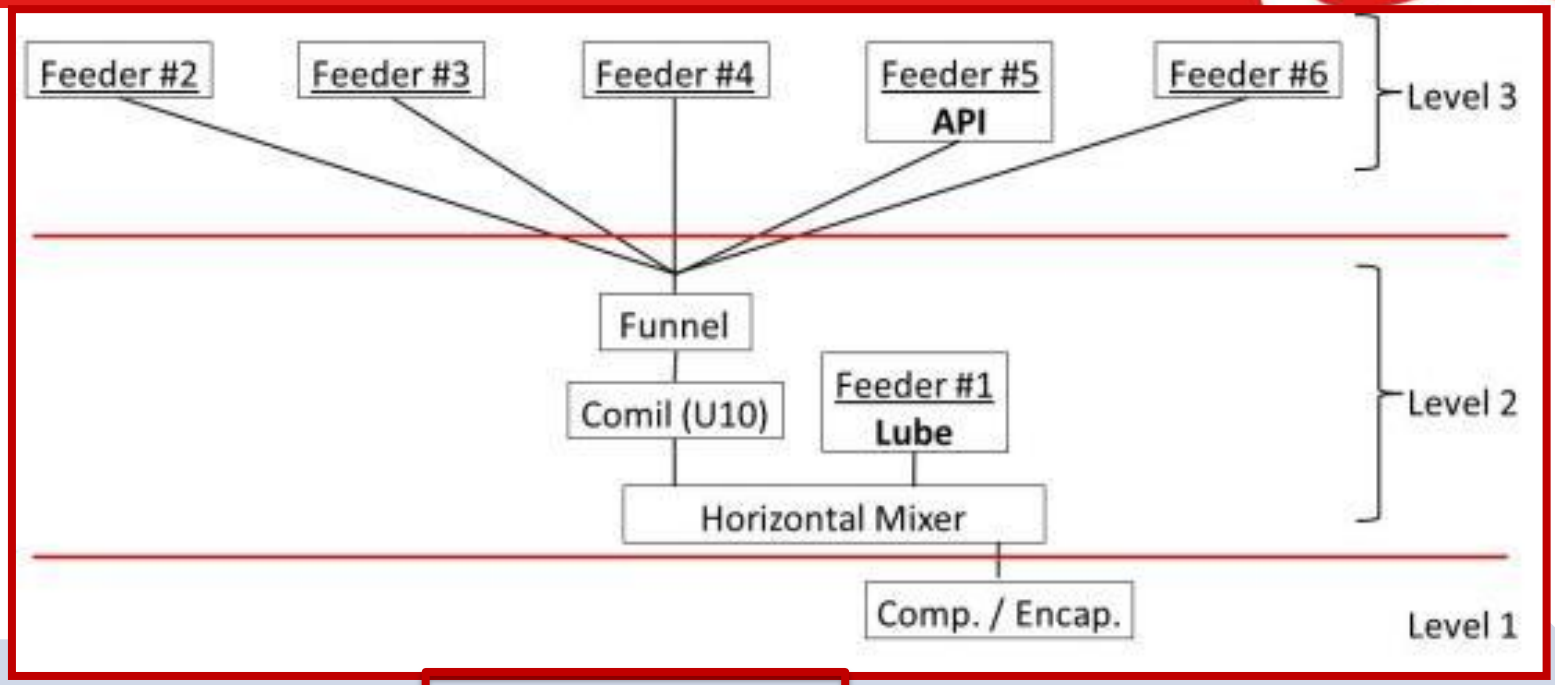
2014
Optimize Design for Broad Applicability

Formulation/
Process Development Work Plans with CM

2015
GMP Capability in Indianapolis

2016
GMP Capability at a Second Site

Lilly's Journey with DP CM



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Lilly's Journey with DP CM

Compound	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5	Compound 6
Risks/ properties	Flowable API	Segregation Risk	Poor Flow (tablet weight control)	Capsules	Segregation Risk	Micronized DS, Flow/Uniformity Risks
Batch process	DC	RC	RC	Blend/Fill	RC	DC
CM process	DC	DC	DC	Blend/Fill	DC	DC
CU Pass/Fail	P	P	P	P	P	P

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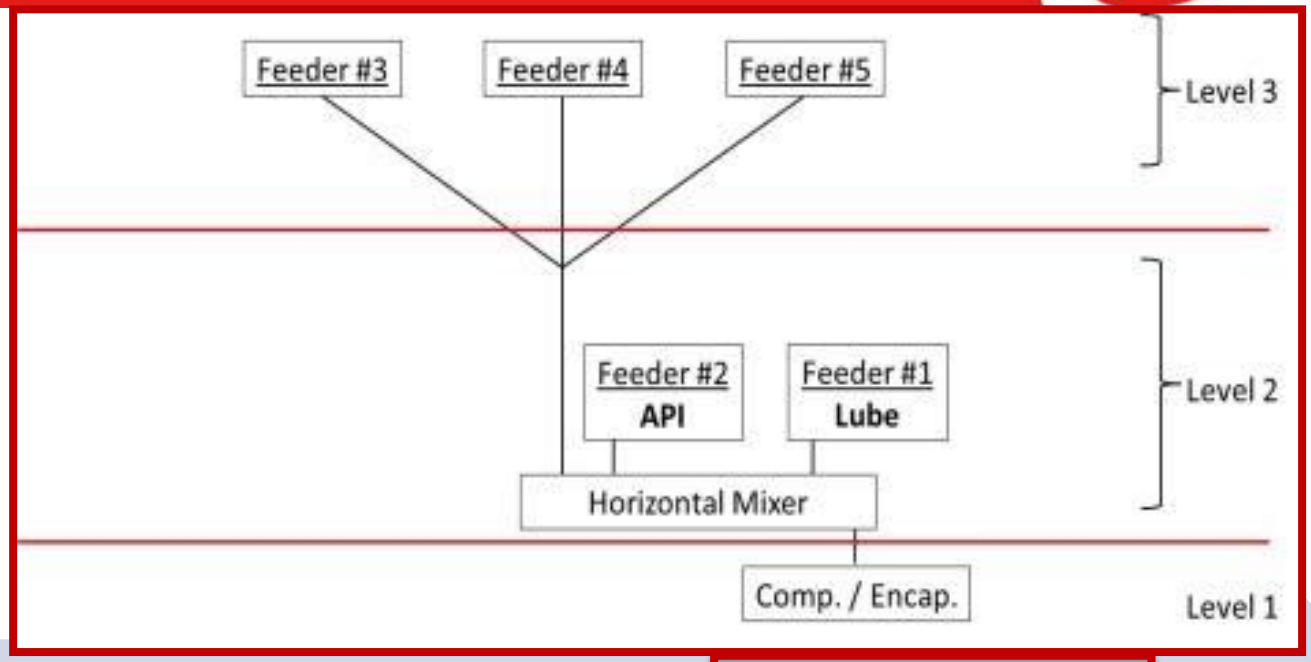

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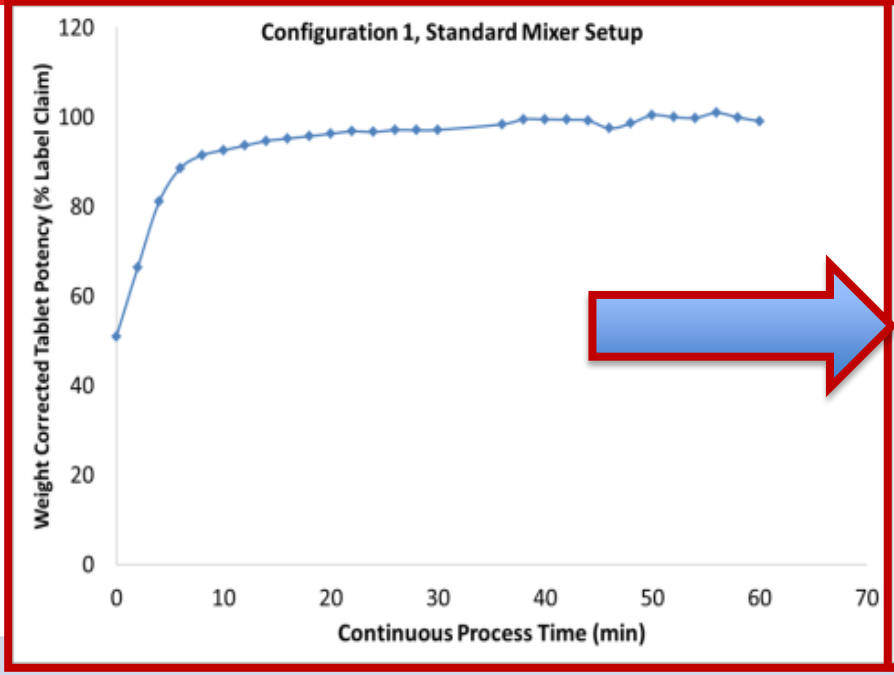

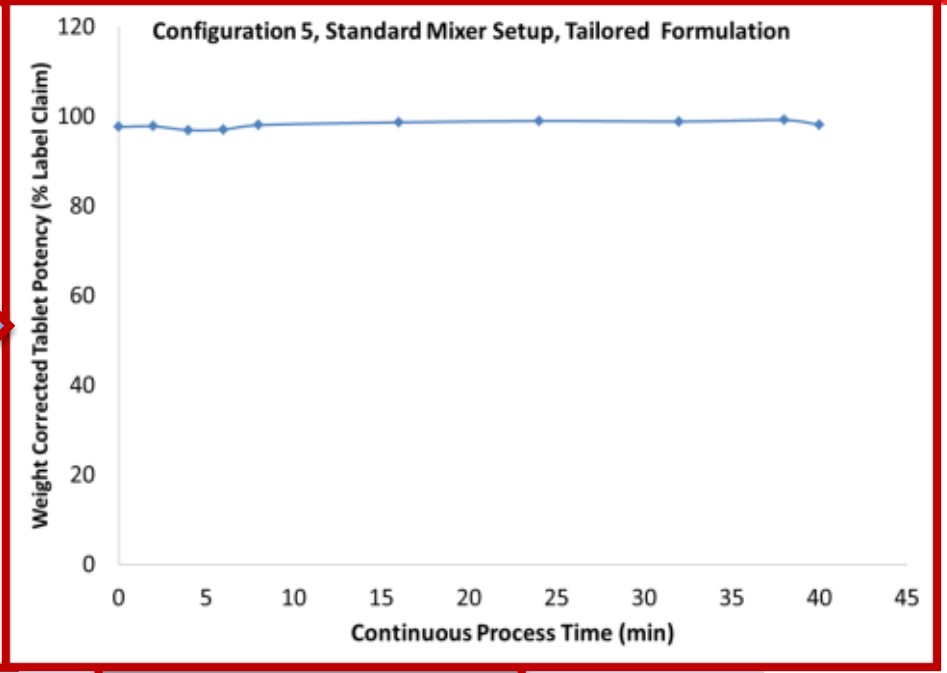

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Lilly's Journey with DP CM

Implementation on Lilly's portfolio

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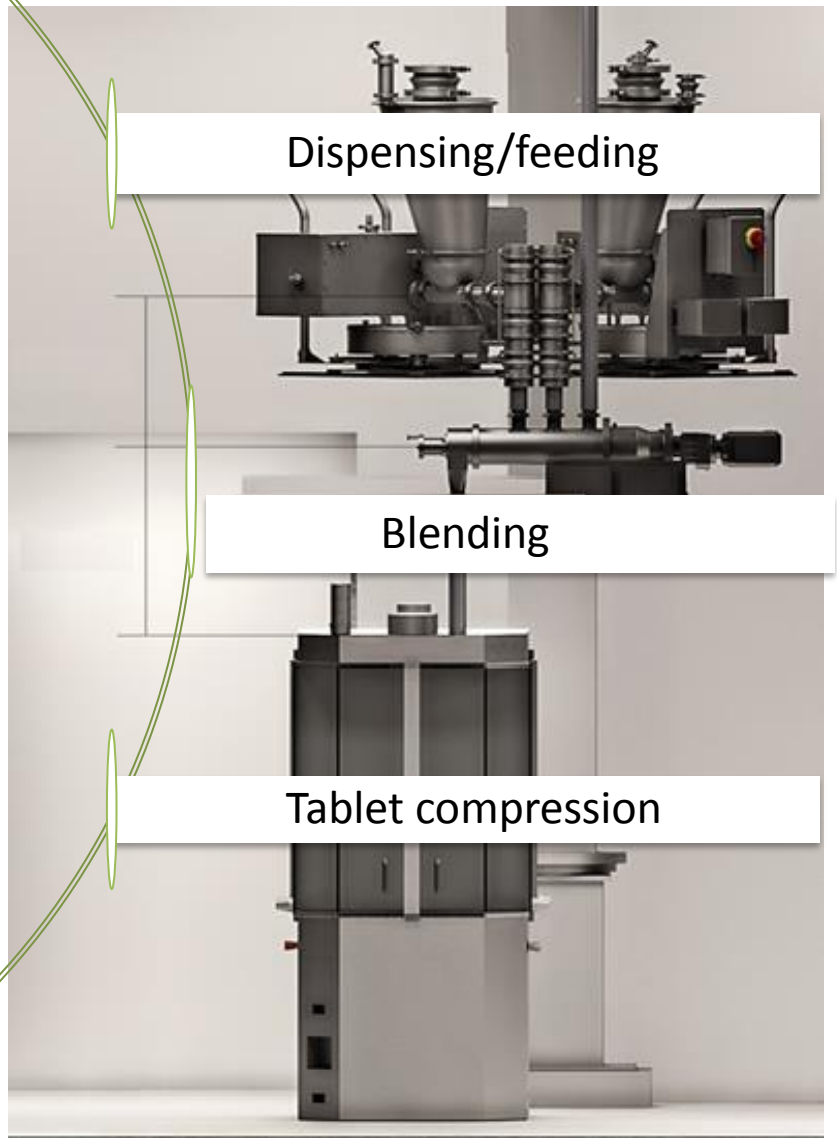
2016
GMP Capability at a Second Site

