SAMPLING AND CONTROL: APPROPRIATE CONTROL STRATEGIES FOR CONTINUOUS DIRECT COMPRESSION

Robert F. Meyer, Ph.D.

Emerging Pharmaceutical Manufacturing Summit OSD Continuous Manufacturing in the Current Regulatory Landscape – Malta – May 2017

Outline

- MSD's Approach to Continuous Manufacturing
- PAT Options: RTD Process Model and Blend NIR
- Process Model for Material Tracking and Rejection
- Sampling for Control and Release
- Benefits to Patients and Company
- Moving Towards Worldwide Acceptance of CM

MSD's Approach to CM for Oral Solid Doses

Why Continuous Manufacturing (CM)?

How we'll start

What we ask of regulators

What comes next

How We'll Use CM to Improve Supply Chains

One batch, every cycle, every strength

- Flexible batch size matched to customer demand
- Fast changeovers between products

High demand products

- Higher quality and efficiency due to elimination of start/stop

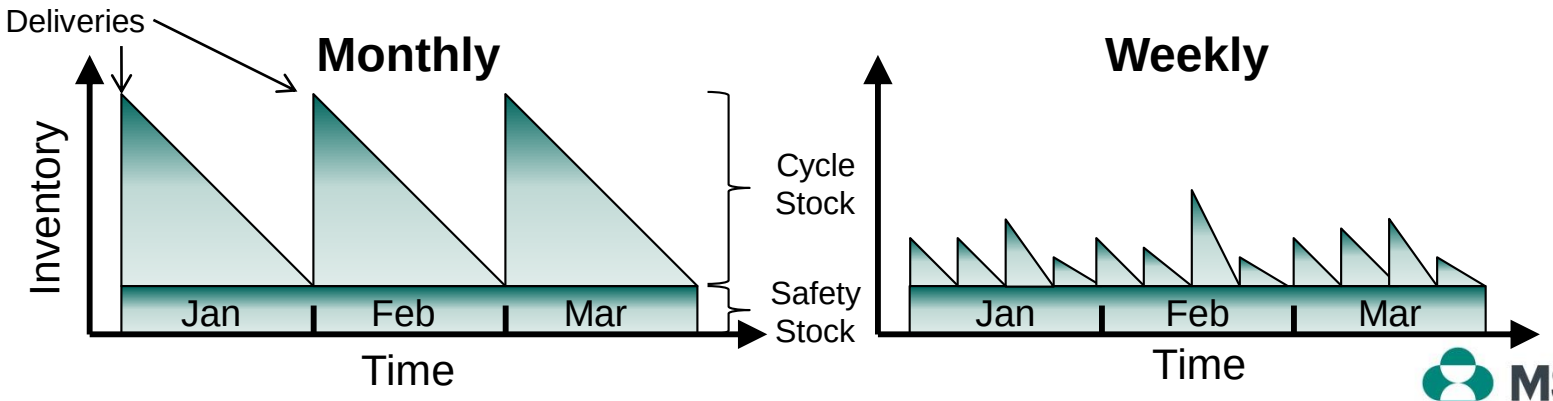
Low demand products

- Increases shelf life by eliminating overproduction and inventory hold

Volatile demand products

- Avoid shortages by reacting quickly to changes in demand

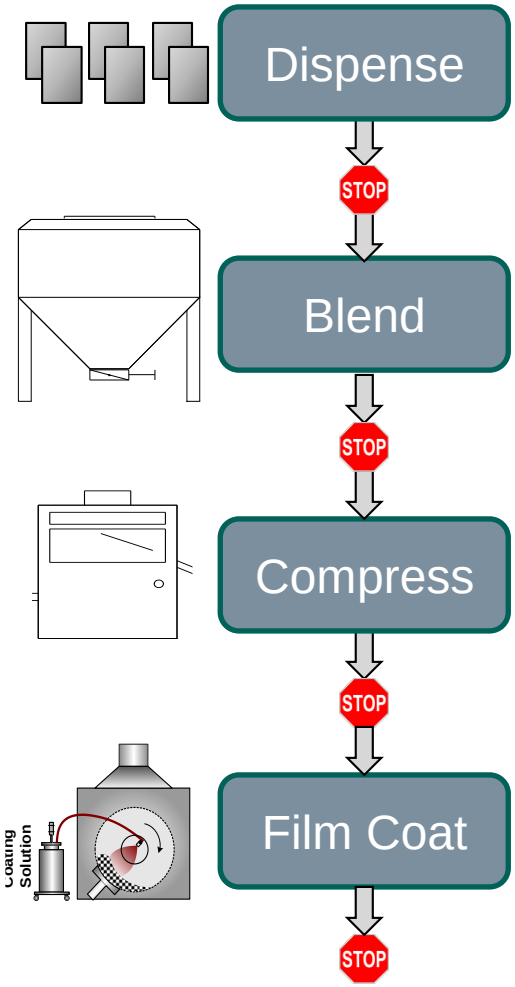
Monthly vs Weekly Inventory Levels



Existing Product & Process Description

Commercial Characteristics

- Available >10yr in most markets
- Multiple strengths
- High overall volume
- Volume dependent on strength



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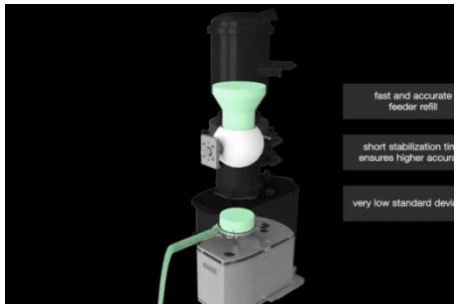
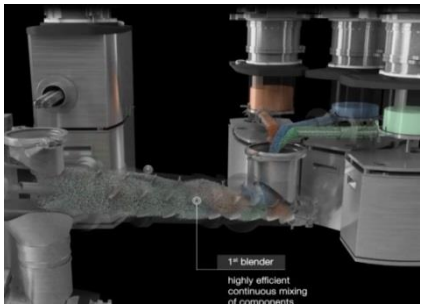
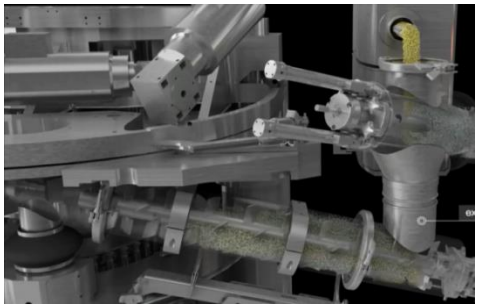
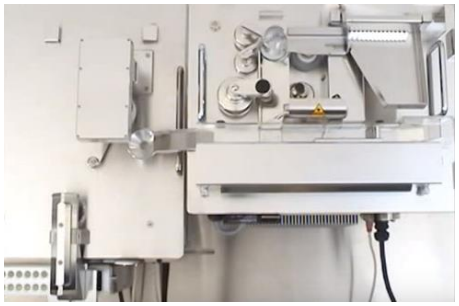
MSD's Continuous Manufacturing Process: GEA CDC-50, Consigma Coater, Bruker TANDEM



