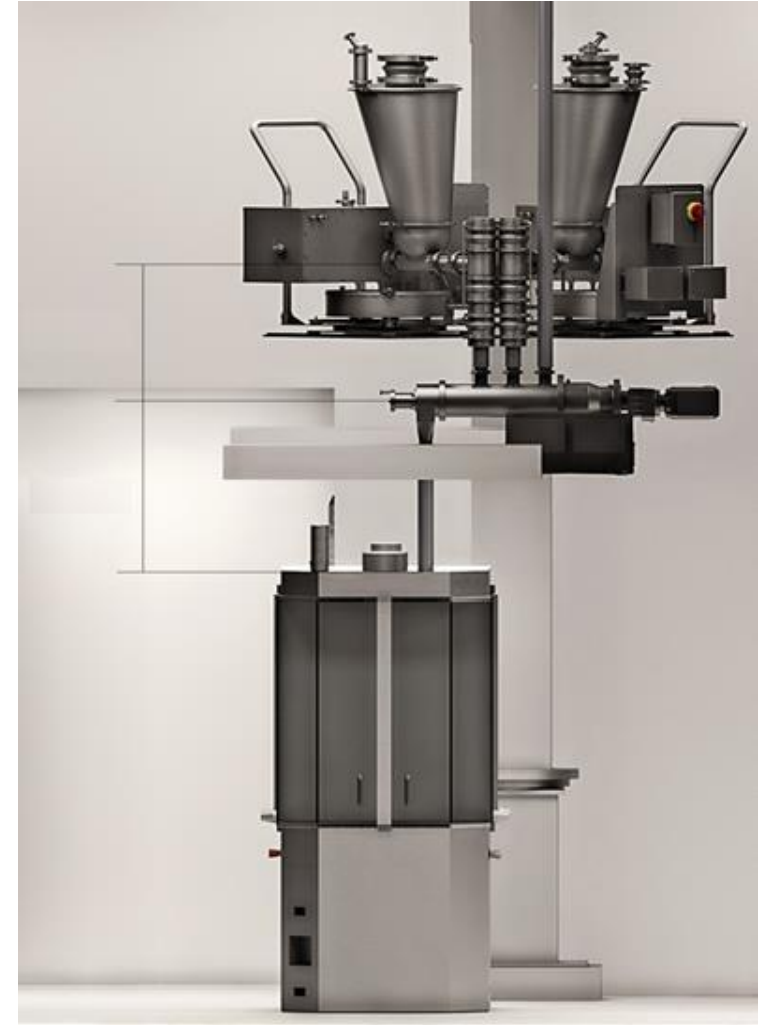


# An Industry Perspective for Transitioning CM from Technology Evaluation to a Default Manufacturing Platform

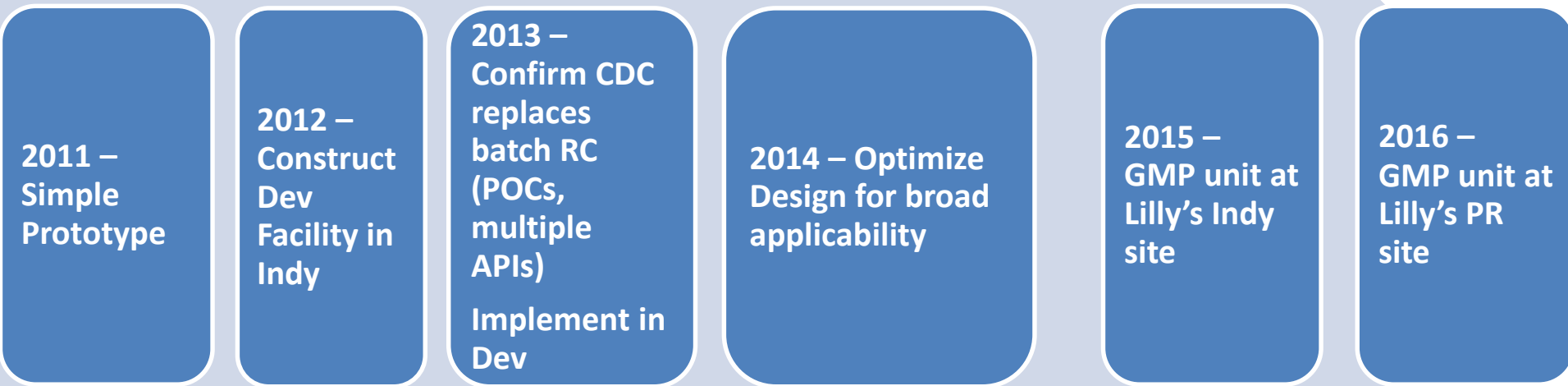
*Wyatt Roth  
Lilly Research Laboratories  
Eli Lilly and Company  
Indianapolis, IN*