Optimized Design

- Unit Utilizes a DeltaV control system, SynTQ PAT controller and data synchronization, and CAMO Unscrambler multivariate analysis (MVA).
- GMP units at Lilly's manufacturing sites have identical equipment, PAT instrumentation and automation to the development unit.

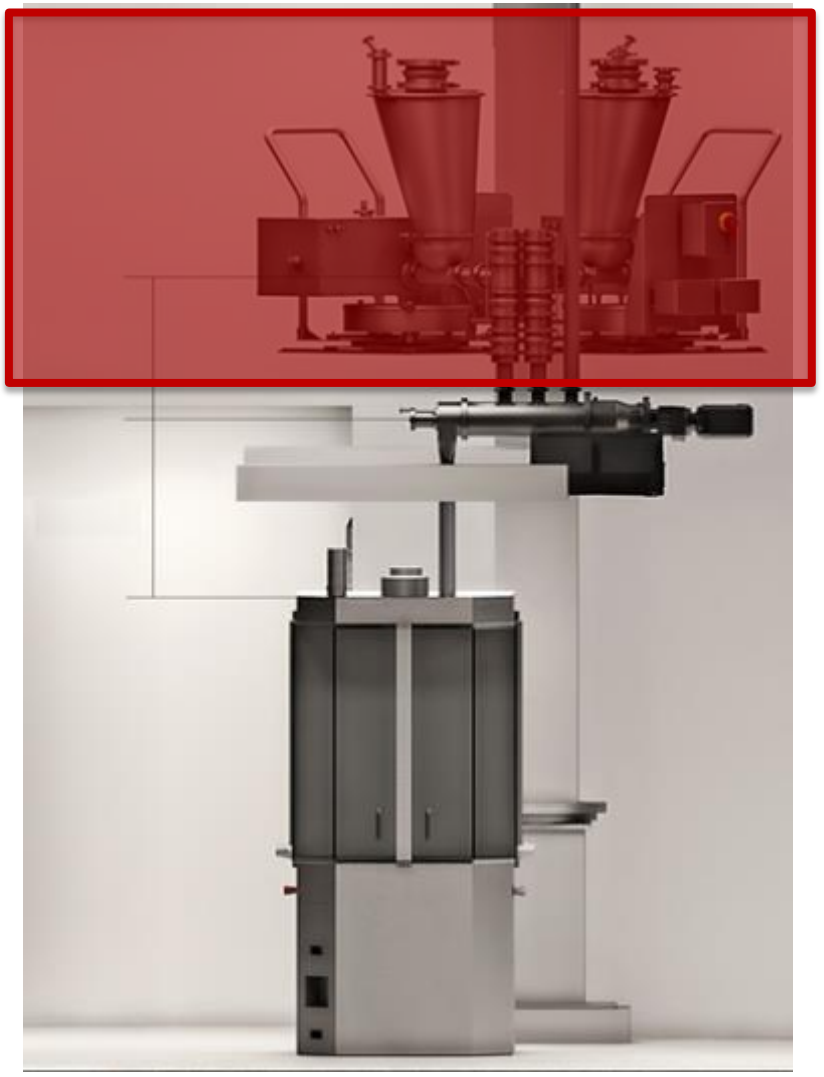


Advantages of Equipment Design Simplification

- Optimized system performance
  - Minimize special cause disturbances related to material flow (i.e., remove potential material accumulation areas and elements that negatively impact consistent material flow).
  - Improve startup phase (minimize startup waste).
- Enabling a robust control strategy
  - Minimize risk of potency and uniformity disturbances by real-time control of feeders, and robust mixer design and operation.
- Allow implementation of automation as part of the control strategy
  - Real time process monitoring and automated product collection/rejection

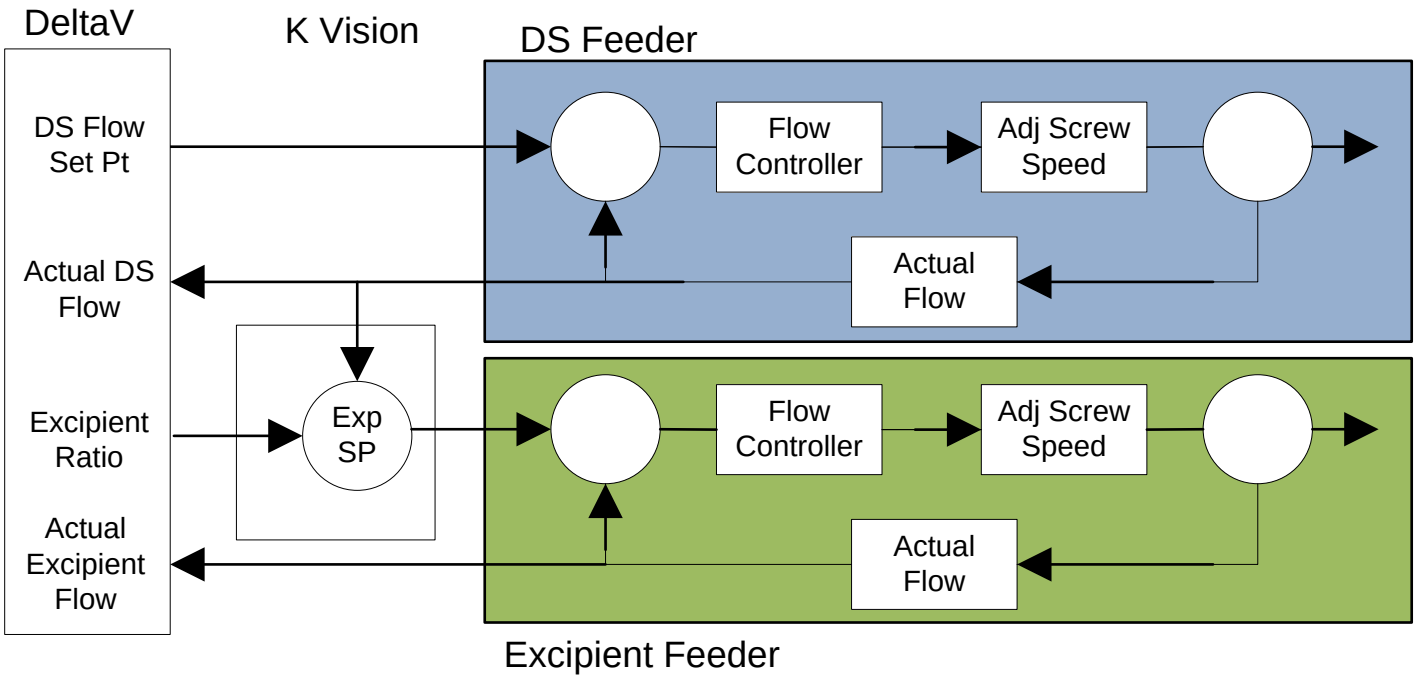
Operating Control Strategy - Feeders

LIW feeder monitoring and control are the primary elements to ensure drug product CQAs



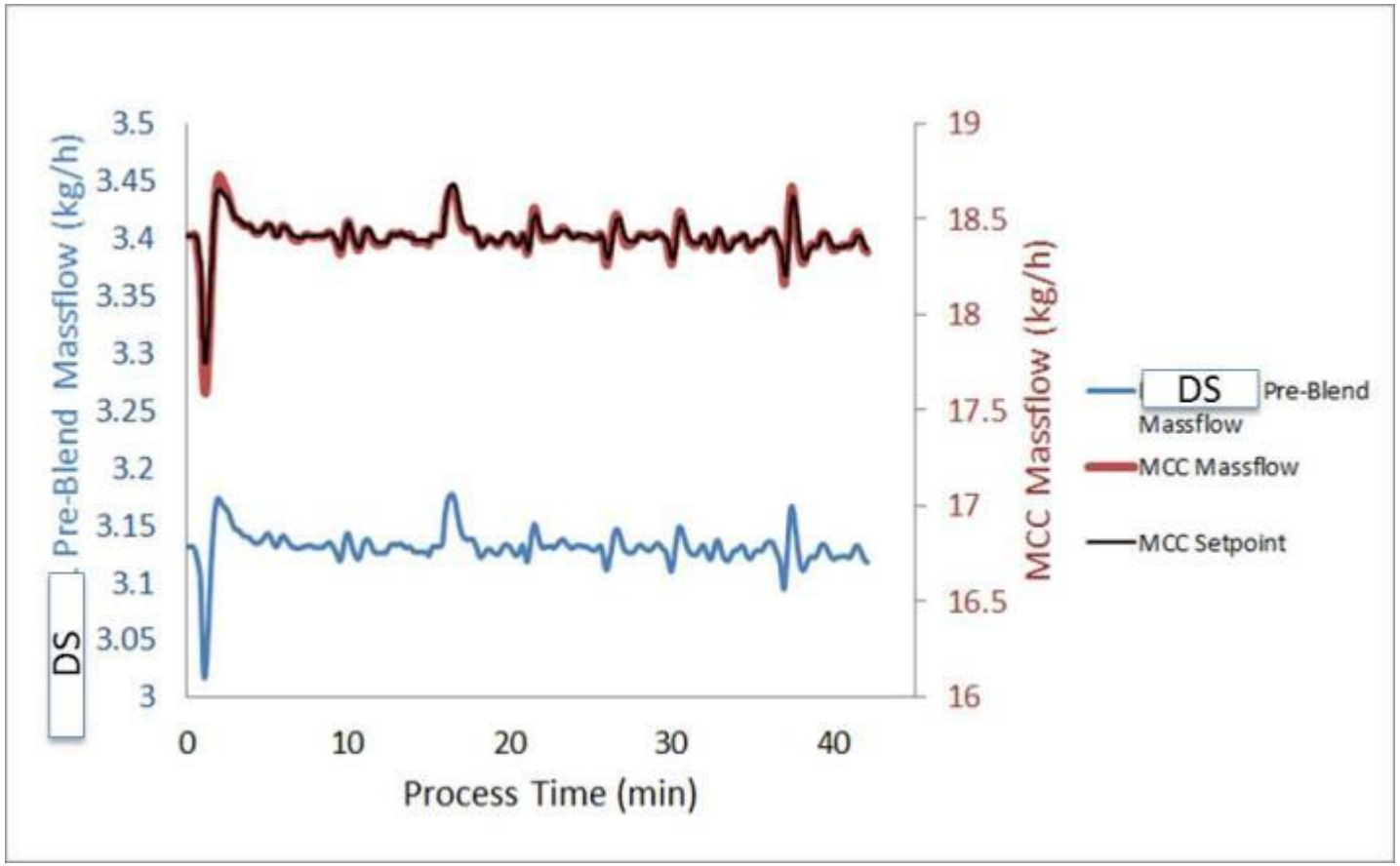
LIW Feeder – Ratio Mode

- Cascade control loop where the actual output from one feeder (e.g. the worst flowing material which is typically the drug substance) is used to calculate the flow rate set points for the other feeders