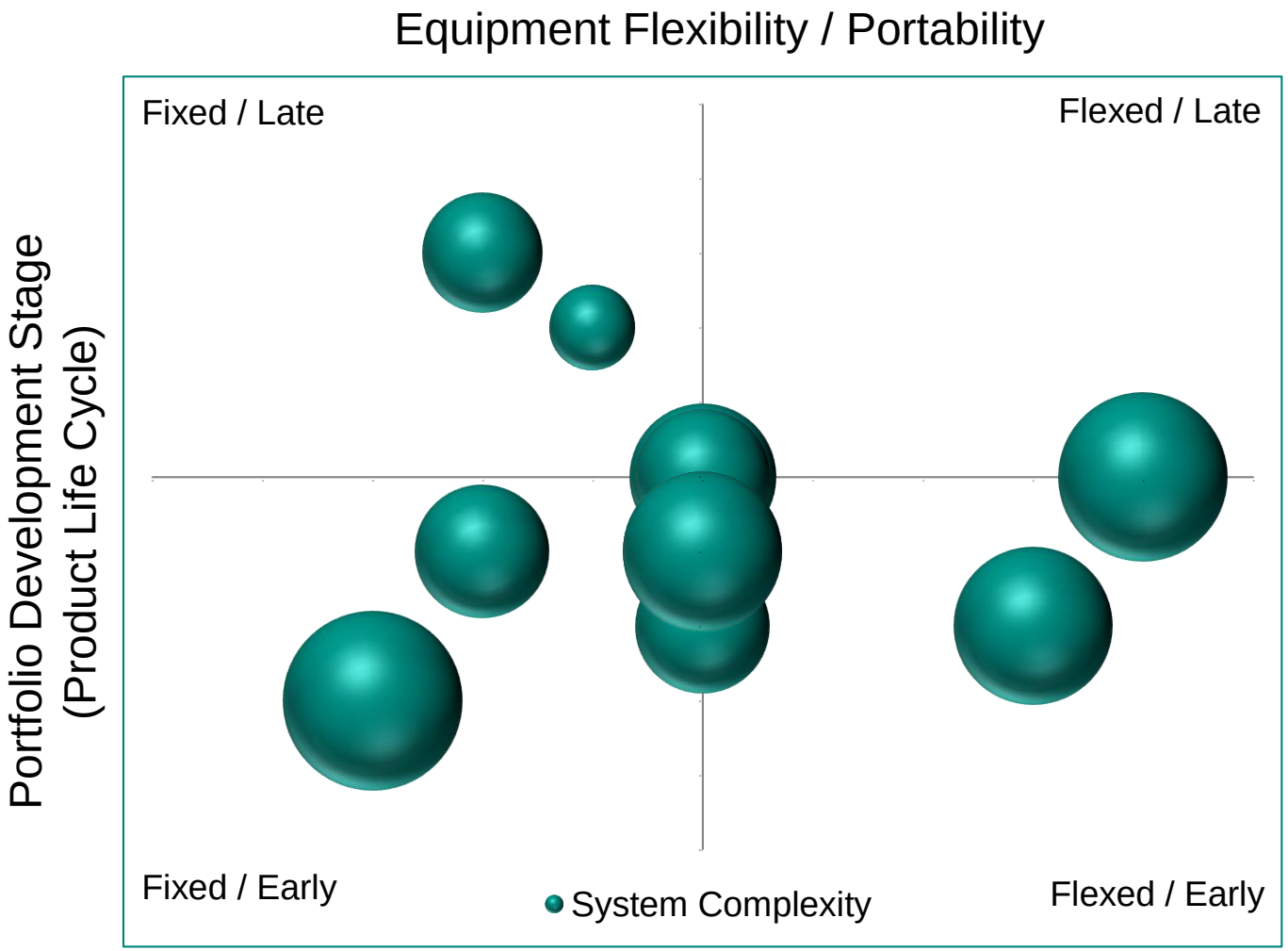






Mapping Different Approaches to CM

Janssen
Vertex
Pfizer
BMS
MSD
Roche
Bayer
AZ
GSK
Lilly
Novartis
Sanofi