# Continuous Manufacturing Overview

- Constant material flow in and out of the process.
- Continuous manufacturing already well established in other industries:
  - Petrochemical, food, polymer industries
- Multiple pharmaceutical companies are moving to Continuous DP manufacturing
- Lilly has advanced continuous API and continuous drug product capabilities into manufacturing.
  - Higher assurance of quality
  - Higher supply chain agility
  - Increased manufacturing and development efficiency
  - Reduced technical transfer risk
  - Development timeline and cost savings



# Lilly's Journey with DP CM



# Platform Robustness

- Lilly's DP CM unit has been optimized for broad applications and has demonstrated broad capability / robustness.

Parameter	Lowest successfully manufactured	Highest successfully manufactured
DS bulk density (g/mL)	0.18	0.77
DS flow properties (FFC)	1.3	11
Particle size ( $d^{10}/d^{90}$ $\mu\text{m}$ )	2 / 19	23 / 167
Drug load (wt. %)	1%	40%

# Lilly's Journey with DP CM

Implementation on  
Lilly's portfolio

2011 –  
Simple  
Prototype

2012 –  
Construct  
Dev  
Facility in  
Indy

2013 –  
Confirm CDC  
replaces  
batch RC  
(POCs,  
multiple  
APIs)  
Implement in  
Dev

2014 – Optimize  
Design for broad  
applicability

2015 –  
GMP unit at  
Lilly's Indy  
site

2016 –  
GMP unit at  
Lilly's PR  
site

# Identical Equipment, PAT and Automation



  
**FOYA** | 2017  
Facility of the Year Awards  
CATEGORY WINNER  
Process Innovation

  
**FOYA** | 2017  
Facility of the Year Awards  
CATEGORY WINNER  
Facility of the Future



CM1

CM2

CM3



# Lilly's Current Strategy

- Accelerate NCE development / launch using CM
- Focus on direct compression and maximizing capability of that platform
- CDC is currently the default manufacturing platform for OSD
- >10 molecules processed through CM direct compression
- GMP experience with CDC since 2015
  - >20 GMP lots manufactured
- 3 sites with replicated equipment train / automation
- Multiple molecules in clinical development supported by CDC

# How about product quality?

Does CM really enhance product quality?

- Batch manufacturing processes are robust and provide high quality products.
- However, CM can provide a higher assurance of quality.



# Process Monitoring Tools: CM vs Batch Processes



- Relative to batch processing, CM offers multiple independent, high frequency data streams that can be collected, calculated or modeled while the process is running.
- Depending on the process and product specific risks, these high frequency data streams can be used as tools for monitoring or control of CM processes.

