Seeq for Analysis of Continuous Manufacturing at Pfizer

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Drug Product Manufacturing (DPM)

Who we are, what we do

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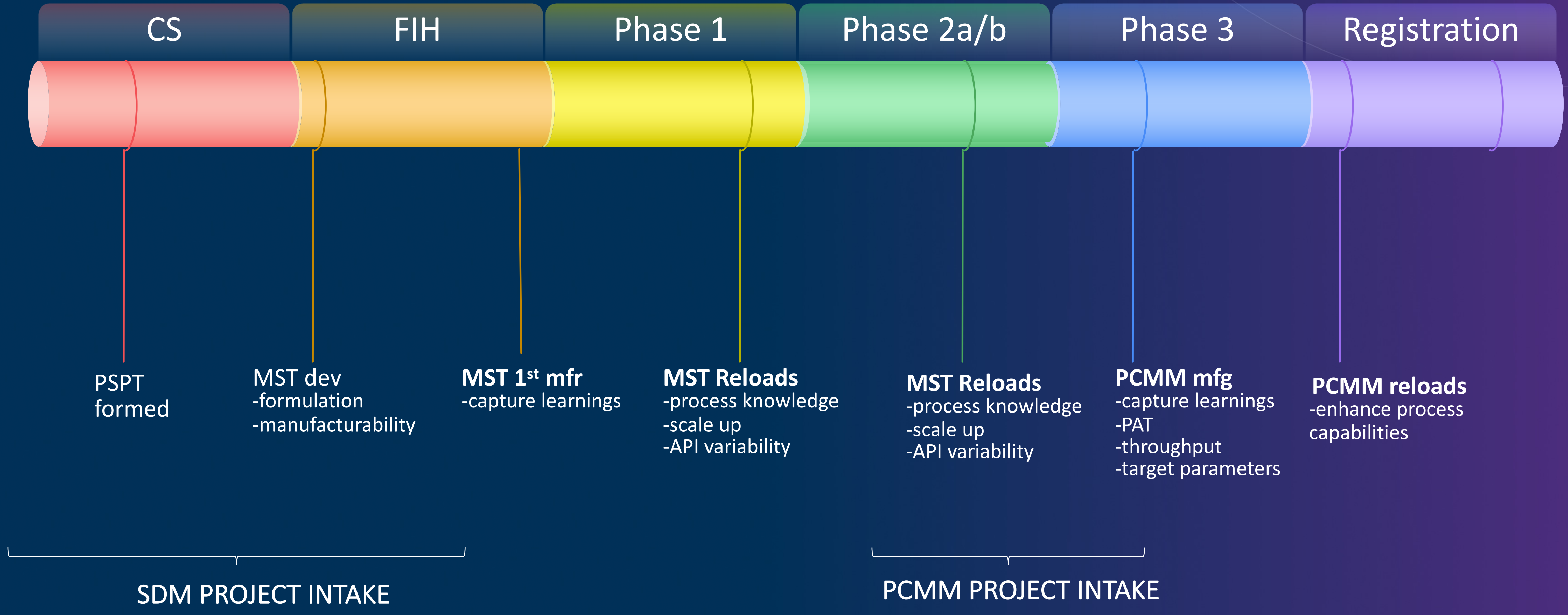
Progressing the Portfolio



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Solid Dose Manufacturing

- Solid dose manufacturing for clinical and non-clinical development use
- Batch Processing from 0.5 – 150 kg
- Facility design for 120 batches/year
- Designed to handle default OEB4 compounds

Material Sparing Tablets (MST)

standardized formulations for immediate release; manufactured using dry granulation or direct compression process; speed & flexibility enables supplies to the clinic faster

Film Coating

Thin polymer-based layer applied to tablets to mask taste, color or alter release rate; enables blinding of clinical studies

Osmotic Tablets

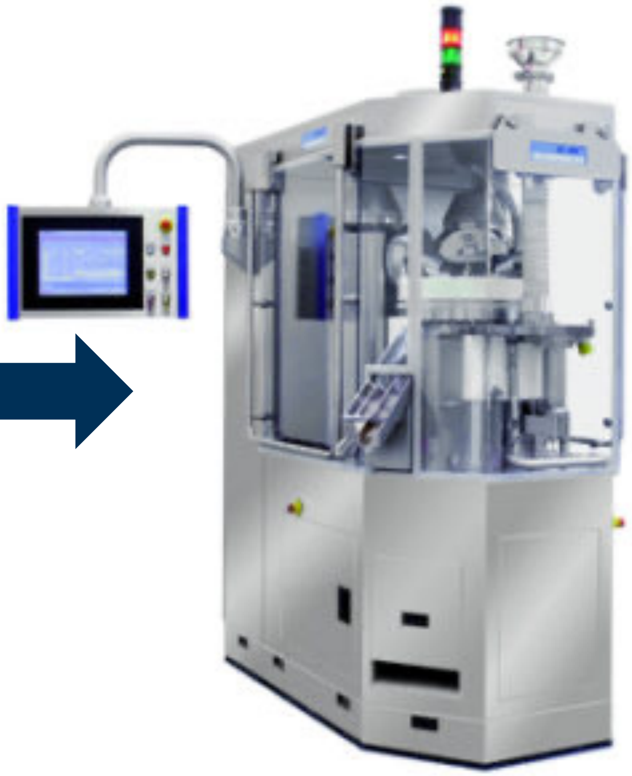
Modified release formulations using either swellable core technology (bilayer) or extrudable core system (single layer) tablets