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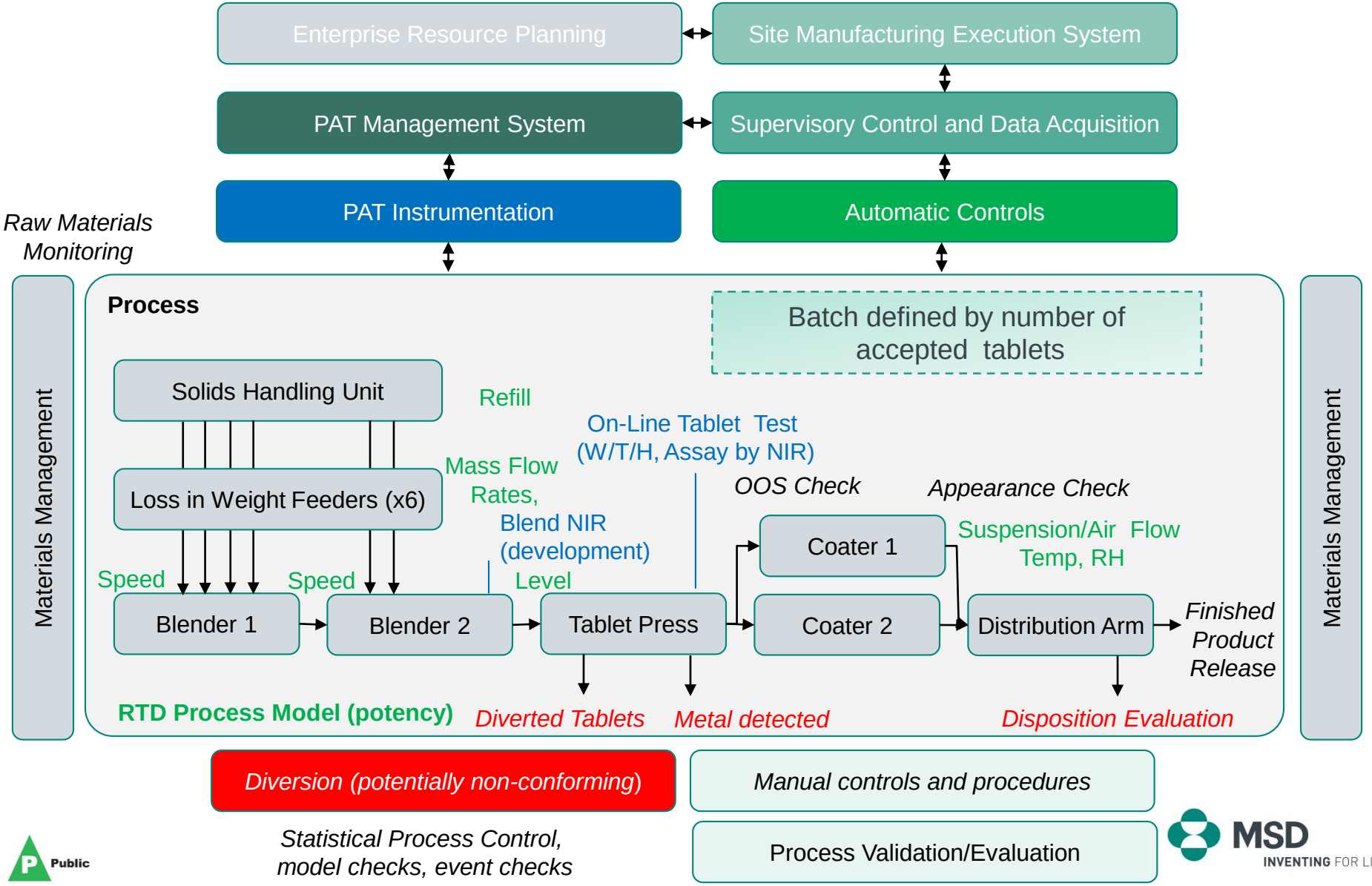
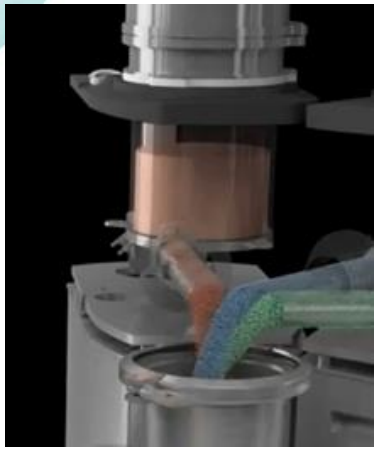
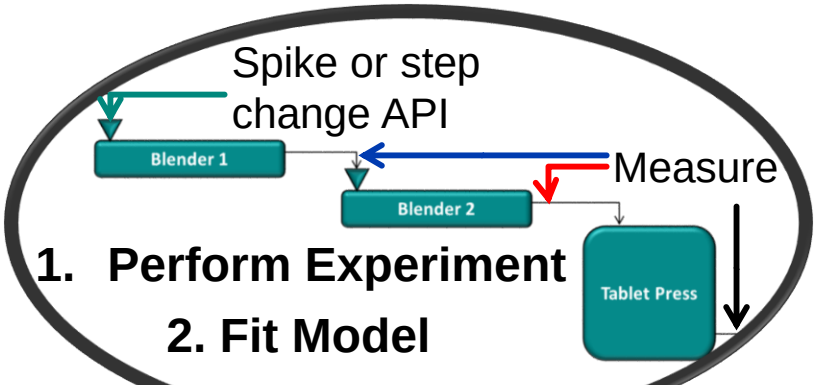
Comprehensive Control Strategy