- ALL FEEDERS working together to feed the unit formula reducing short term duration disturbances

Ratio Mode Example Using a Poorly Flowing Drug Substance

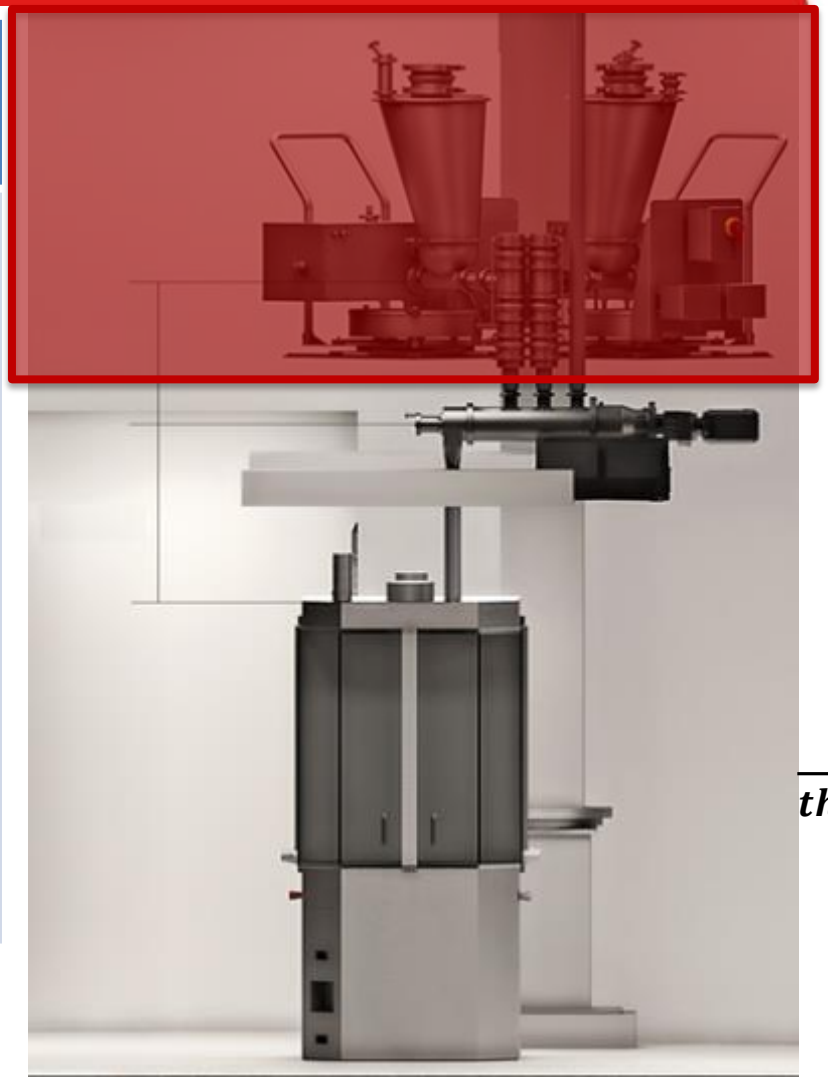


- Both common cause (random) variation and deviation from target are judged to be low risks to drug product CQAs when using Ratio Mode.

Operating Control Strategy - Feeders

Feedback Process Control

- Individual Feeder Control:
  - Vary screw speed to maintain flow set point
- Feeders Ratio Mode Control:
  - Vary flow set point to maintain unit formula



Feed Forward Process Control

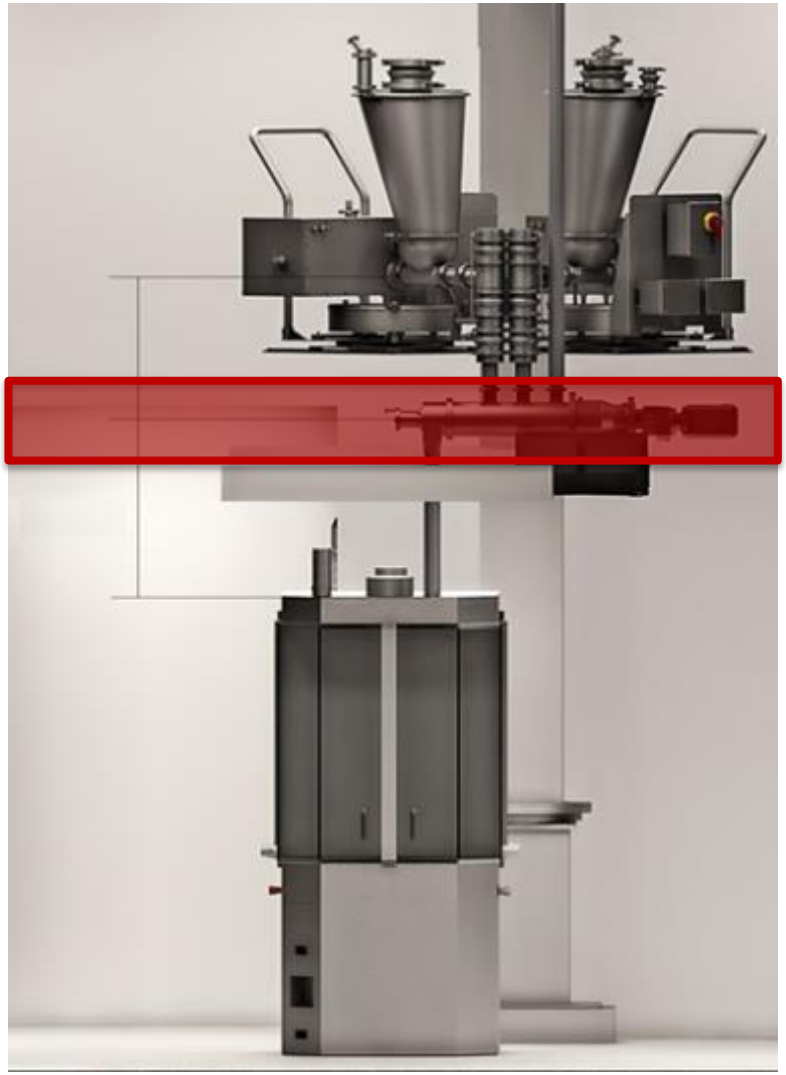
Input into the Reduced System Model

Tablet collection/rejection decisions based on

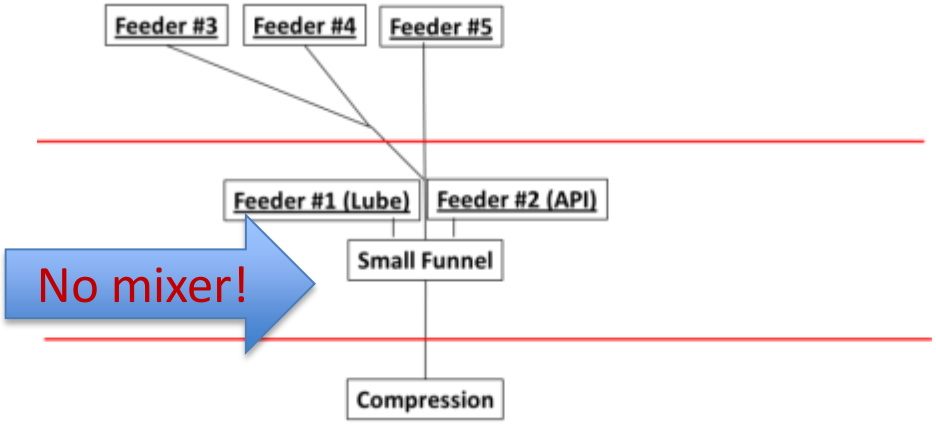
fed concentration (% theoretical)

$$Fed\ Conc\ \%Theoretical = \frac{\frac{flow\ rate\ DS}{flow\ rate\ total}}{theoretical\ drug\ load} * 100$$

Operating Control Strategy – Horizontal Mixer

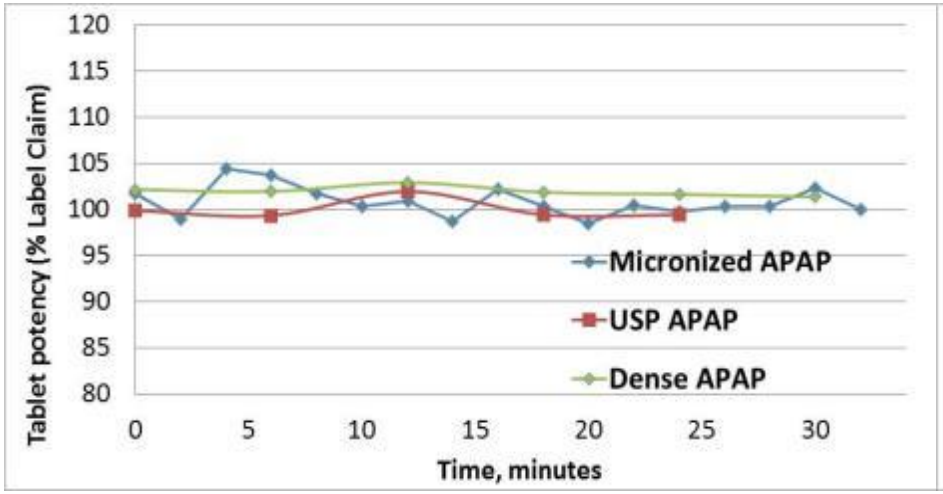


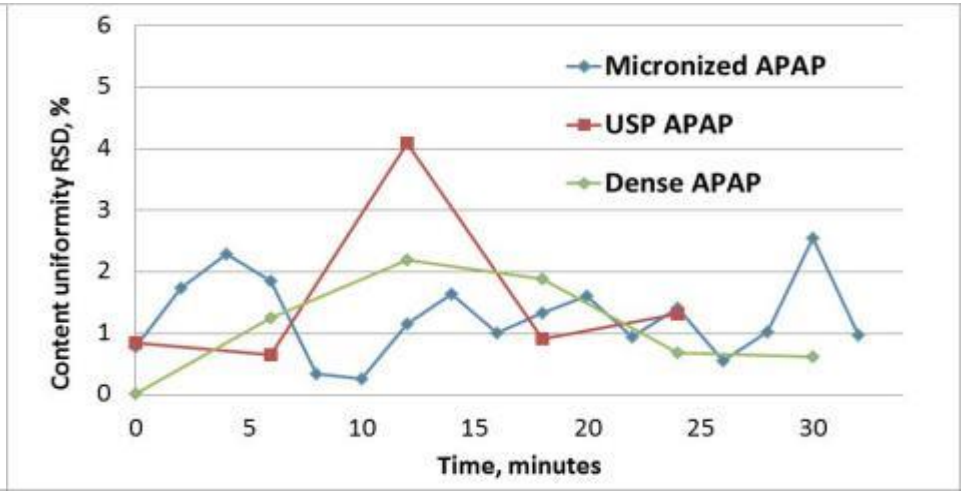
What Contributes to Adequacy of Mixing with CDC?



Continuous direct compression manufacturing processes:

- Assurance of uniformity starts with LIW feeders.
- All steps in the integrated process may contribute to mixing.





Optimized Design

The appropriate location for assessing adequacy of mixing :

- The outlet of the power-assisted tablet press feed frame,

OR

- The actual compressed tablet cores.