# Process Monitoring Tools

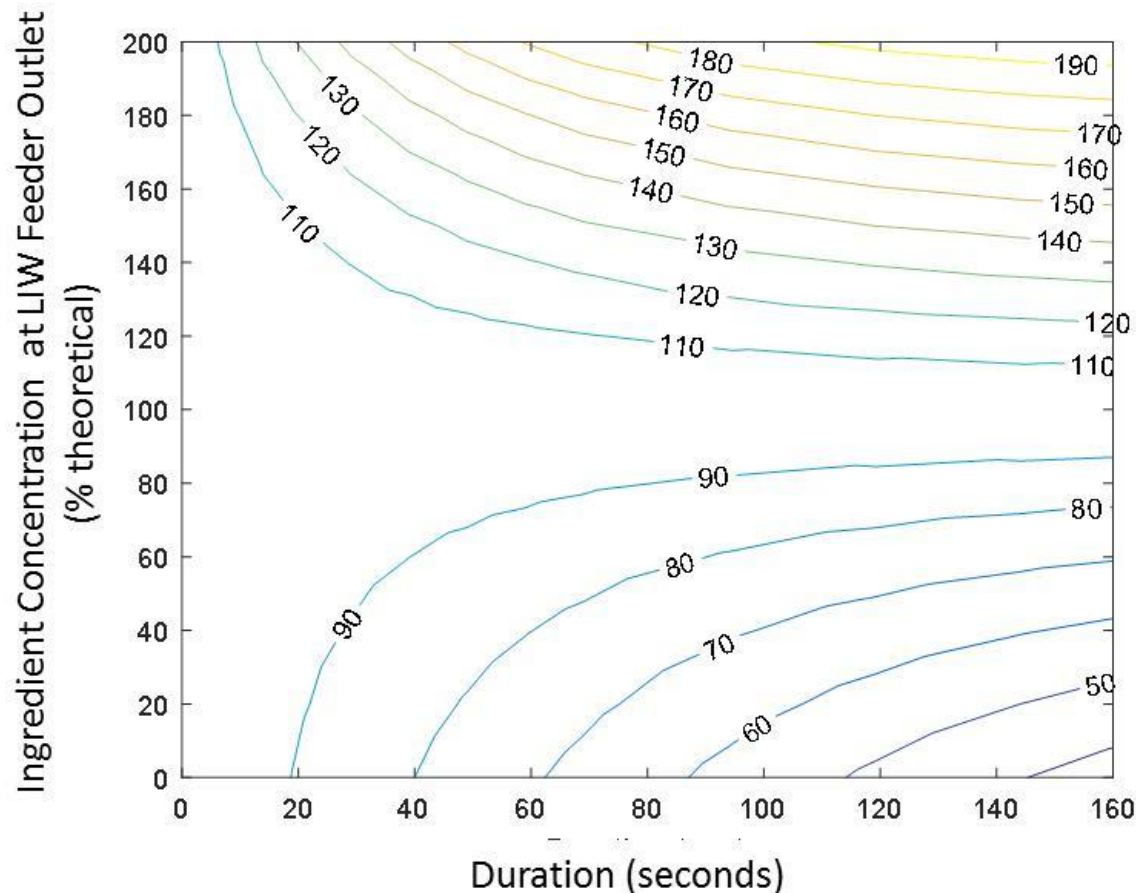
## Robust Equipment/Process Design

(minimize occurrence/magnitude of disturbances)



- The goal for process monitoring is to **confirm** uniform product quality throughout the batch and react to process disturbances if/when they occur.
- Each unit operation is monitored throughout a batch
- Include elements and appropriate responses to address:
  - Common cause variation
  - Drifts
  - Potential special cause variation

# RTD Understanding - Funnel Plots



Simulations using flow sheet model generated “funnel plots”

Contour lines represent predicted ingredient concentration (% theoretical) in the tablet press feed frame based on magnitude and duration of feeder upsets.

Funnel plots can be created for all feeders (i.e., for each formulation ingredient).

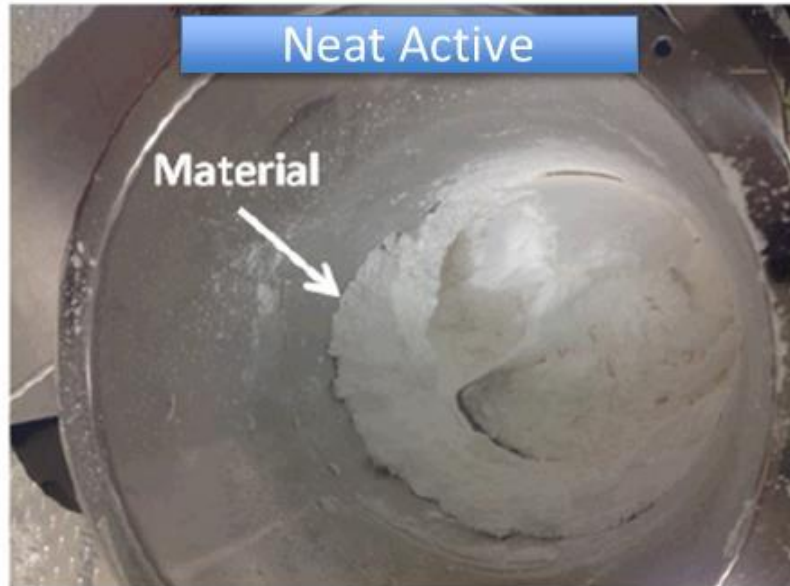
# Case Study I



- NCE molecule already formulated for a batch manufacturing process.
- Converted process to CDC for pivotal clinical supplies.
  - DS concentration at 6.25% w/w
- DS exhibits cohesive nature driven by its relatively high specific surface area ( $\sim 3.5 \text{ m}^2/\text{g}$ ) and small particle size.