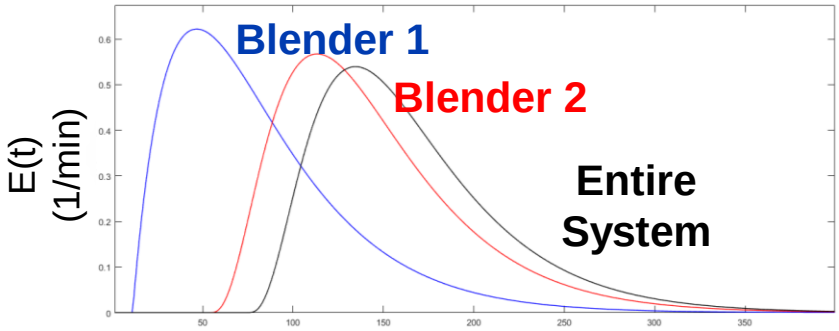


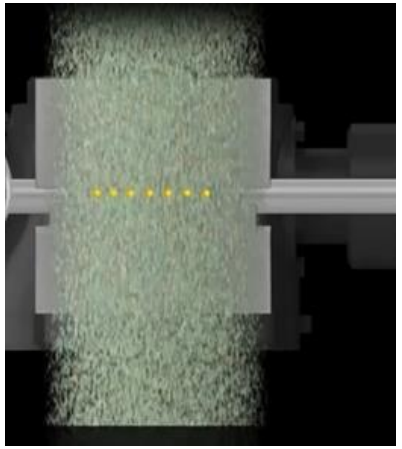
Background on RTD and NIR



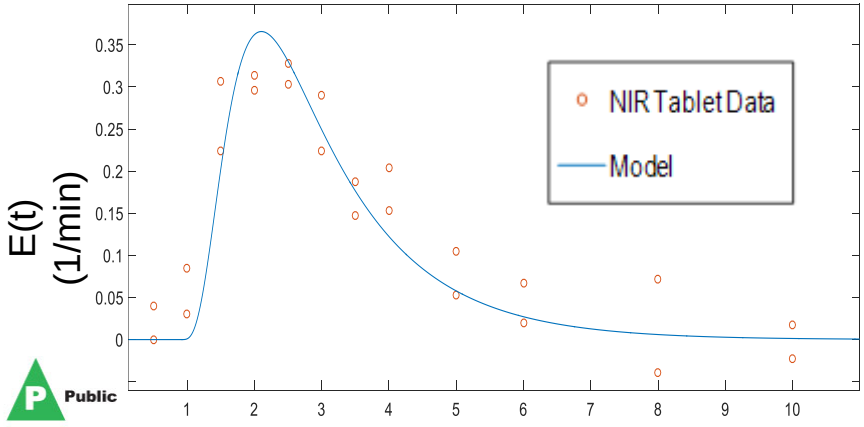


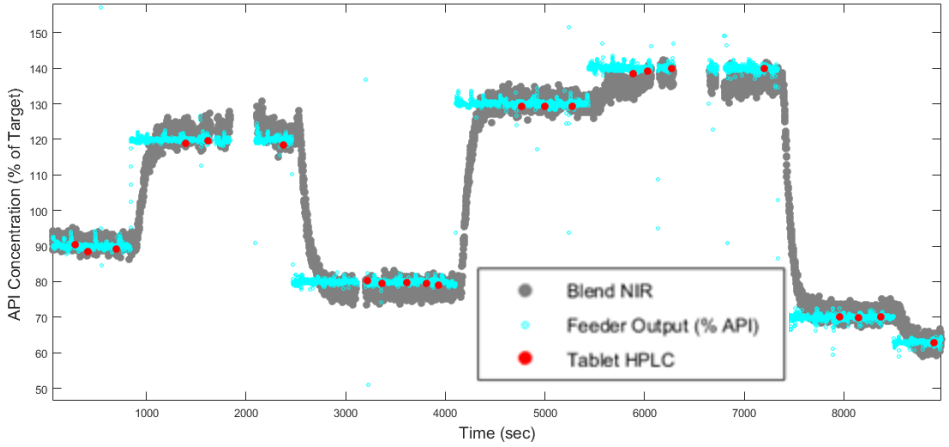
1. Perform Experiment
2. Fit Model



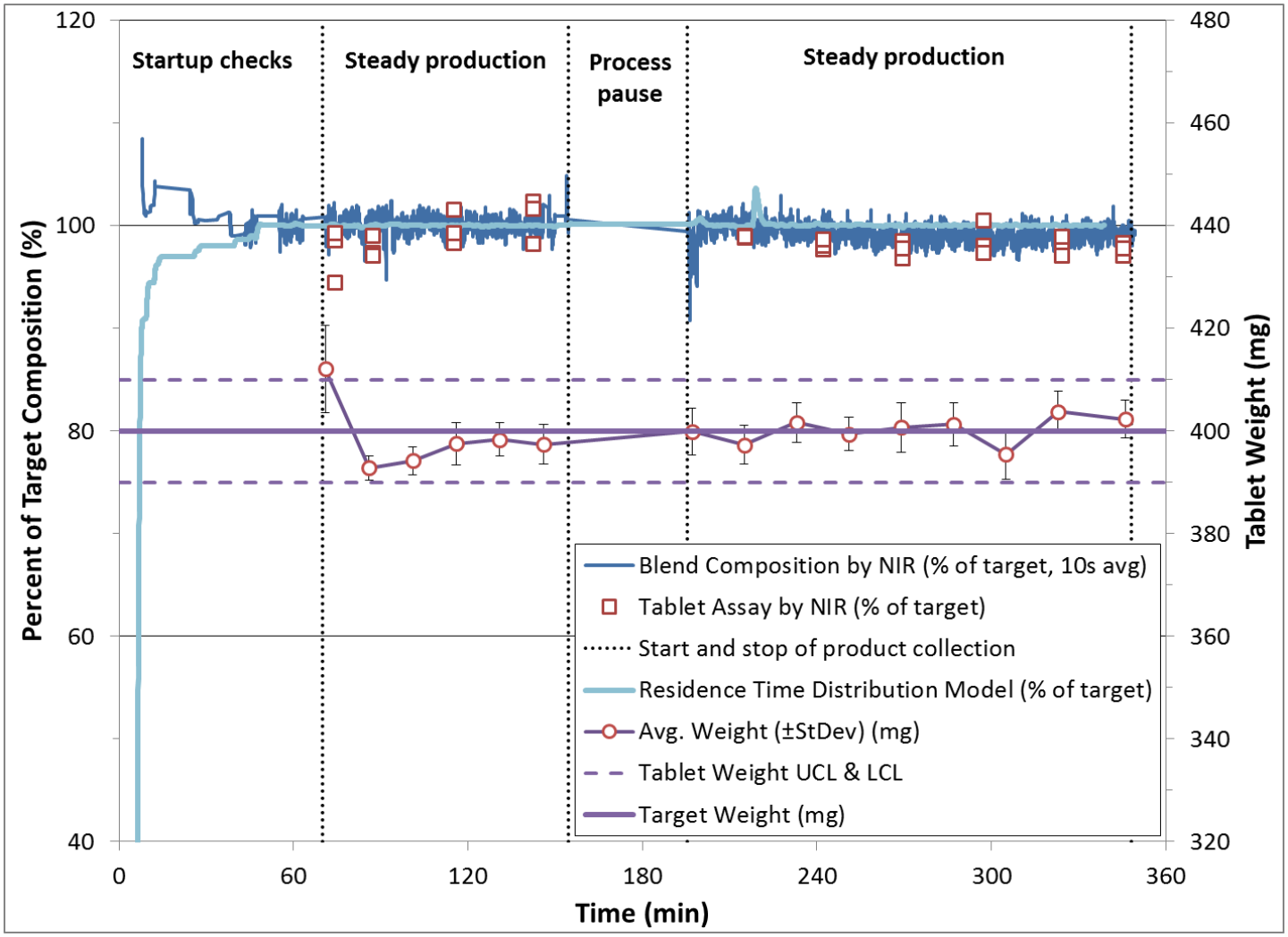


3. Check Model Predictions





Experiments Using Redundant PAT Demonstrate Low Risk If Single Method Used



"All things being equal, the simplest solution tends to be the best one."

William of Ockham

PAT Summary: Examining Operations & Robustness of RTD Model and Blend NIR

Factor	RTD Process Model	Blend NIR
Method Basis	**First principles** calculation	**Empirical** multivariate calibration
Scale of Scrutiny	**Average** prediction for >10 tablets	Sample size ≈ 1/4 tablet
Prediction Location	Predicts **blend and tablet API concentration**	Measures **API concentration in blend** at feed frame entrance
Model Robustness	Sensitive to **material properties and process parameters** that affect **flow or blending**	Sensitive to **physical properties** and **process parameters** that affect **sample presentation**
Blind Periods	Flow rate assumption during **~3 s feeder refill**	No measurement during ~2min **probe cleaning**
Signal to Noise Ratio	**High**	**Medium**
Fouling / Equipment	**Low risk** to feeder load cells	Dependent on **adhesion properties** of product
Model Maintenance Requirements	**Updates required** based on bulk density, flowability, or process parameter changes	**Updates required** based on probe, spectrometer, material property or process parameter changes
Universal Applicability	Can **predict** concentration of **any component** as needed	Applicable for components with **characteristic NIR bands** with sufficient specificity

RTD vs. NIR Deep Dive

Assumptions:

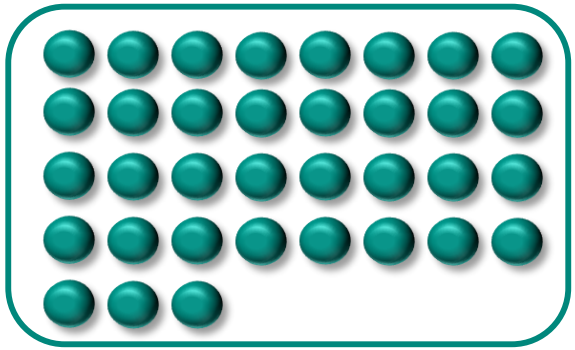
50 kg/hr throughput

400mg tablet

1 Hz RTD prediction

NIR: Seven 5mm rectangular windows

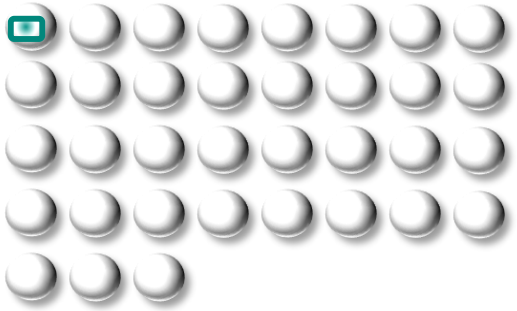
Sample Fraction per Second RTD vs. NIR



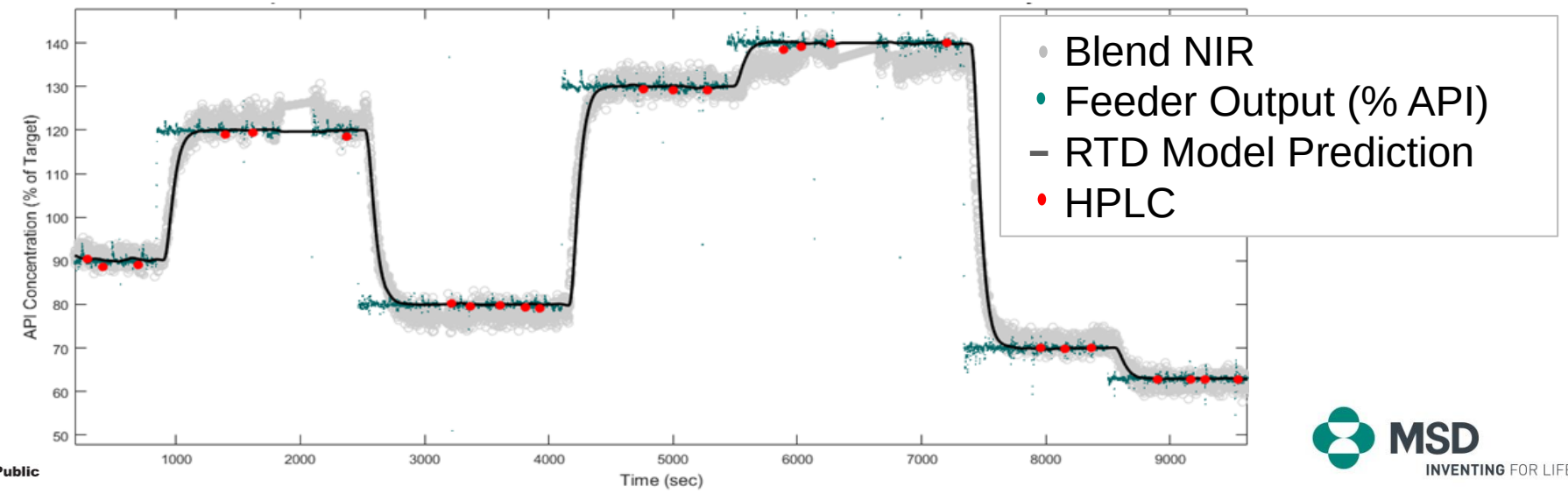
= measured tablet

= unmeasured tablet

= sample size

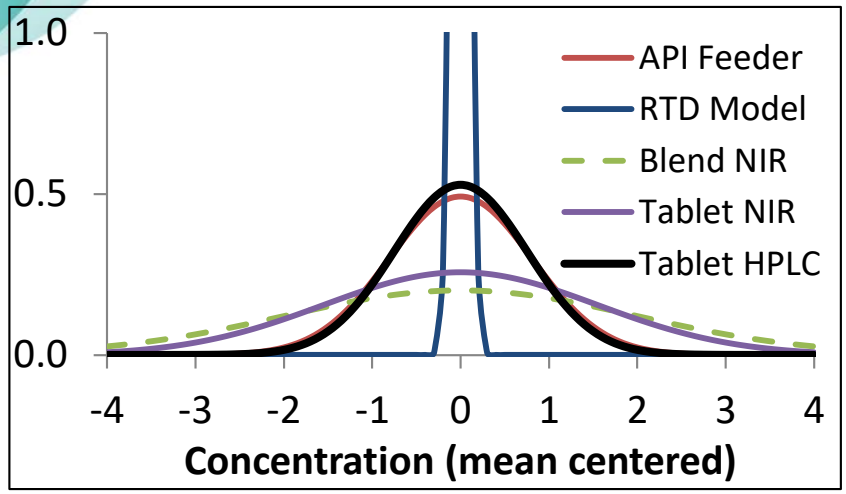


Signal to Noise Ratio Compared with HPLC Results



RTD vs. NIR Deep Dive

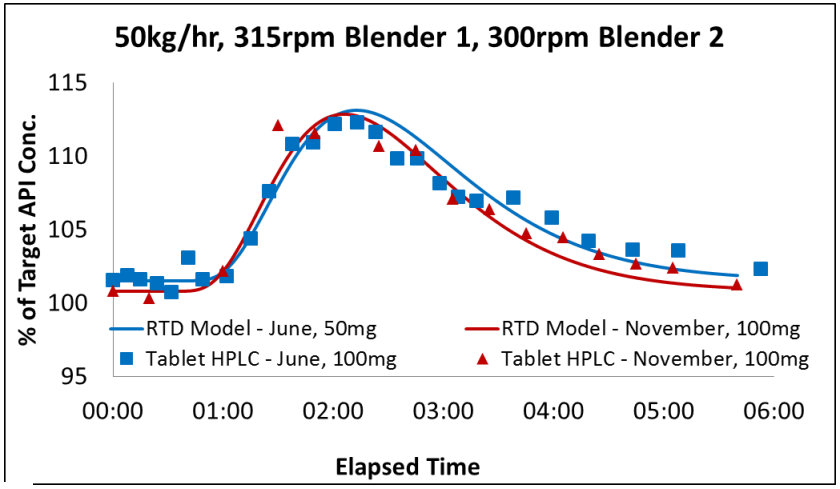
Model Accuracy vs. HPLC

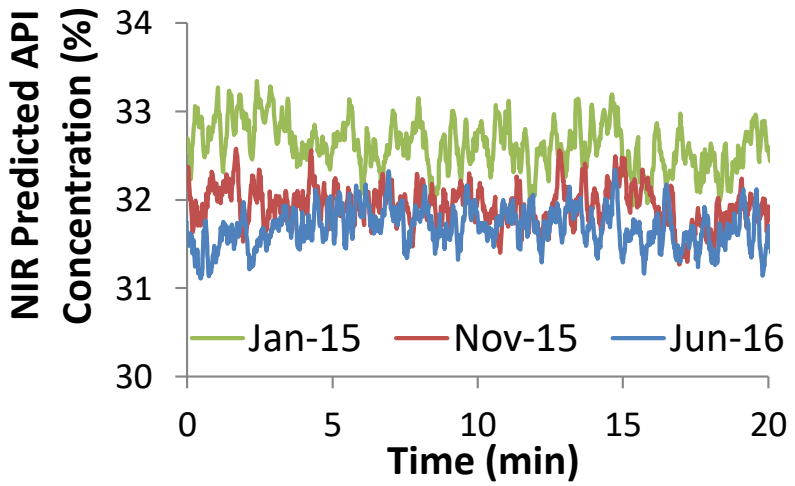


Method error ≈ 0.46

n = 30	St. Dev.
API Feeder	0.81
RTD Model	0.08
Blend NIR	1.98
Tablet NIR	1.55
Tablet HPLC	**0.76**