PAT instrumentation:

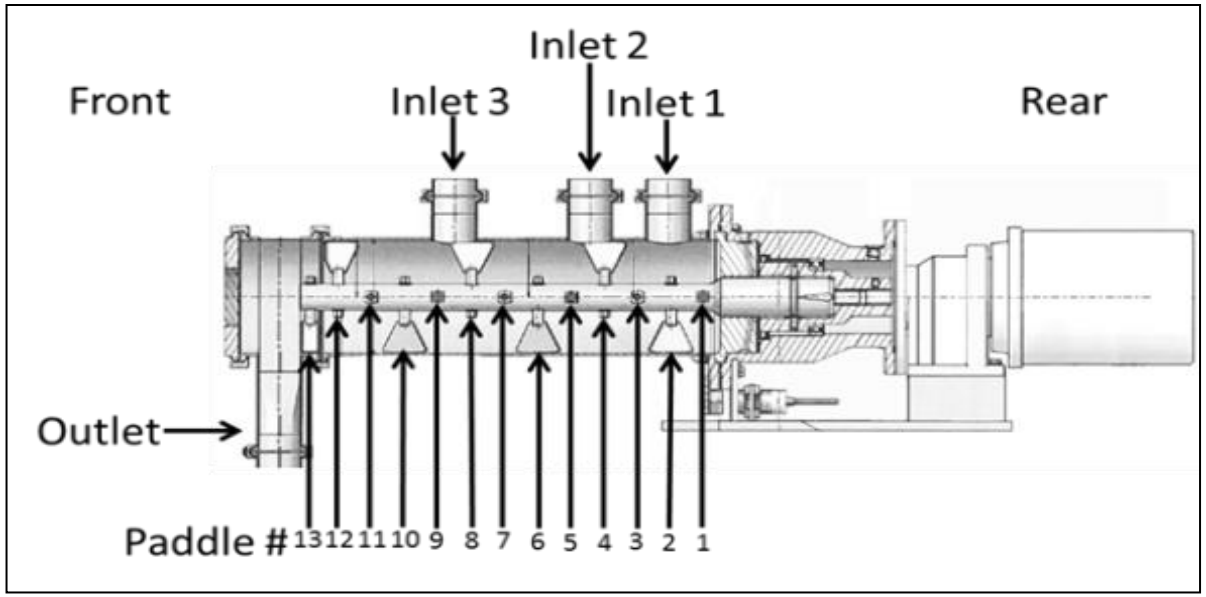
- A reflectance NIR probe in the tablet press feed frame.

And

- A tablet tester with automated sampling that measures core tablet mass, thickness, breaking force, and transmission NIR spectrum.

Robustness of Continuous Mixers

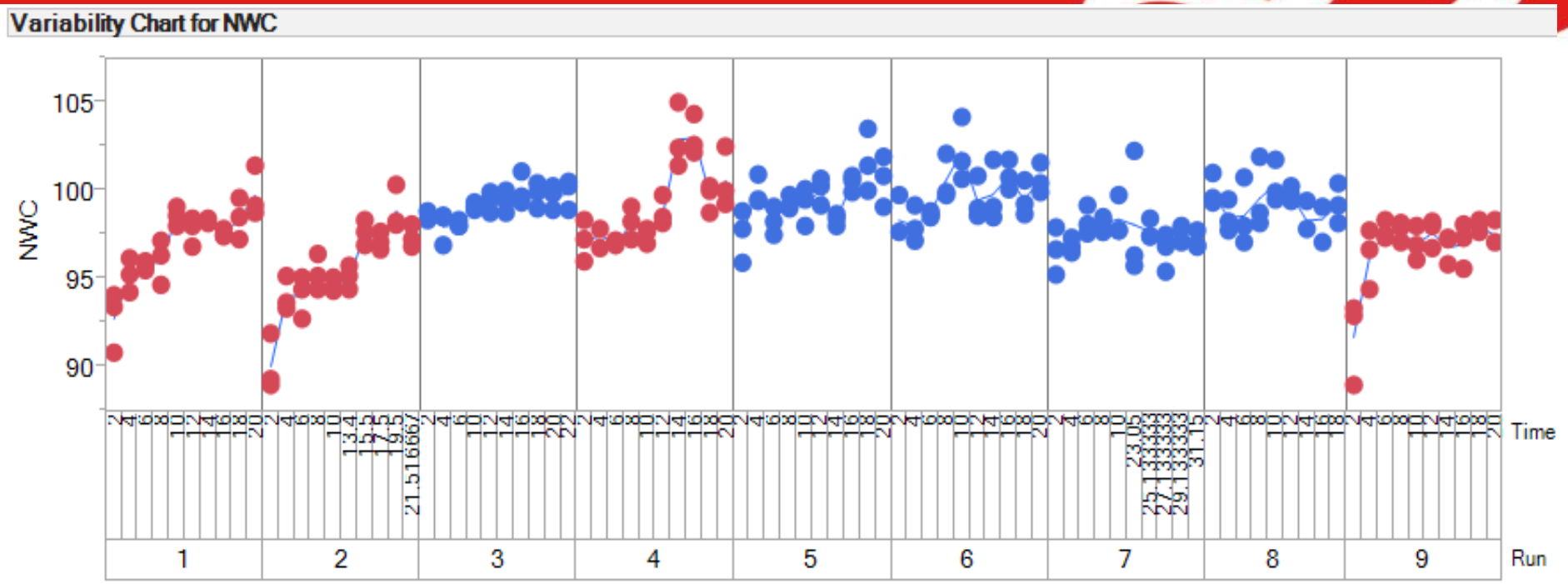
- Purpose of horizontal mixer is to dampen LIW feeder variation.
- A mixing DOE was executed to understand horizontal mixing robustness with a challenging formulation (micronized API, relatively low drug load).



Factors tested:

- Paddle Angle & Direction
- Mixer Speed
- Mass Flow Throughput

Mixer and Throughput DOE

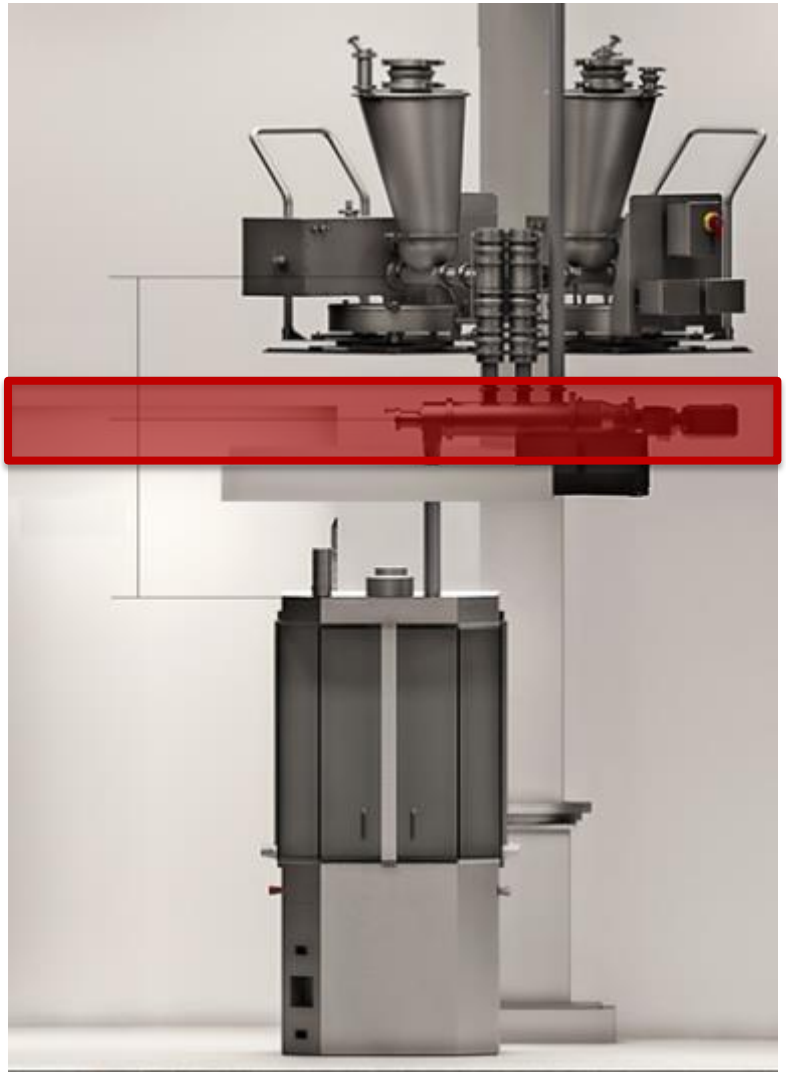


- Mass throughput was the only variable that showed an impact
  - impacted Potency start-up only. No impact to CU, Description or Release Profile.
- Red = Low Throughput; Blue = High Throughput
- Strong correlation of both overall variability and start-up with throughput
  - No other mixing factors were significant with respect to potency and CU

Operating Control Strategy – Horizontal Mixer

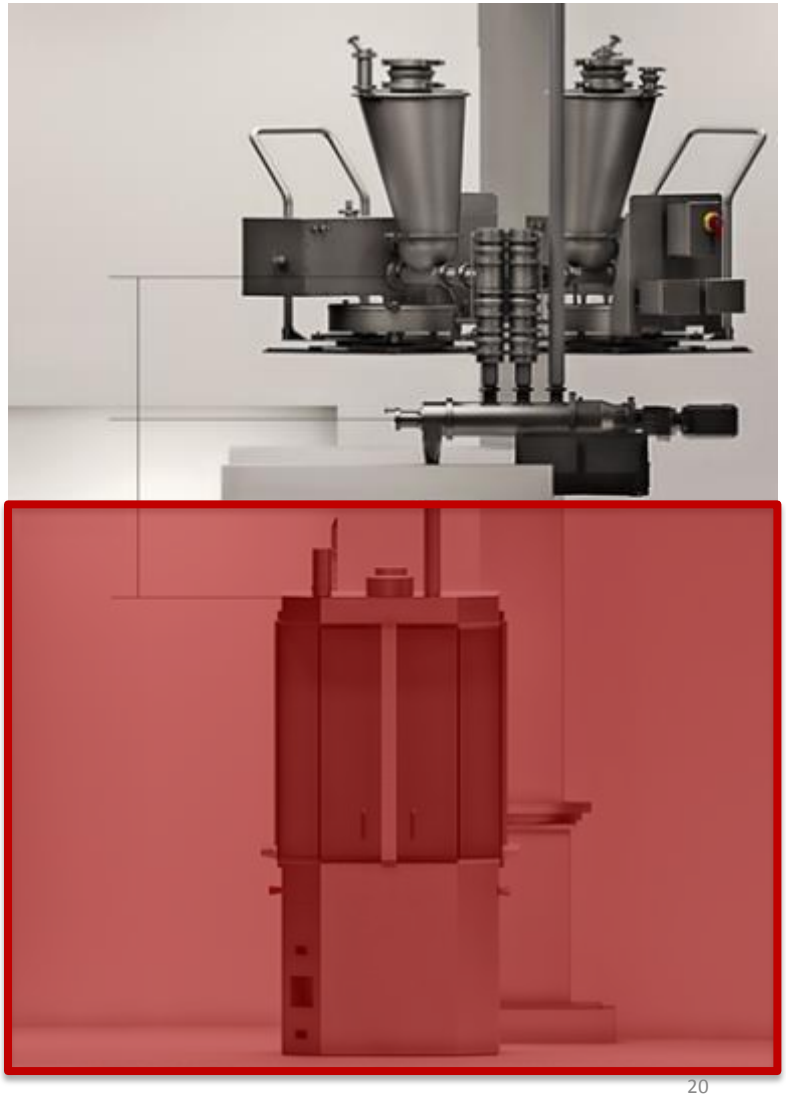
Robust mixer design and operation.