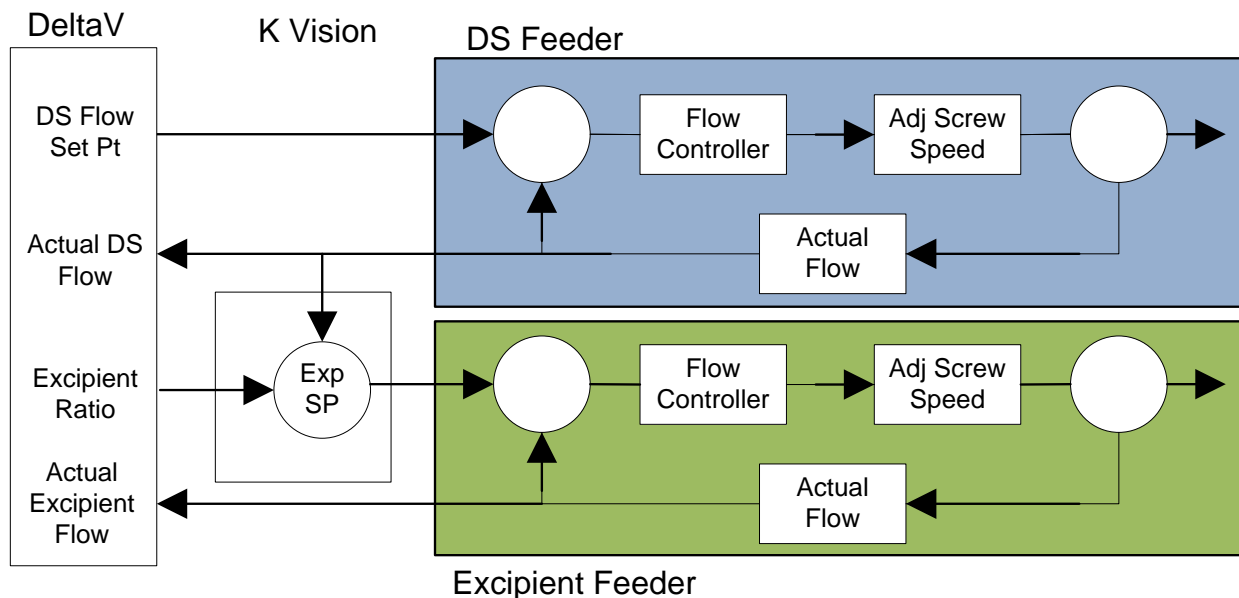
# Feedability

- Because of the poor flow properties and high surface area of the neat drug substance, it was pre-blended with other formulation ingredients to improve feed-ability through LIW feeders.