Model Maintenance

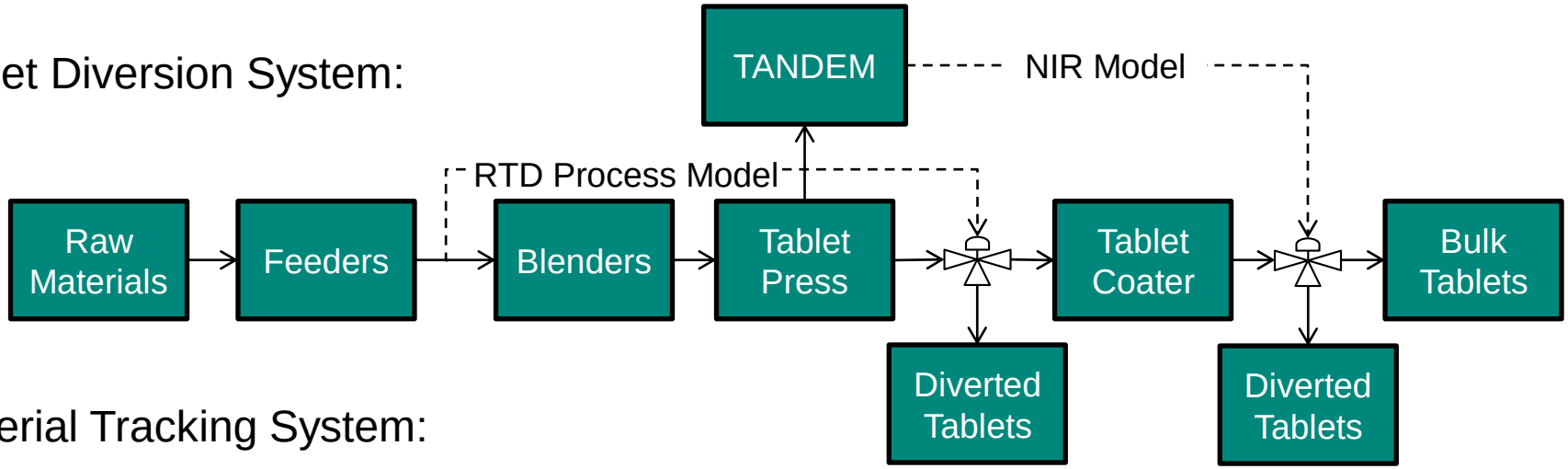




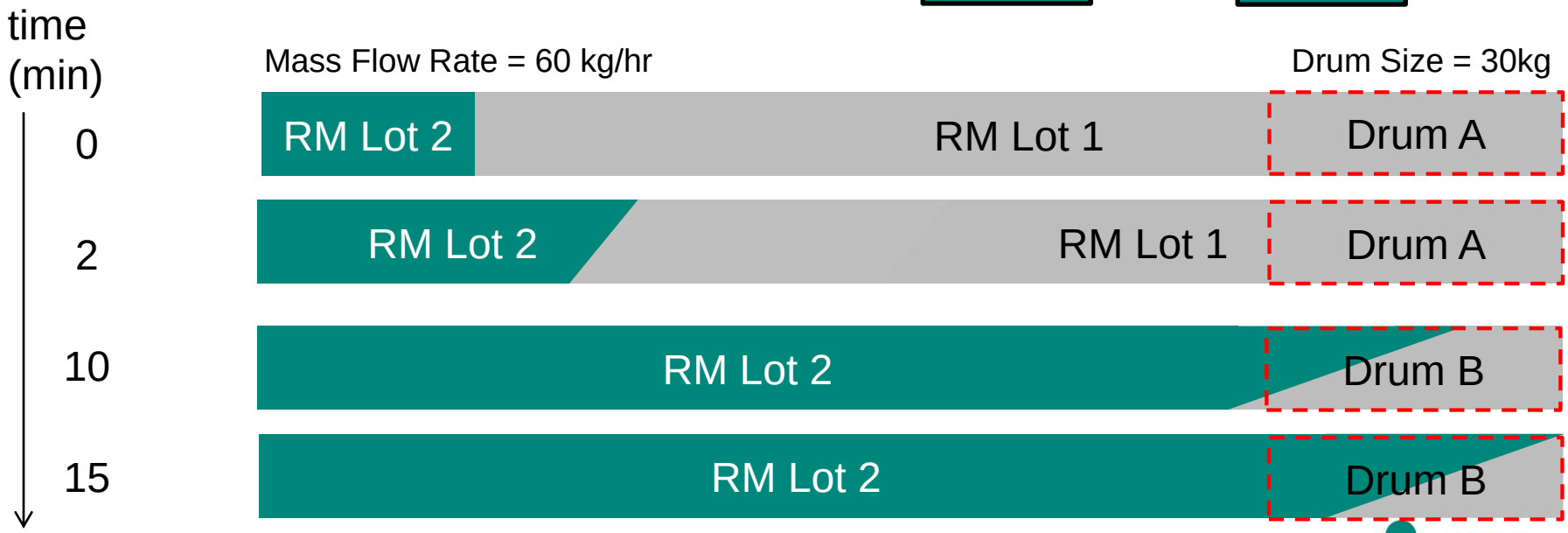
RTD Model for Raw Material (RM) Tracking

Model provides exquisite ability to track RM from start to end

Tablet Diversion System:



Material Tracking System:



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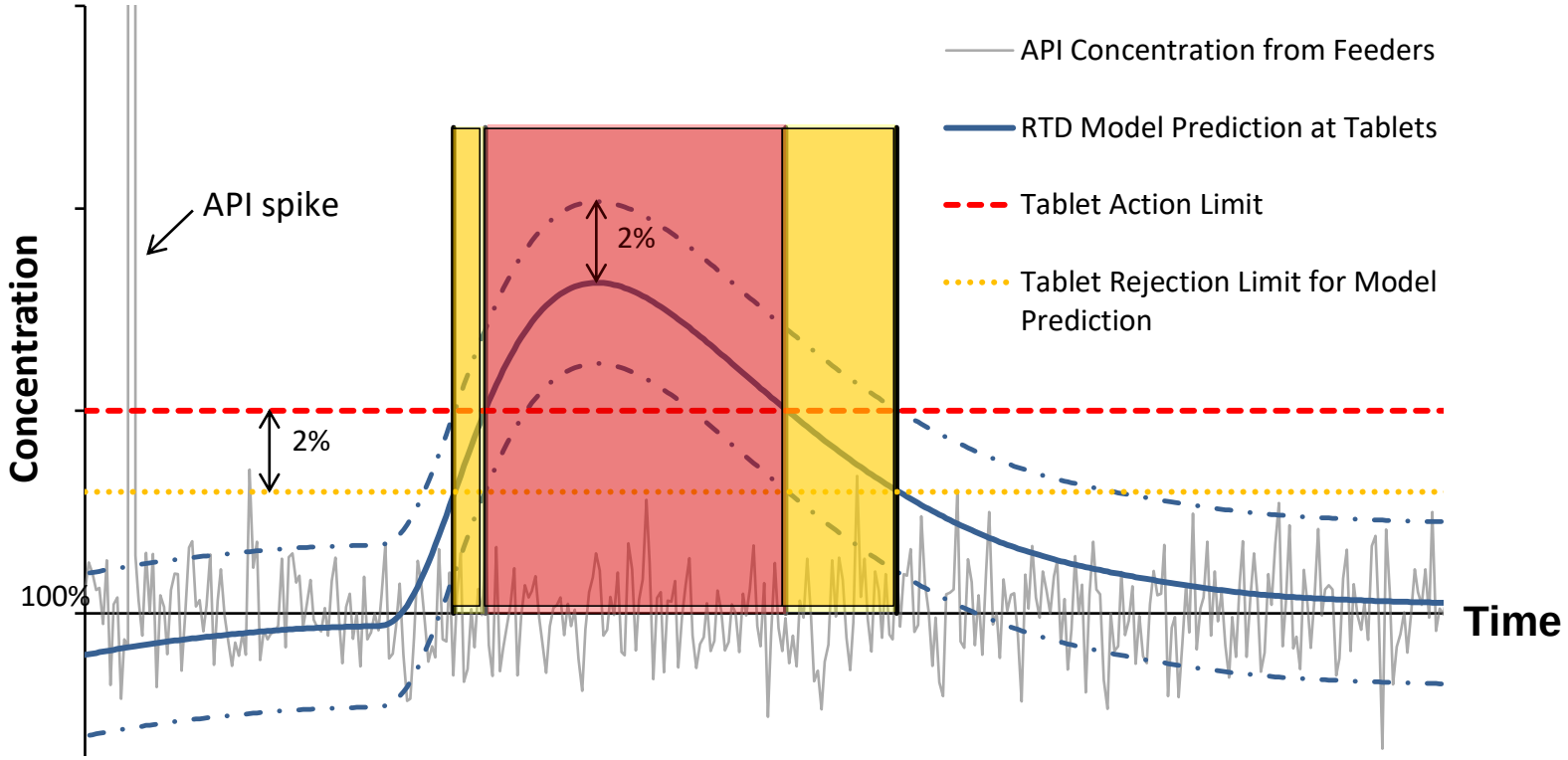
Implementation of the RTD Process Model for Material Rejection