With appropriate LIW feeder control, horizontal mixer mechanical set up and operation have low risk of impacting drug product CQAs



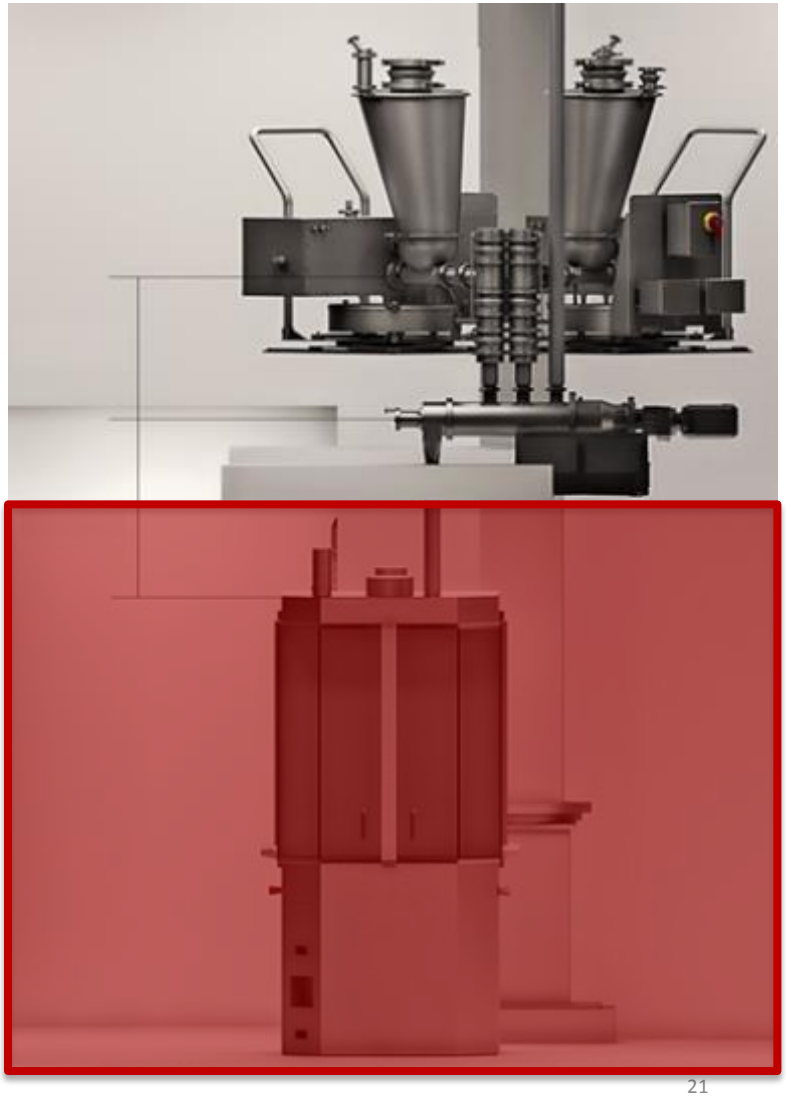
Operating Control Strategy – Tablet Press

Leverage the existing internal control loops within the modern, highly sophisticated tablet compression machines (and more!)



Operating Control Strategy – Tablet Press

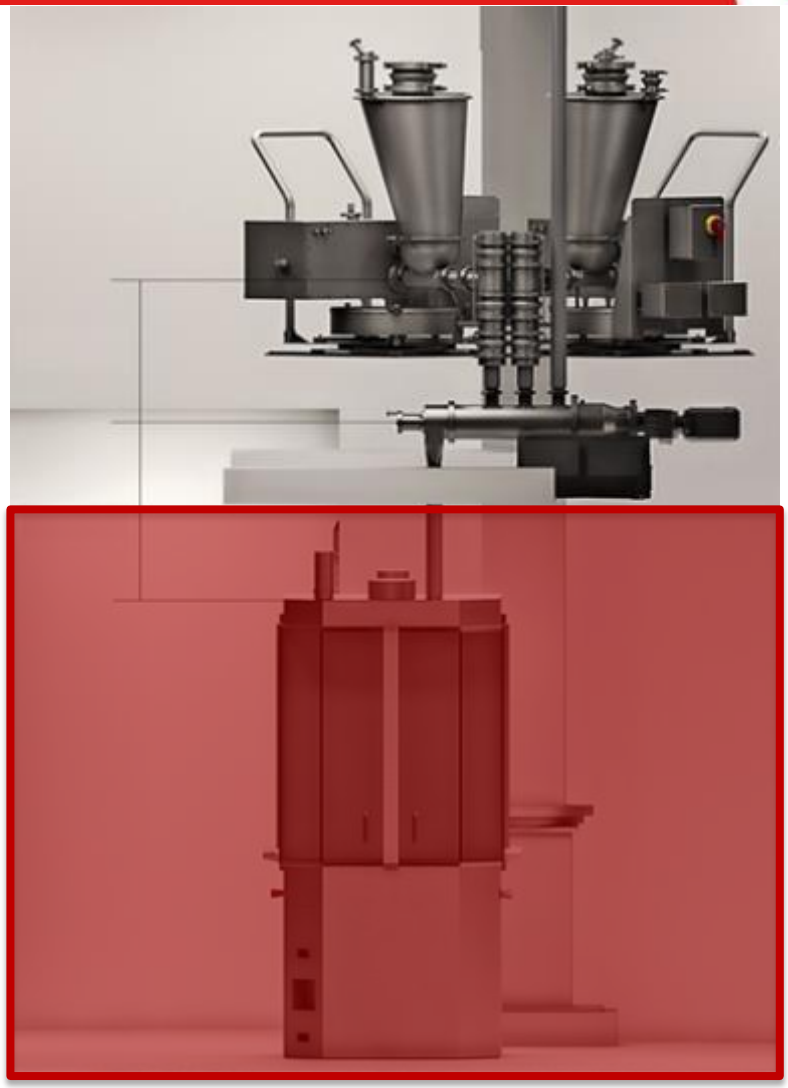
- Tablet Press Force and Weight Control Loops are the same as existing batch processes
- System only accepts tablets within acceptable range of target weight



Operating Control Strategy – Tablet Press

Data Source	Feedback Process Control
Tablet Press	Tablet weight (Force Control Loop)

Data Source	Feedback Process Control
Tablet Tester	Tablet weight (Weight Control Loop)

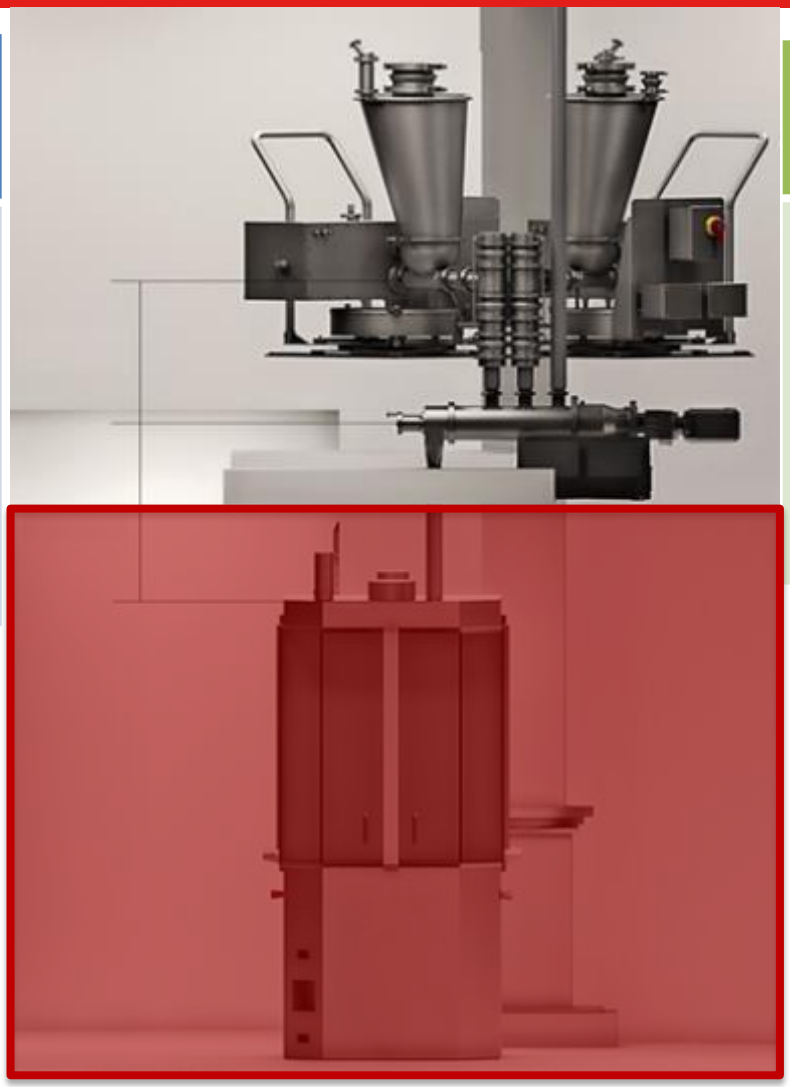


Data Source	Feed Forward Process Control
Tablet Press	Tablet collection/ rejection decisions based on tablet main compression force

Data Source	Option
Tablet Tester (NIR)	RTRt option (UDU/ assay)

Operating Control Strategy – Tablet Press

Data Source	Feedback Process Control
Tablet Press Surge Hopper Level	Tablet press turret speed (Level Control Loop)

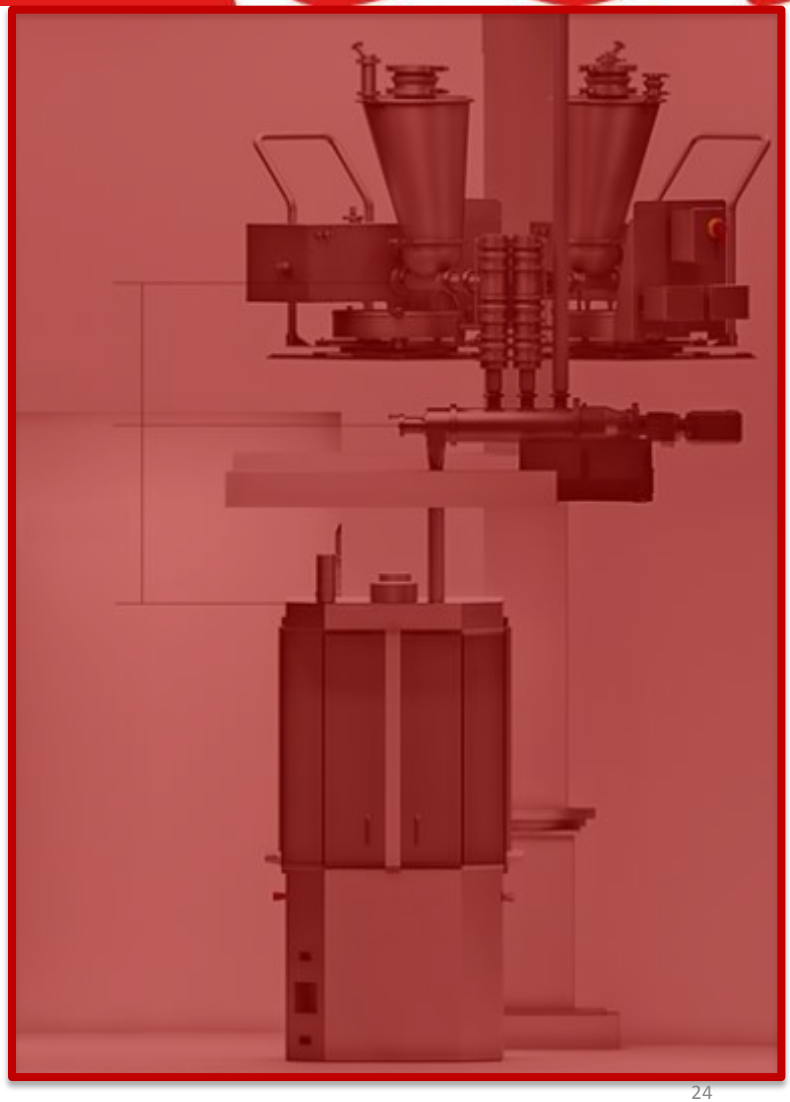


Data Source	Feed Forward Process Control
Tablet Press Surge Hopper Level	Input into Reduced System Model (Time to product and time to clear)

Operating Control Strategy – RTD Based Reduced System Model

Leverage the high capability of LIW feeders along with process modeling as part of the operating control strategy.

This is facilitated by the simple physical equipment design.