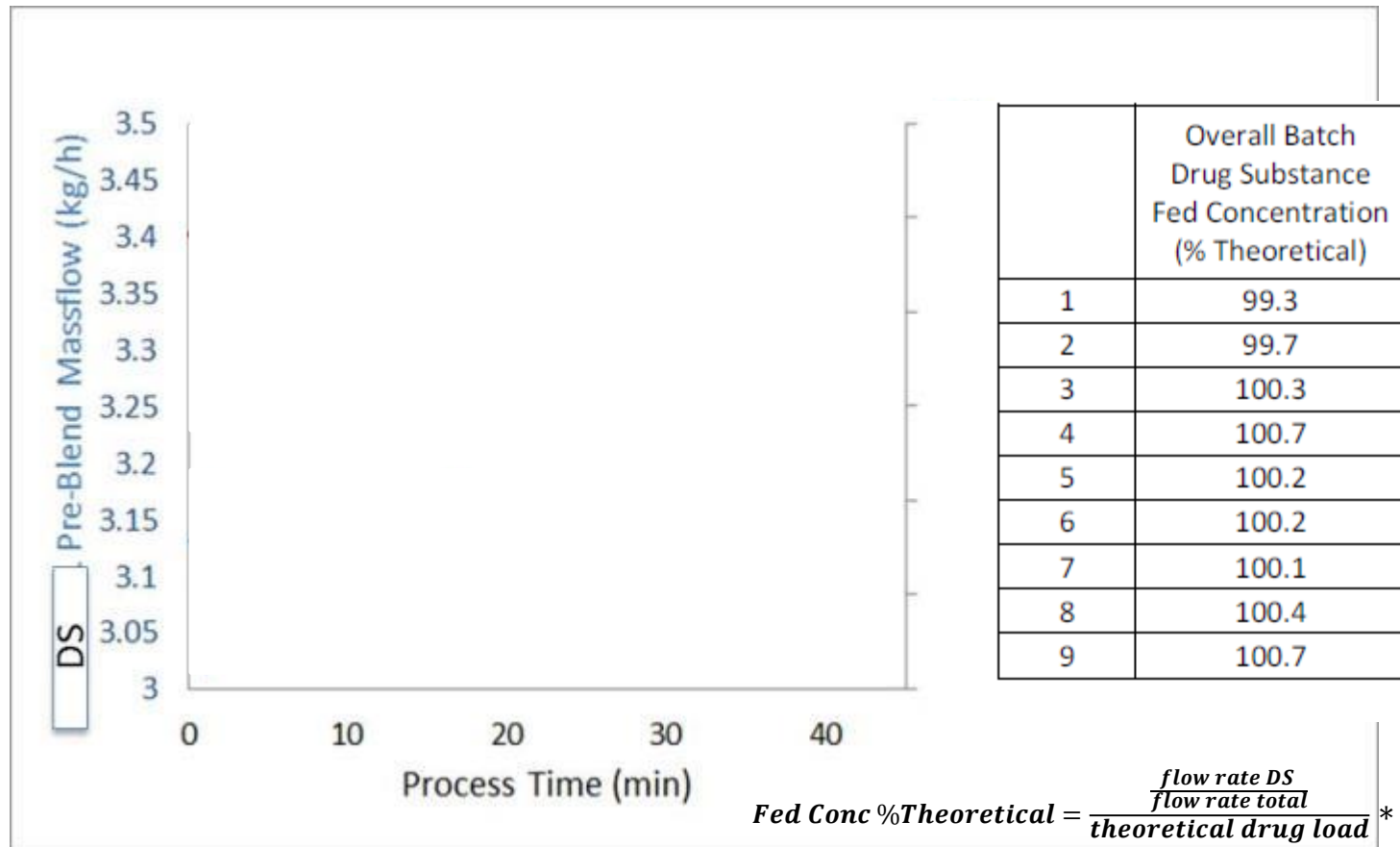


# Feeding Control

- Pre-blending improved feed-ability, but pre-blend still exhibited poor flow properties ( $FFC_{2000}$  1.3 and 2.3 for neat DS and pre-blend, respectively).
- Feeder Ratio Mode addresses this feeding risk
  - Cascade control loop that allows all feeders to work together to feed the unit formula



# Feeder Ratio Mode Effectiveness for Poorly Flowing DS



Feeder ratio mode addresses both common cause variation and deviation from target  
All feeders are driven in the same direction as the DS feeder variation  
Ratio mode is in addition to individual Feeder controls (Level 1 control)



# Mixer and Throughput DOE – Impact to CQAs

Journal of Pharmaceutical Sciences 106 (2017) 1339–1346



ELSEVIER

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: [www.jpharmsci.org](http://www.jpharmsci.org)



Pharmaceutics, Drug Delivery and Pharmaceutical Technology

## A Demonstration of Mixing Robustness in a Direct Compression Continuous Manufacturing Process



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### ARTICLE INFO

#### Article history:

Received 26 September 2016

Revised 2 January 2017

Accepted 10 January 2017

Available online 30 January 2017

#### Keywords:

mixing  
tableting  
compression  
processing

### ABSTRACT

The purpose of this work was to assess the impact of continuous mixing on tablet critical quality attributes (CQAs) manufactured using a continuous, direct compression process. A 9-run design of experiments (DoE) that bracketed the range of commercially relevant mixer speeds, mixer orientations, and mass flow rates was executed using a formulation containing a cohesive drug substance at relatively low drug load. Drug substance dispensed concentration using loss-in-weight feeders was within 1% of target for each experiment with 30-s mass flow relative standard deviation values of 3.5% or less. Higher mass flow rates resulted in first off tablets closer to target potency, a shorter tablet potency startup phase, and greater assurance of passing content uniformity testing. Dissolution profiles from the DoE runs that bracketed mixer shear conditions were similar, indicating mixing had minimal impact on drug substance release from the tablets. None of the DoE experiments had a significant impact on the dissolution CQA.

# Case Study II

- Formulated for CDC
- Multiple tablet strengths requiring different mass flow rates
- Well behaved DS and DP:
  - Very desirable DS physical properties:
    - DS FFC ~ 3.5 – 4.0
    - Minimal cohesion
  - Excellent final blend flowability and tablet weight control
    - FFC ~ 8 – 10, tablet weight RSD  $\leq$  1.5%
  - Excellent compact robustness
    - Friability  $\leq$  0.2%
- Experience at three different CM lines
  - CM1 development line in Indianapolis.
  - CM2 GMP line in Indianapolis.
  - CM3 GMP line in Puerto Rico.

# State of Control

- “A condition in which the set of controls consistently provides assurance of continued process performance and product quality”
- Defined multiple layers for assuring state of control
  - One of these layers is:
    - real time handling of disturbances