(a) beginning of tablet rejection

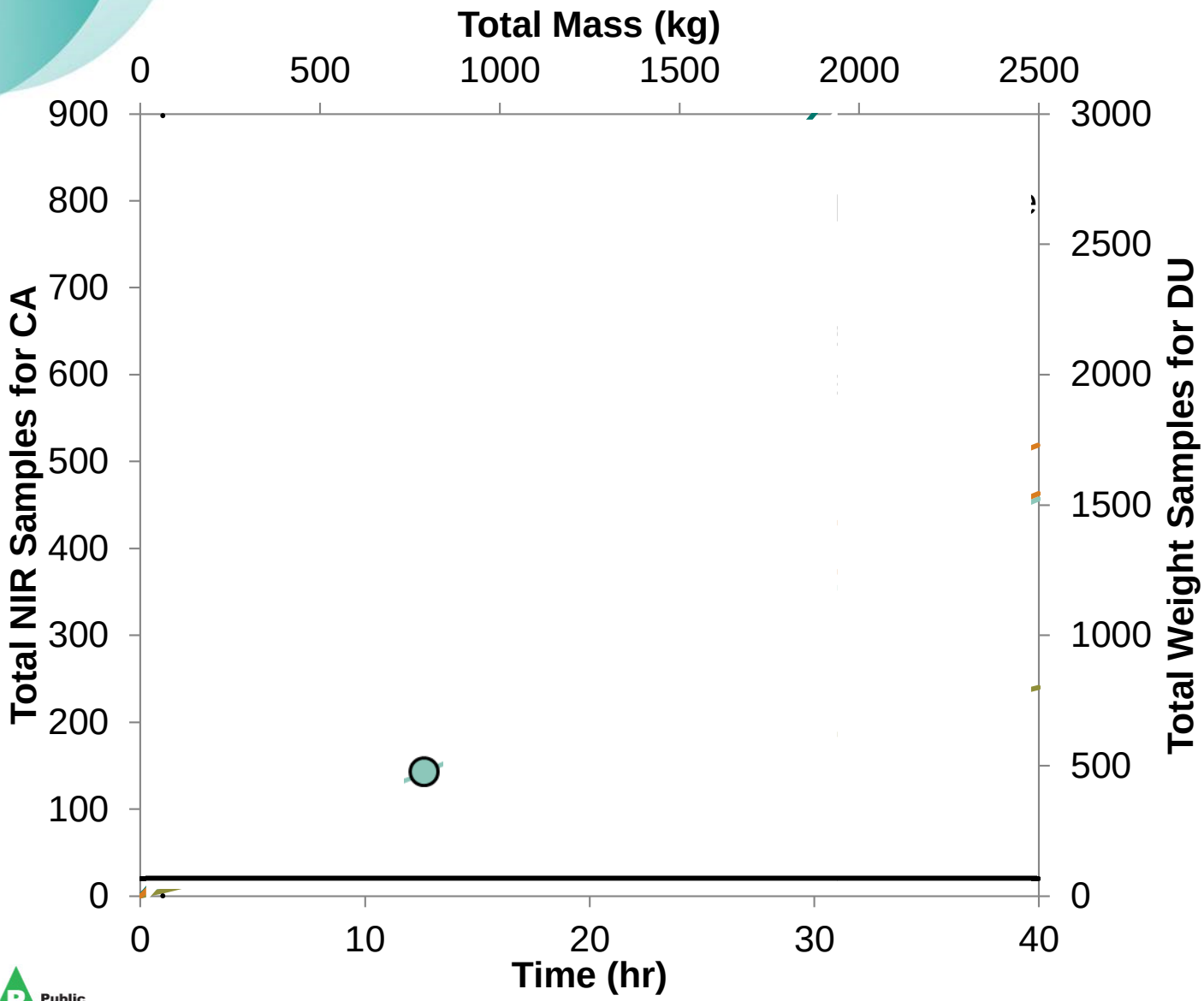
(b) first predicted average tablet potency outside acceptable limits

(c) predicted average tablet potency returns to acceptable range

(d) tablet rejection ends

- **Yellow shaded regions** indicate conservative diversion of tablets
- **Red shaded region** indicates diversion of tablets predicted to be outside of acceptable limits

Preliminary Thoughts on Sampling During CM



- Most monitoring & control loops operate at f ≥ 1Hz
- TANDEM used for control and release: weight / hardness / composite assay
- Sampling must be statistically representative
- If process is capable (Cpk>1.3) and in state of control:
  - Strict criteria on sampling interval not needed
  - Risk between samples is to the business, not the patient
- Monte Carlo modeling will inform final decision

Moving Towards Acceptance of Continuous Manufacturing Technology

What Industry Can't Do

- We cannot run different control strategies for different regulatory regions
- We cannot maintain different RTRT models for same test for different markets
- We cannot develop a single technology platform without assurance of global acceptance

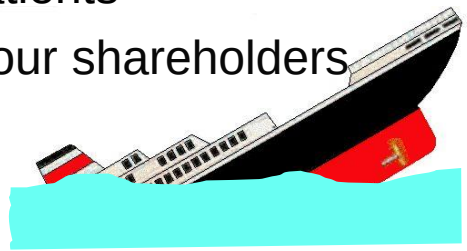
We embrace O'Connor, Yu and Lee's proposal (Int. J. Pharm. 509 (2016) p. 492)

- "international harmonization of approaches for expediting the global adoption of emerging technologies."