Operating Control Strategy – RTD Based Reduced System Model

Fed Concentration (% ***Theoretical***)

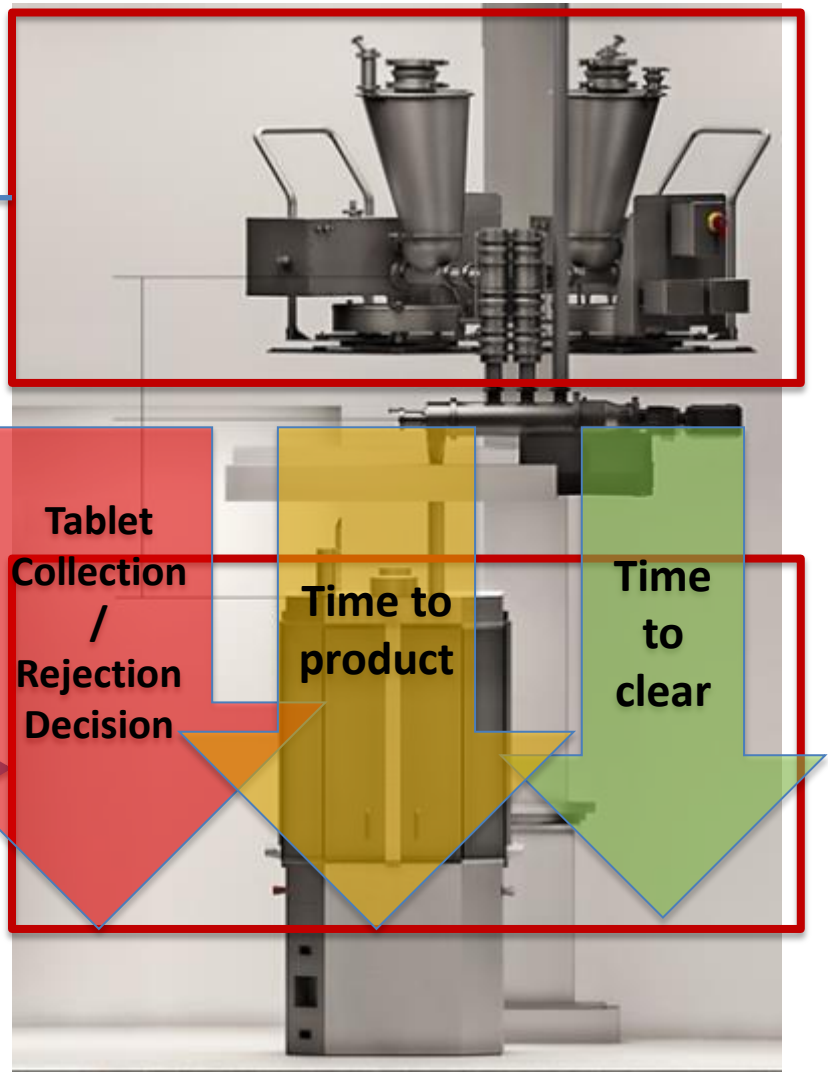
(concentration dispensed into mixer)

RTD based System Model

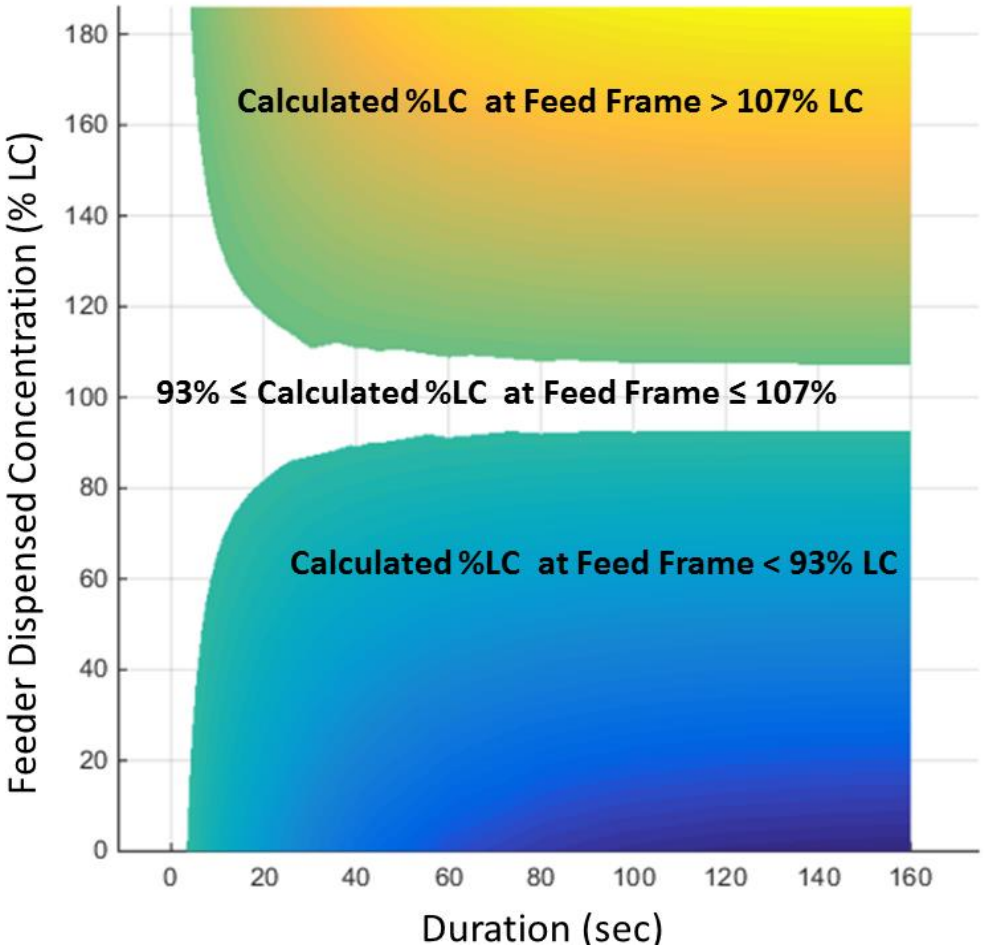
Feed Frame Concentration (% ***Theoretical)***

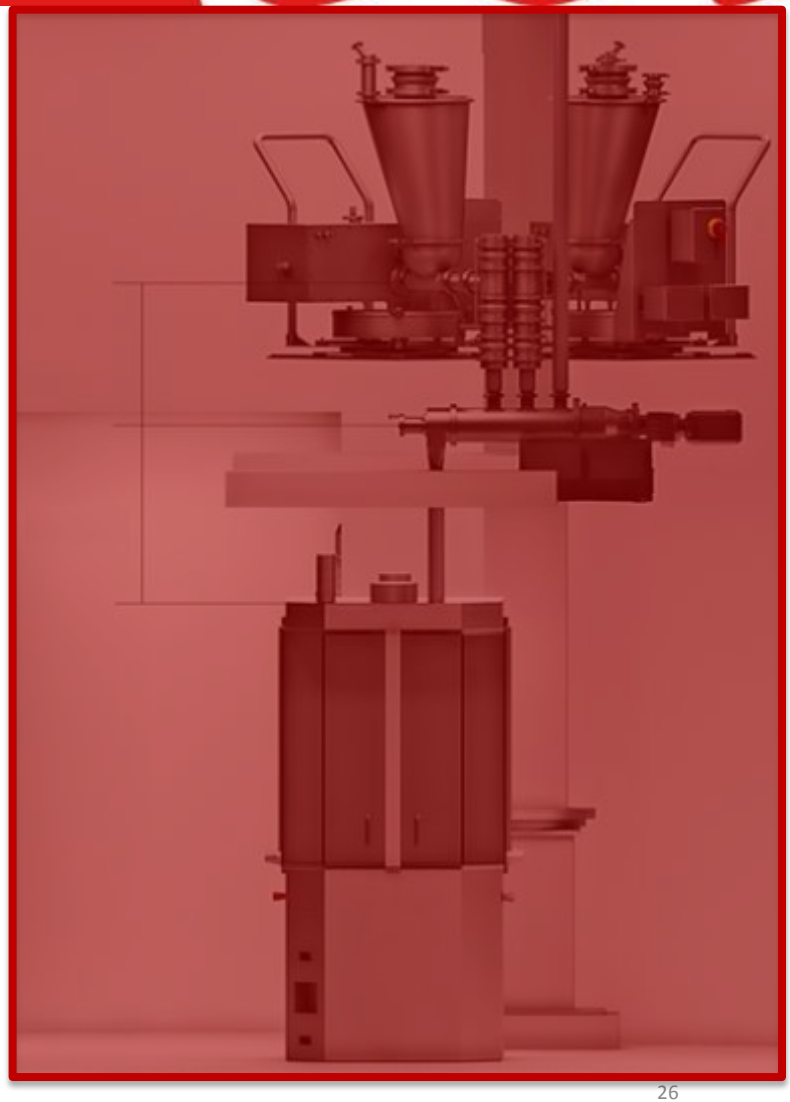
(predicted (future) conc in tablet press feed frame)

Compare to pre-defined collection criteria



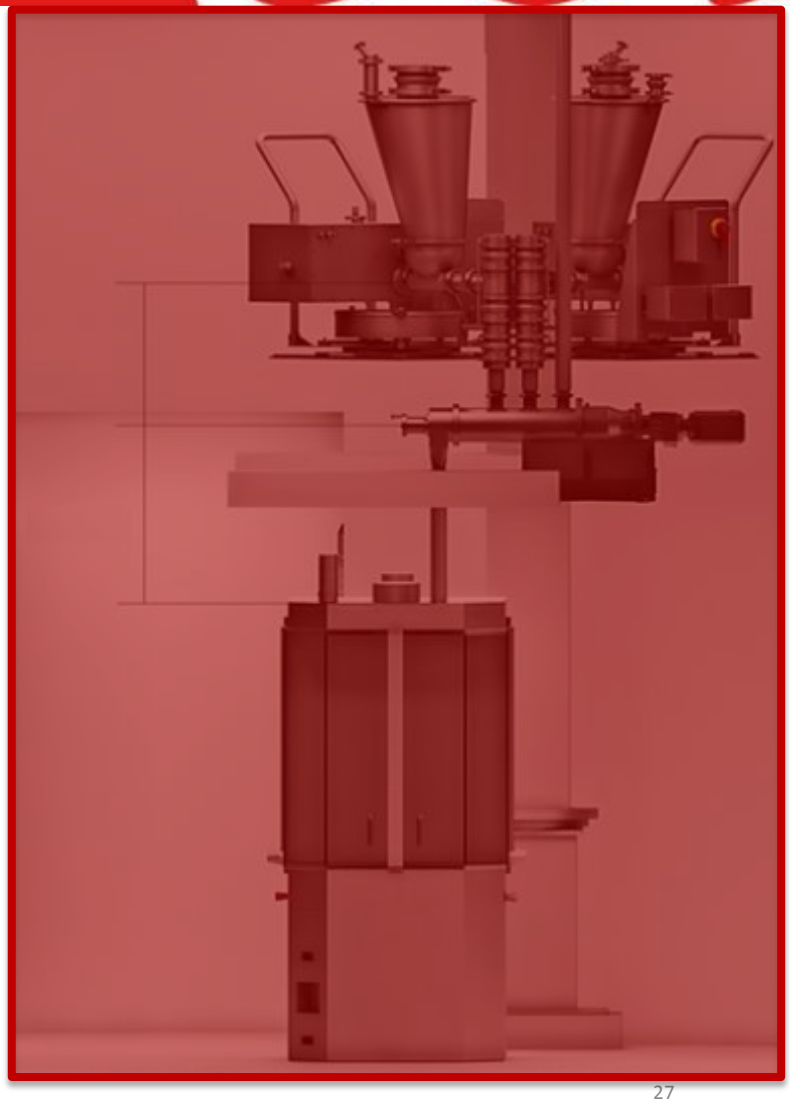
Operating Control Strategy – RTD Based Reduced System Model