# Real-time handling of disturbances

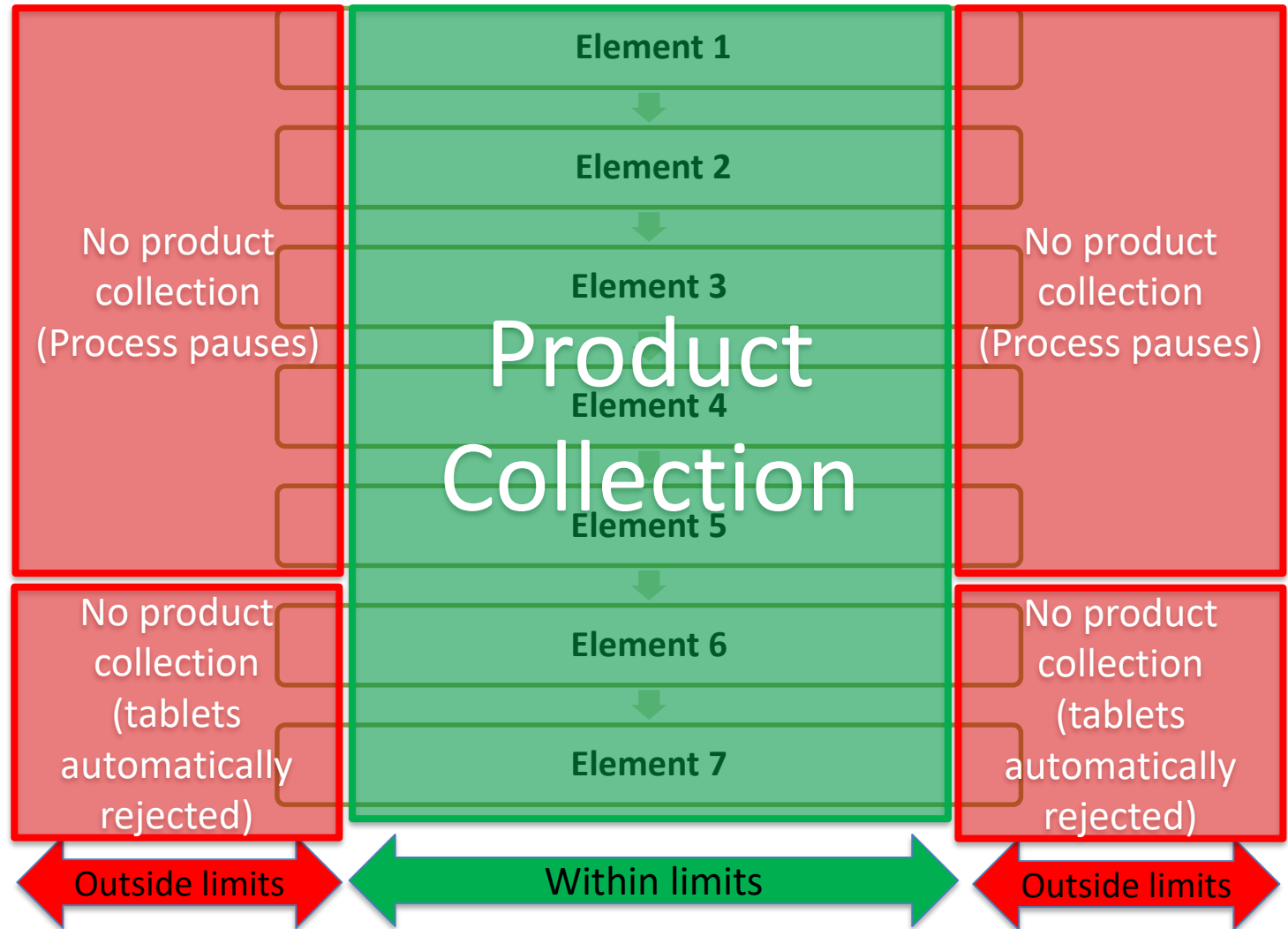
- *“... during normal operation, although the continuous process will typically maintain a state of control, there may be temporary process disturbances or upsets over the course of a production run. If the disturbance cannot be mitigated by the process, it is important to remove the impacted material.”*

Lee, S.L.; O'Connor, T.F.; Yang, X.; Cruz, C.N.; Chatterjee, S.; Madurawe, R.D.; Moore, C.M.V.; Yu, L.X.; Woodcock, J. “Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production,” *J. Pharm. Innov.*, **2015**, 191-199.

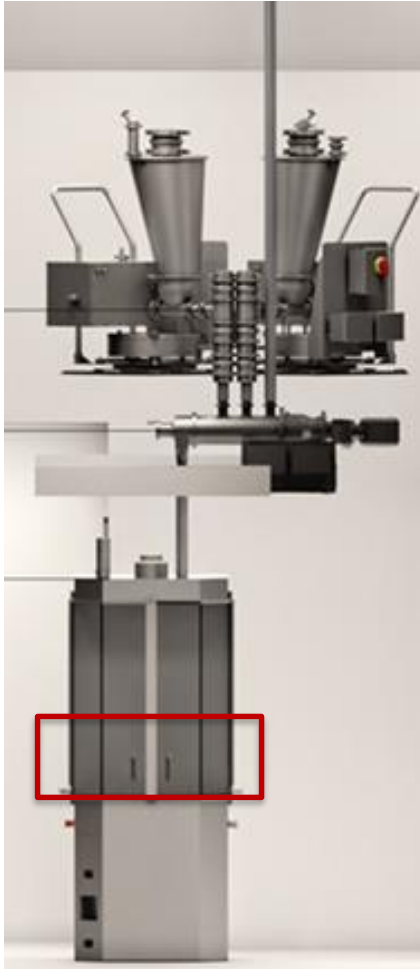
- Methods for real-time handling of disturbances are desirable even for highly capable processes (i.e., “guardrails” for special-cause events).