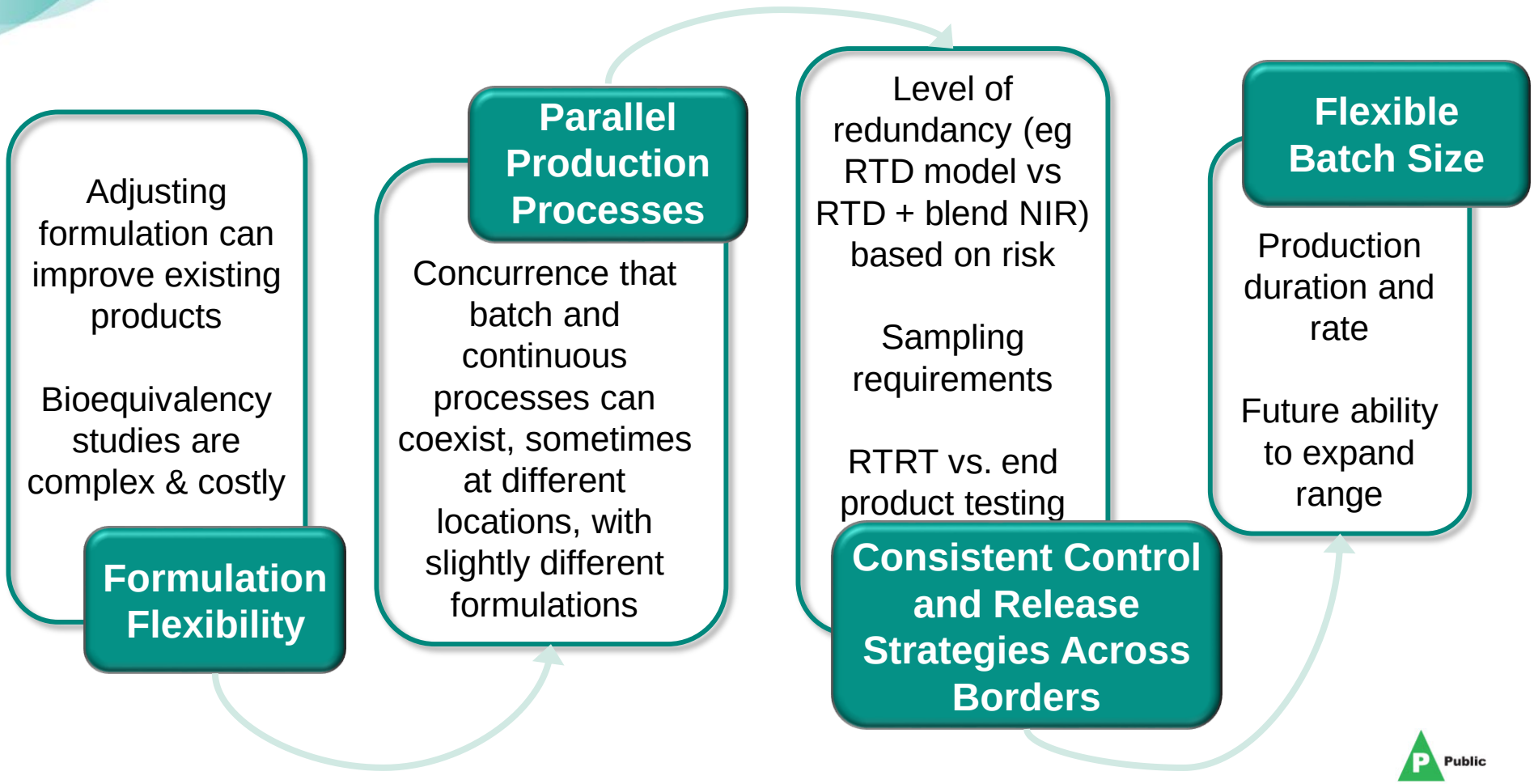
An Ethical Dilemma?

- We want the highest assurance of quality of drugs for patients
- We want the most economical manufacturing to benefit our shareholders
- We want to be able to supply all markets

Failure to gain approval of any of these components ***in any regulatory region*** *sinks the entire ship*



What agreement is needed from global regulators to move CM forward efficiently?



*To best serve our patients, we want the **flexibility** to deliver our medicines to any patient **worldwide***

Public

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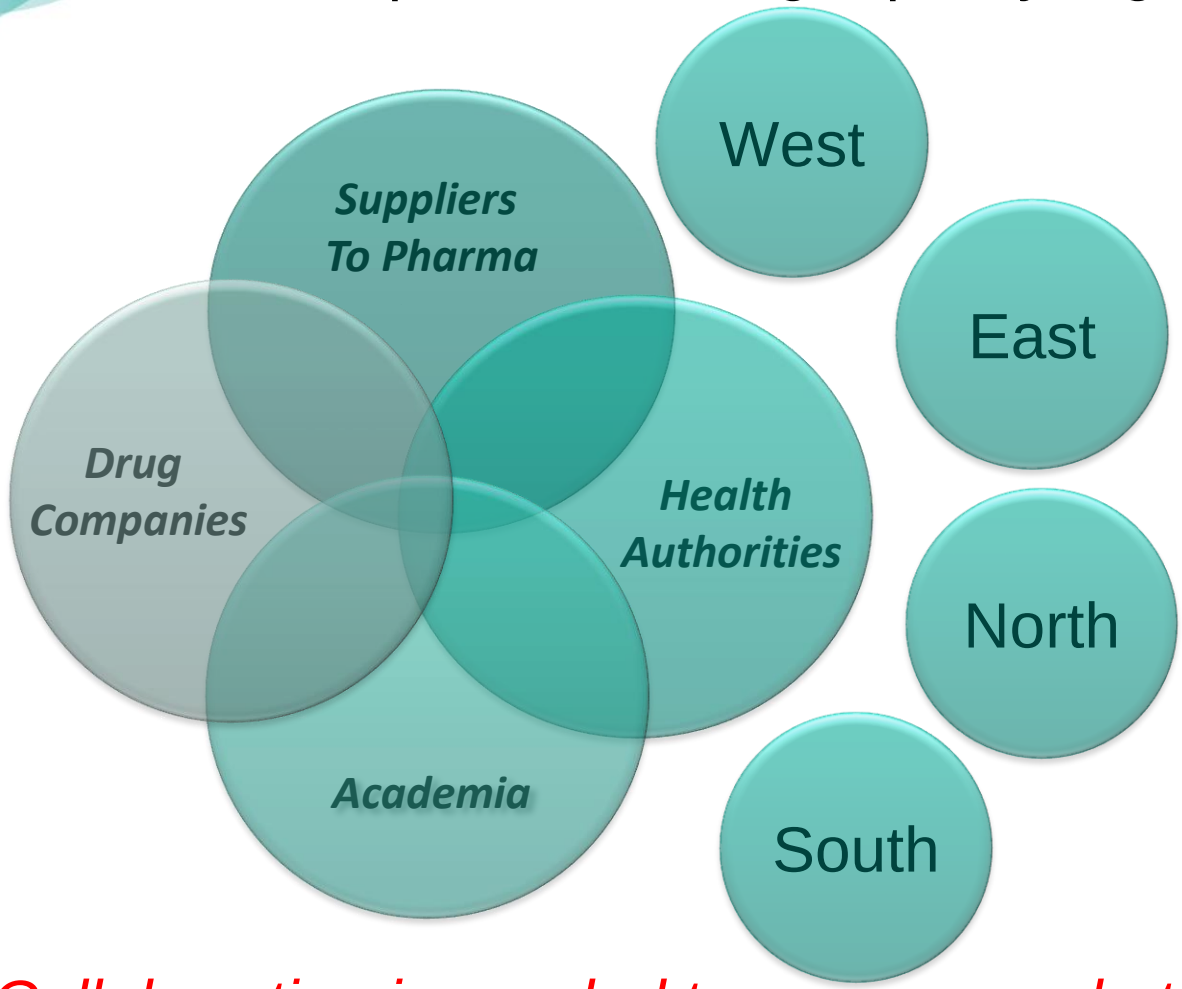
Conclusions

Continuous manufacturing offers benefits to manufacturers and to patients through quality, agility and flexibility



Continuous direct compression, film coating, and RTRT for an existing product provides a risk-prudent way to

- Demonstrate proof of operations
- Achieve regulatory acceptability

Eventually enabling future applications of continuous manufacturing technologies for new products

Collaboration is needed to overcome obstacles and allow patients to reap the benefits of CM

Public

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Cindy Starbuck

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Mano Ramasamy

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GRAZZI

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