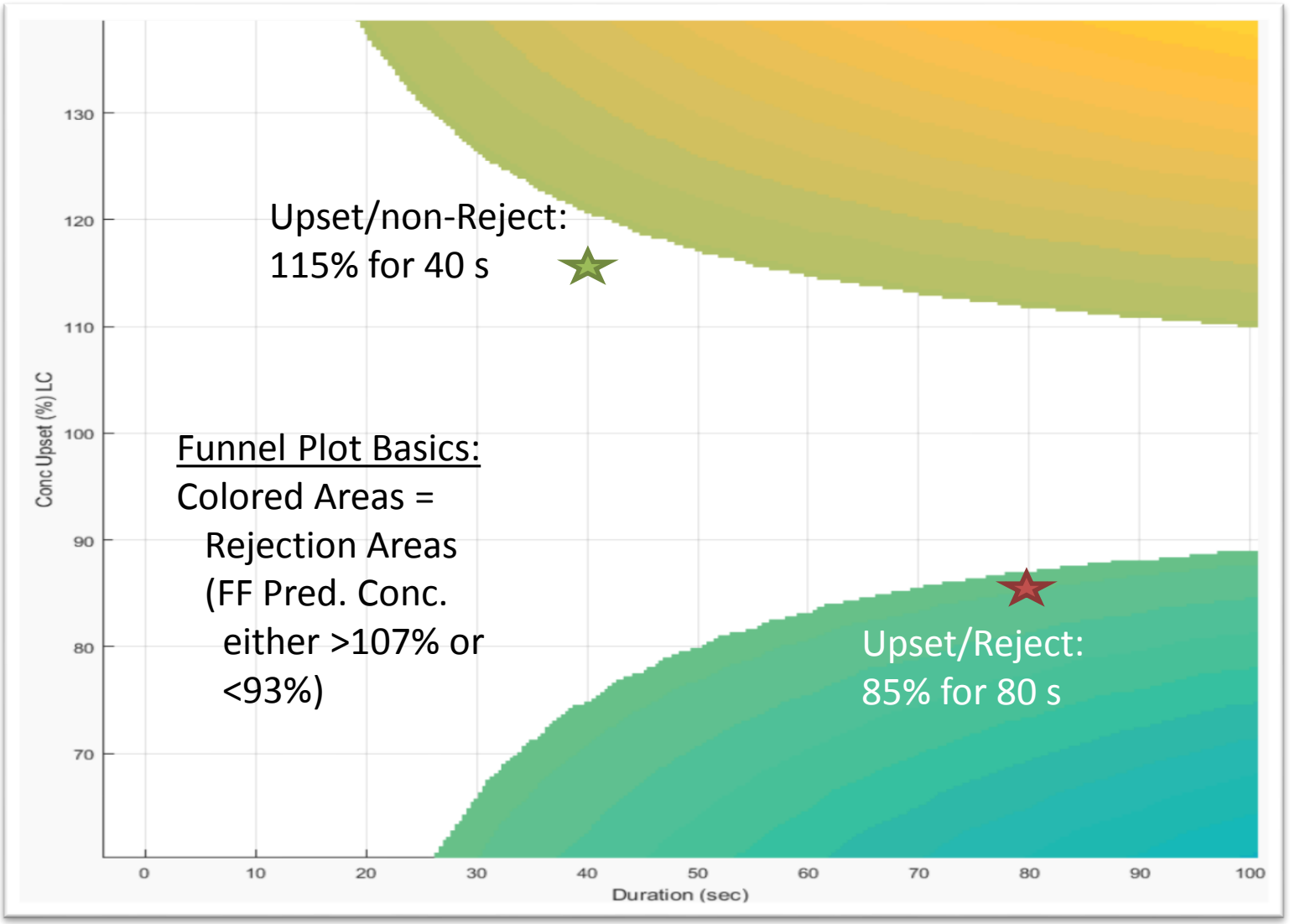


Operating Control Strategy – RTD Based Reduced System Model

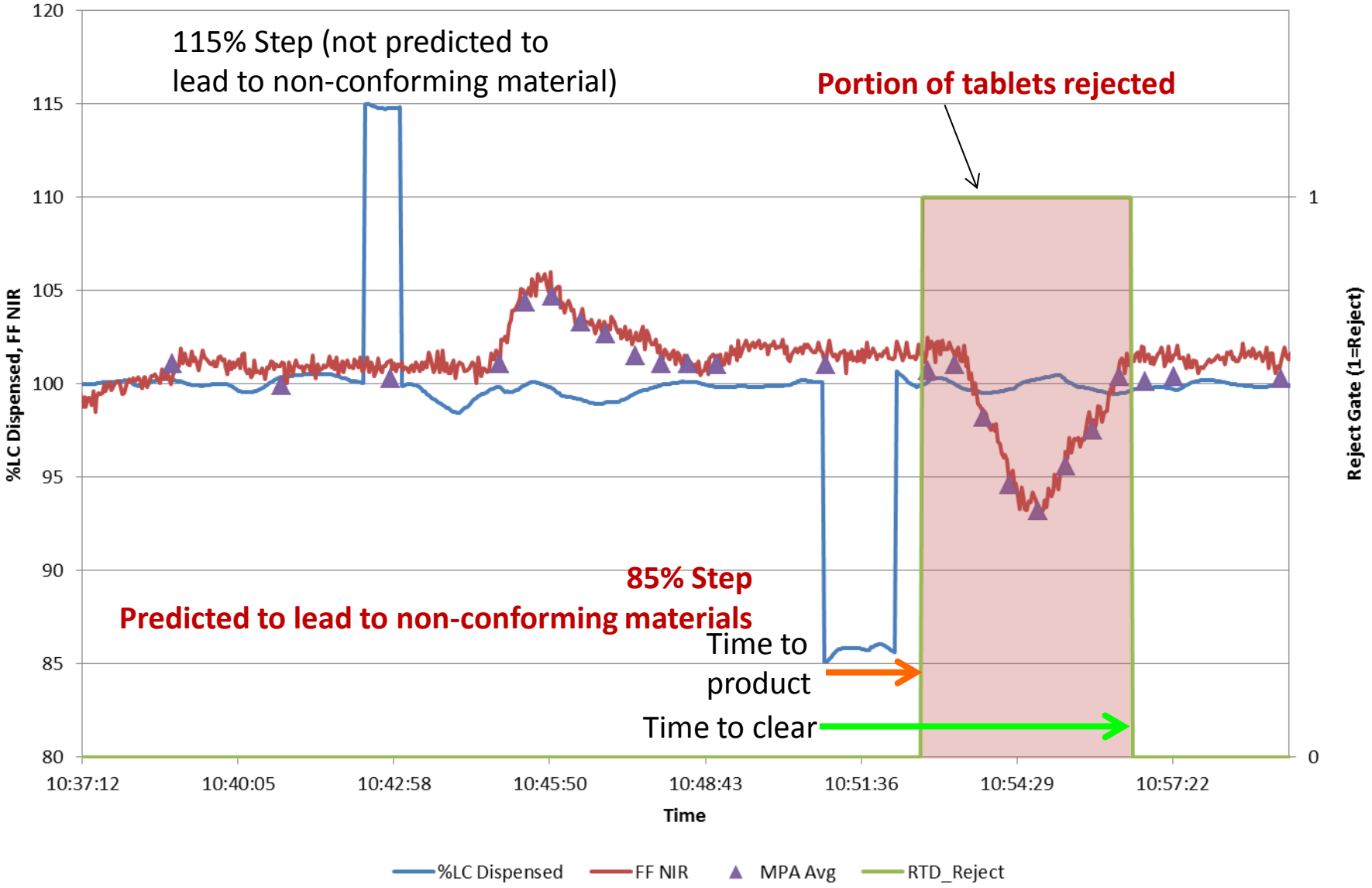
- Because of the high capability of the LIW feeders, testing the Reduced System Model is similar to automobile safety crash tests; you intentionally trip the system and let it “crash” and see how the system responds to this disturbance.
- Demonstrate process control due to a special cause failure mode.
- For the purpose of this “crash” test, we are using product collection criteria of 93 – 107%



Example – Reduced System Model – LY2, Tablet strength 1

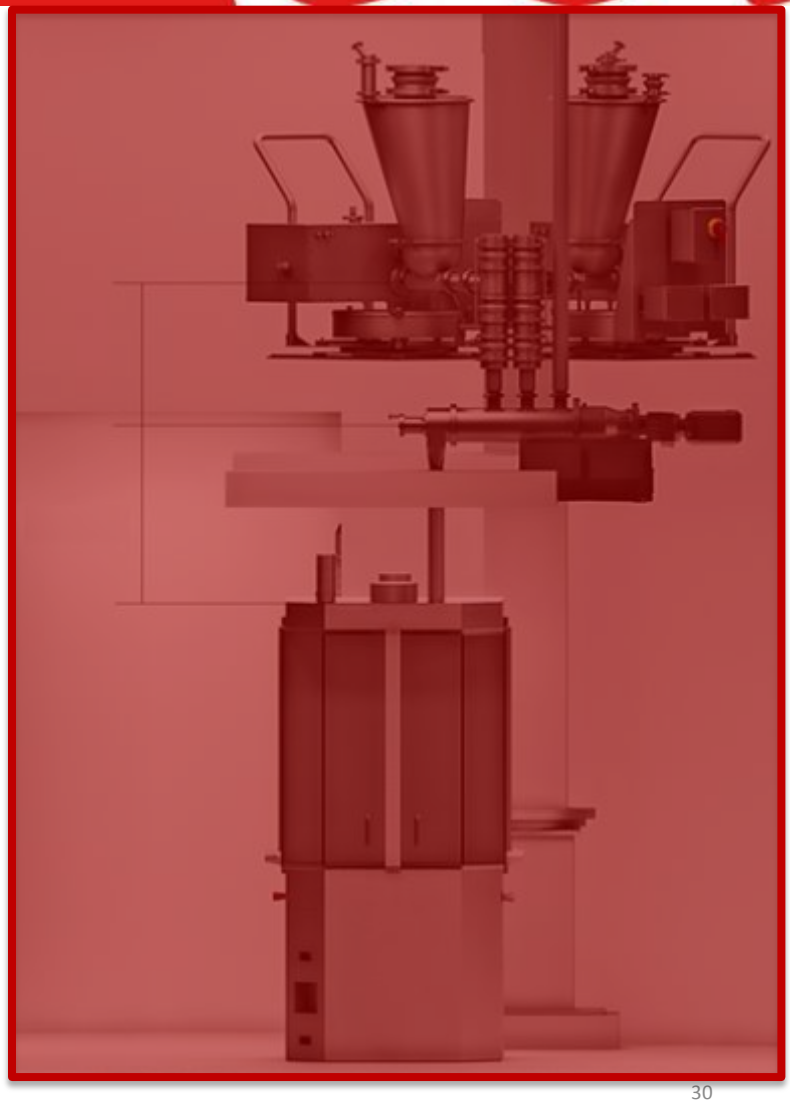


Example – Reduced System Model – LY2, Tablet strength 1



Operating Control Strategy – RTD Based Reduced System Model

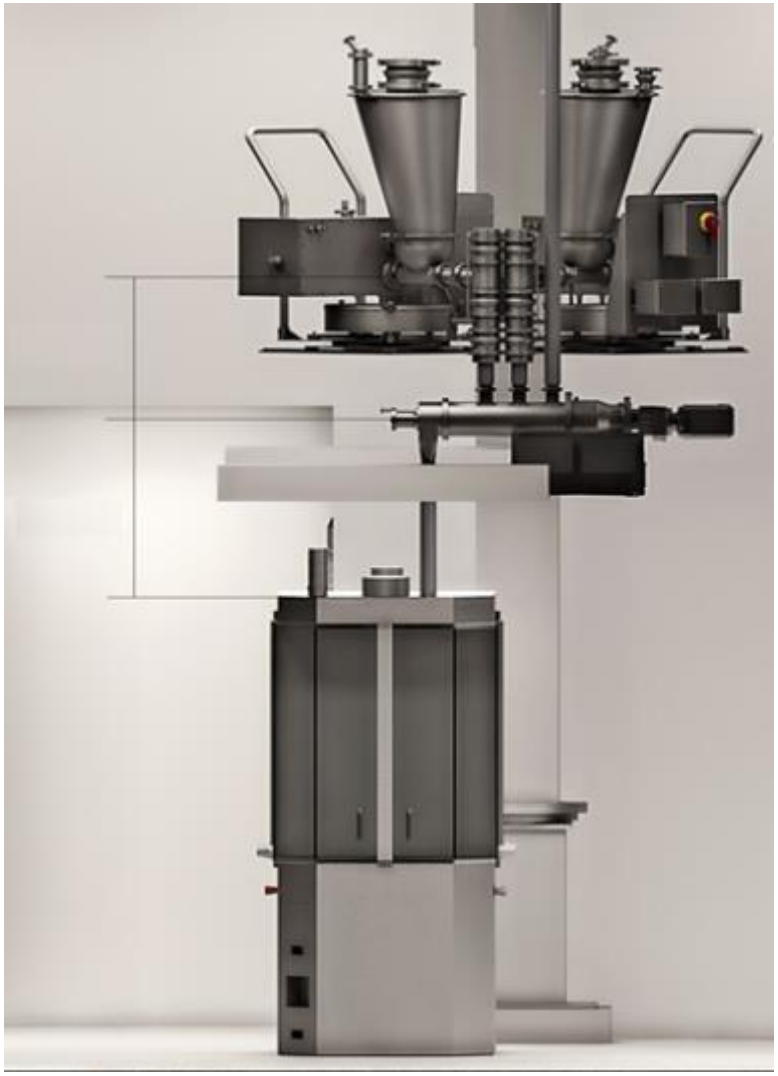
Data Source	Feed Forward Process Control
Reduced System Model	Tablet collection/rejection based on calculated concentration in tablet press feed frame



Are High Frequency Measurement Tools Downstream of the Feeders Needed?