# State of Control - Real Time Handling of Disturbances

The system is very capable (e.g., CpK for feeding  $\geq 2$ ). Nonetheless, these 7 elements are special cause variation detectors



# Feed Frame DS Concentration



- Drug substance concentration in the tablet press feed frame is one element of the product collection criteria.
- The final blend drug substance concentration in the tablet press feed frame will be within pre-defined limits.

# Feed Frame DS Concentration

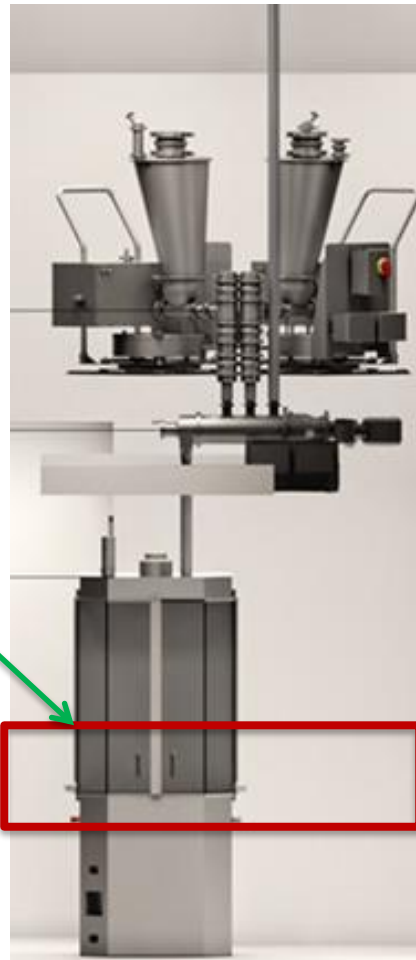
Measurement by NIR continuously throughout production

Measured just prior to compression

Protects against potential failure modes originating at or downstream of the feeders

Can be leveraged for RTRT

This is in addition to all upstream feeders' controls



- FF NIR measurement combined with process automation permits real-time handling of disturbances
- Automated product collection decisions (i.e., automatic tablet accept/reject) based on FF NIR measurement of DS concentration in tablet press feed frame



# Combined tablet weight and tablet concentration control



## **Tablet Weight**

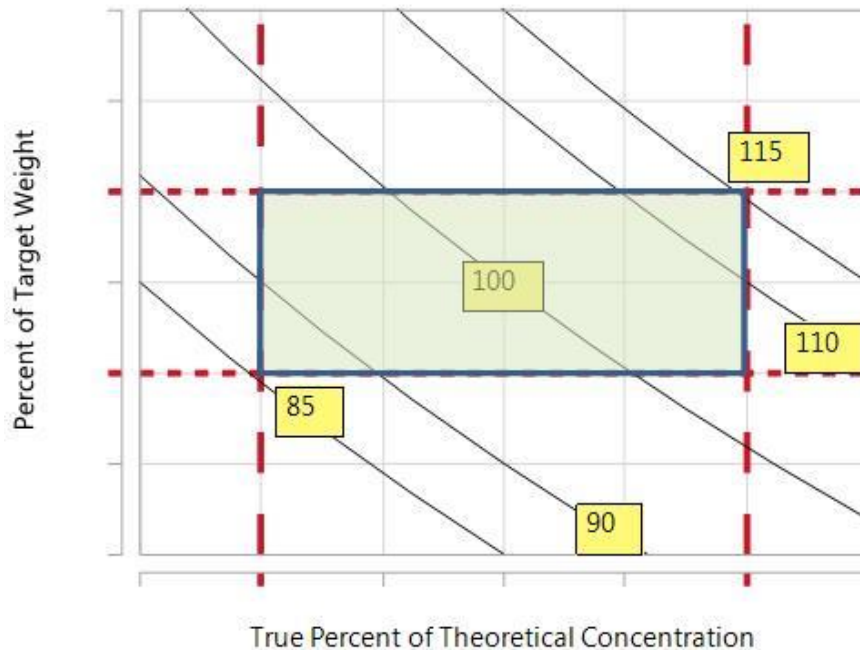
- Controlled to target via tablet press controls
  - Force Control Loop
  - Weight Control Loop
- Out of limits tablets automatically rejected by press via individual tablet reject system

## **Drug Substance Concentration**

- Controlled to target via feeder controls
  - Feeder local controls
  - Feeder ratio controls
- Out of limit concentration tablets automatically rejected by press -FF NIR logic

This is relevant to multiple CQAs  
Example for UDU on next slide

# Control achieved by combining FF NIR product collection with tablet press weight control

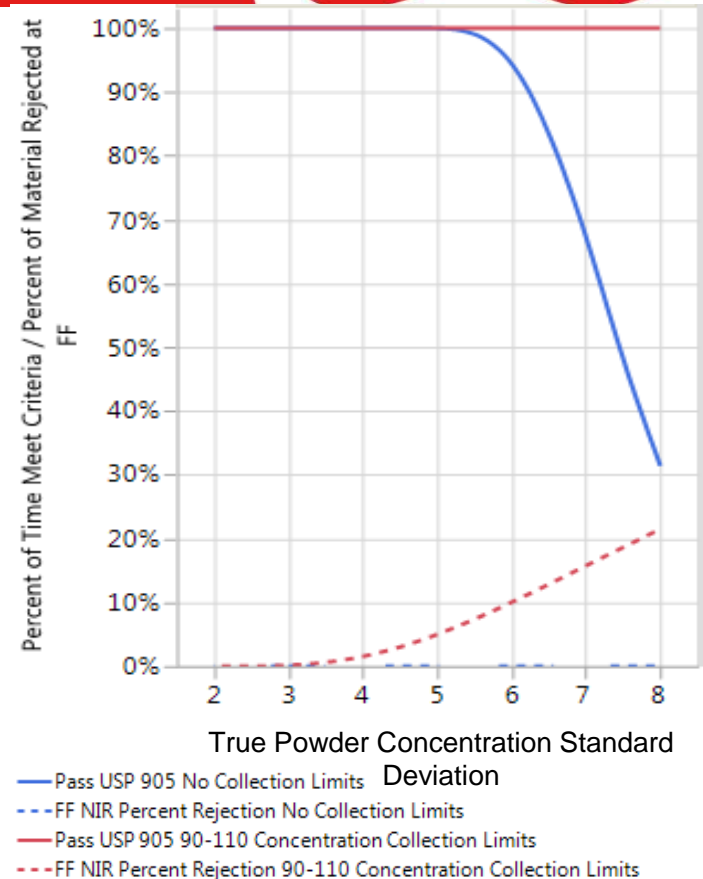


*% Label Claim is a function of DS concentration and tablet weight*

*Shaded box – tablets collected for forward processing*

*Outside of shaded box – tablets automatically rejected by press*

Appropriate limits on DS concentration by NIR (NIR tablet collection logic) and tablet weight (tablet press controls) ensure a high percentage of tablets remain within limits of label claim



Operating characteristic (OC) curves demonstrate that using in-process NIR for product collection control ensures content uniformity requirements will be met

# Conclusions from Case Study II

- Robustness of CDC has been demonstrated across multiple CM lines.
- Robust, simple equipment design is coupled with high process capability.
- Nonetheless, appropriate tools to detect and address potential special cause variation are also needed throughout the operation from feeding through compression.
- Robust FF NIR application successfully implemented for:
  - Process monitoring
  - One element of the automated product collection/rejection.
  - RTRT tool.

# Lessons from our experience in adopting CM



- Learn from others - consortia, academic collaborations
- Don't underestimate the power of internal data to convince doubters and win stakeholders
- Tailor the message to your internal audience – what's in it for them?
  - Manufacturing, Quality, Clinical organization, Development organization
- Development and Manufacturing organizations have to be on the same page
- Role of senior management – long term vision!
- Be open minded and try not to hinder innovation and creativity!
  - You will be amazed what your teams will come up with if you let them think and work outside the box
- Need multi disciplinary teams - incorporate different perspectives in building and optimizing the platform and the automation
- And don't forget to redefine your internal work plans – they will look way different (and faster) with CM!
- Inter-company networking and pre-competitive collaboration
  - IQ drug product continuous manufacturing working group
  - Other organizations – ISPE, AIChE etc.
  - 1:1 benchmarking with other companies

# Acknowledgements



- Ahmad Almaya
- Leo Manley
- Evan Hetrick
- Jeff Hofer
- David Mota
- Jason Melnick
- Matt Foster
- Beatrice Romeu
- Ivelisse Sanchez
- Sal Garcia
- Joshua Hanson
- Ian Leavesley
- Adam Butterbaugh
- Lukas Barnes
- Kirk VanDer Kamp
- Tim Kramer
- Zhenqi Shi
- Bryan Castle