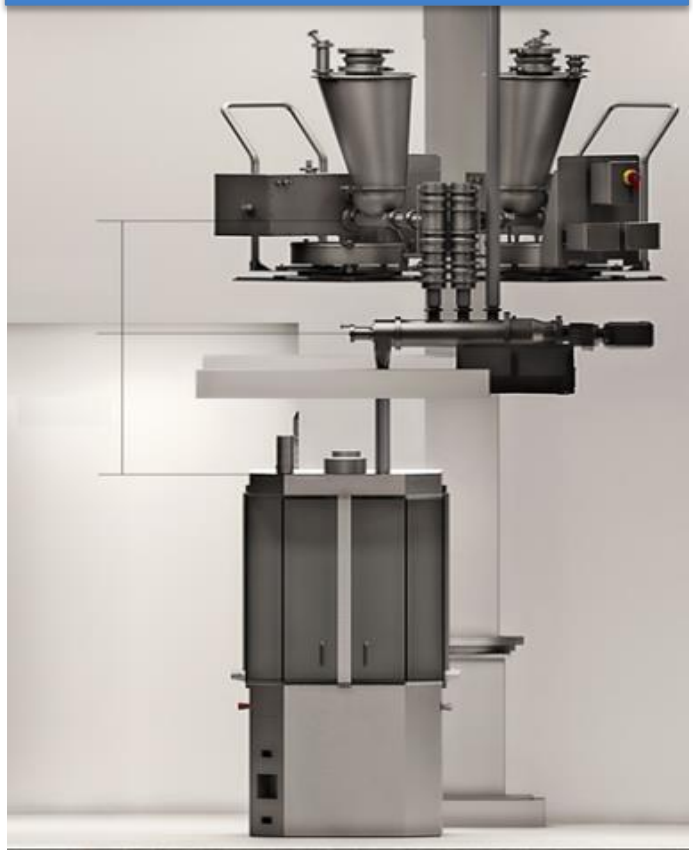
- Based on Lilly's experience in CDC (2013-2016, multiple formulations, sites, campaigns), with our optimized simple design, the majority of special cause/transient disturbances are related to LIW feeders. Managed by:
  - Feeder controls and
  - RTD Based Reduced System Model.

- The need for other tools downstream of feeders are risk based on a project by project basis. The need for those tools downstream of the feeders are related to inconsistent material flow, which was designed out of the optimized equipment configuration.



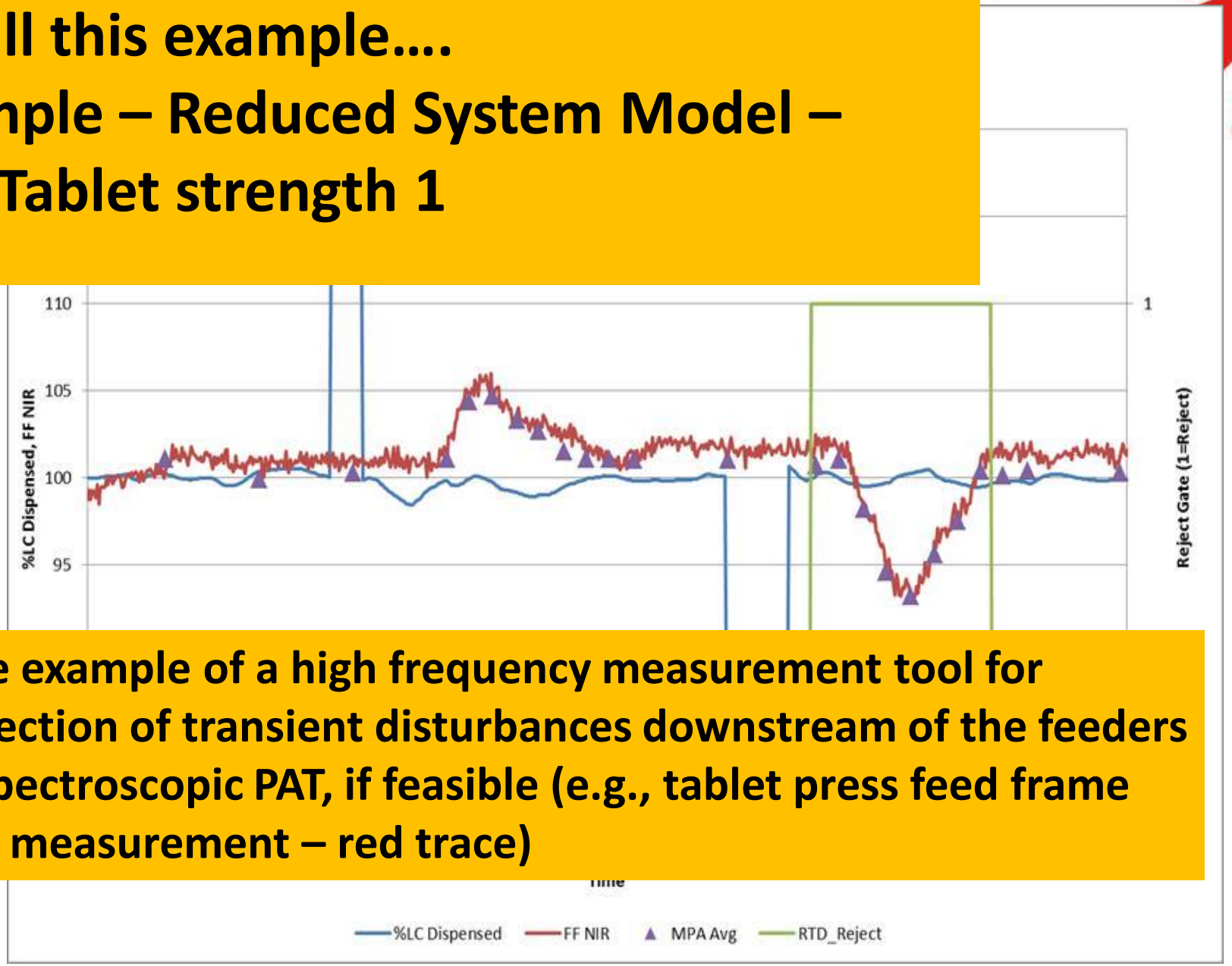
Operating Control Strategy – Transient Disturbances

Robust, simple equipment design (minimize occurrence and magnitude of transient disturbances)



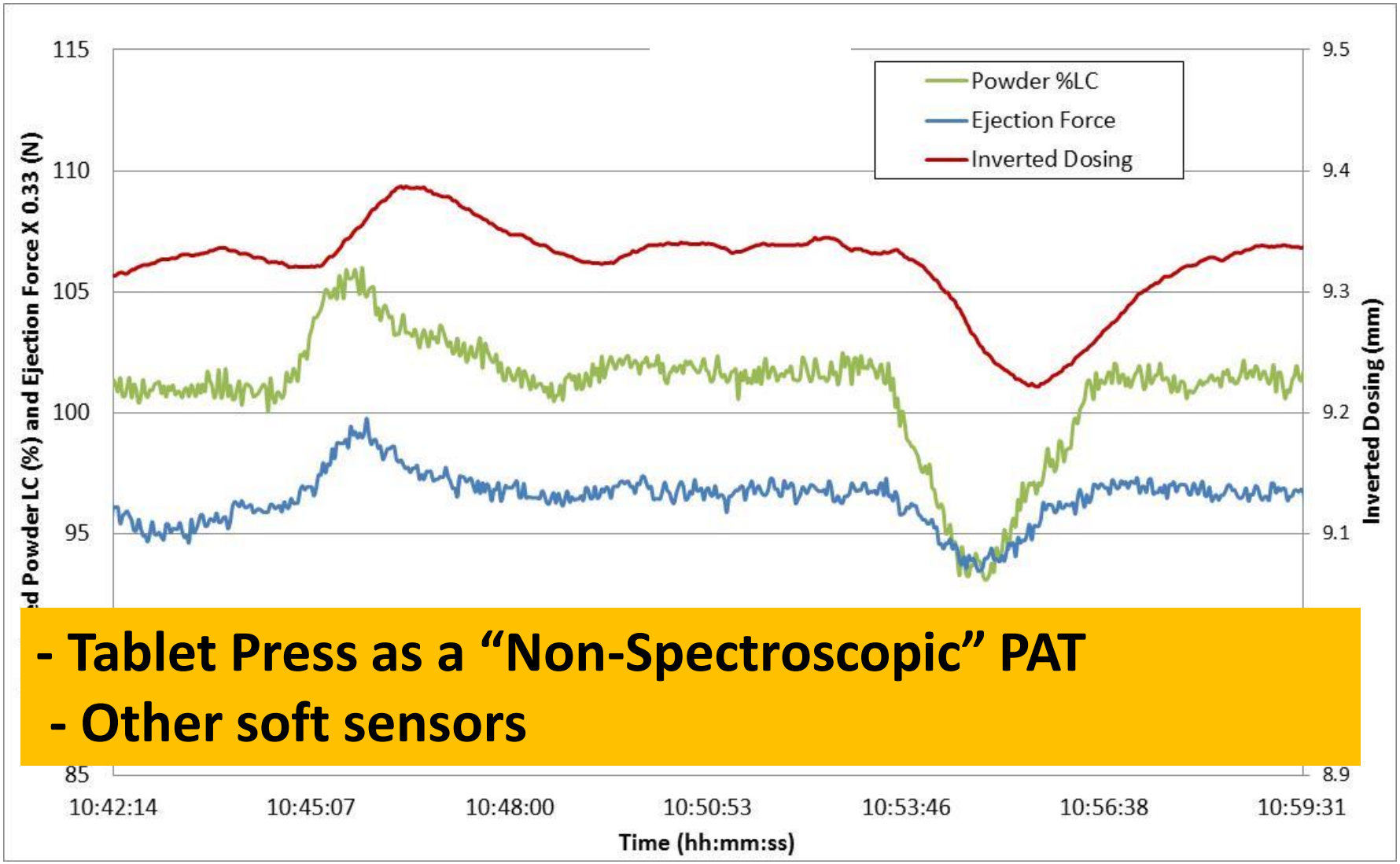
Feeder Control	**Feedback Process Control**	
	Individual Feeder Control + Feeders Ratio Mode Control	
RTD Reduced System Model	**Feed Forward Process Control**	
	Tablet collection/rejection based calculated conc in tablet press feed frame	
Tablet press control loops	**Feedback Process Control**	**Feed Forward Process Control**
	Tablet weight Force Control Loop + Weight Control Loop	Tablet collection/rejection based on tablet main compression force
If project specific risks require additional layers (on top of above layers)	**Data Source**	**Feed Forward Process Control Option (if needed)**
	Feed frame powder NIR (if feasible) and/or Tablet press diagnostics (or other soft sensors)	Process monitoring option If needed, may be used for tablet collection/rejection

Recall this example….
Example – Reduced System Model – LY2, Tablet strength 1



One example of a high frequency measurement tool for detection of transient disturbances downstream of the feeders is spectroscopic PAT, if feasible (e.g., tablet press feed frame NIR measurement – red trace)

How About Other High Frequency Measurement Tools?



- Tablet Press as a "Non-Spectroscopic" PAT
- Other soft sensors

Improved Process and Quality Control

Integrated, Multi-layer Approach of Control – Greater Assurance of Quality

Final product testing is the last layer

Acknowledgements

- Ian Leavesley
- Sal Garcia
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- Evan Hetrick
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- Trent Sommer
- Ron Ruff