Multiparticulates

Melt-spray-congeal process to produce microspheres and coating for taste masking (eg, pediatric use) or modified release; encapsulation optional

MST Example Equipment

Compaction



Compression

Coating

Portable Continuous Miniature Module (PCMM)

- Solid Dose Manufacturing for late clinical usage
- Continuous processing at max throughput of 30 kg/hr
- Advanced NIR PAT Soft Sensors
- Mass Balance Model Control

Continuous Wet Granulation

Twin screw wet granulation and a 6-celled fluid bed dryer allows material to be continuously granulated, dried, milled and transferred to the Direct Compression line to compress higher dosage tablets.

Continuous Direct Compression

Raw materials are individually fed into Pfizer's proprietary Continuous Mixing Technology (CMT) before being compressed into tablets.

Advanced Analytics and Data Capture

Capture process data into historians for real time and post manufacture trending of critical parameters. Utilize soft sensors and in-process analytics to monitor and control quality attributes of tablets.

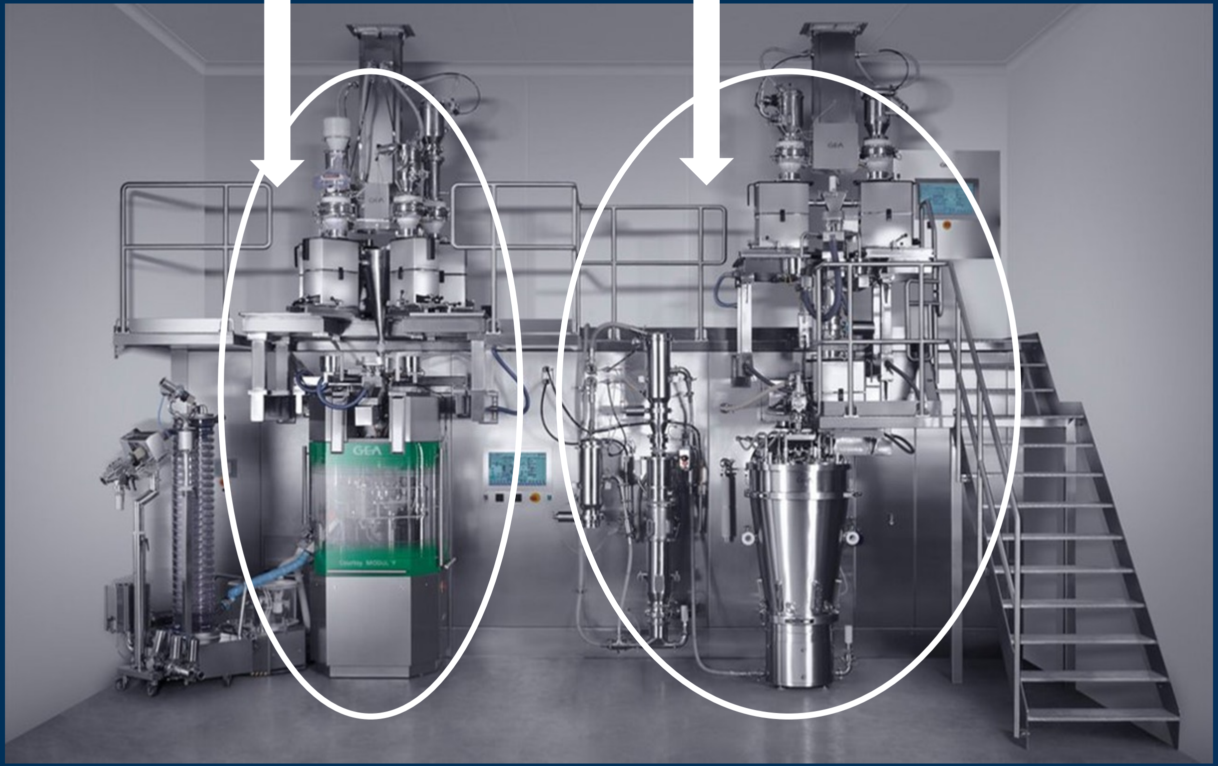
Continuous Film Coating

The final unit operation uses 2 high speed film coaters to continuous film coat tablet cores produced from the compression unit operation. The coatings are used to enable blinding during clinical studies or product differentiation following approval.

PCMM Equipment

Direct Compression

Wet Granulation



Film Coating

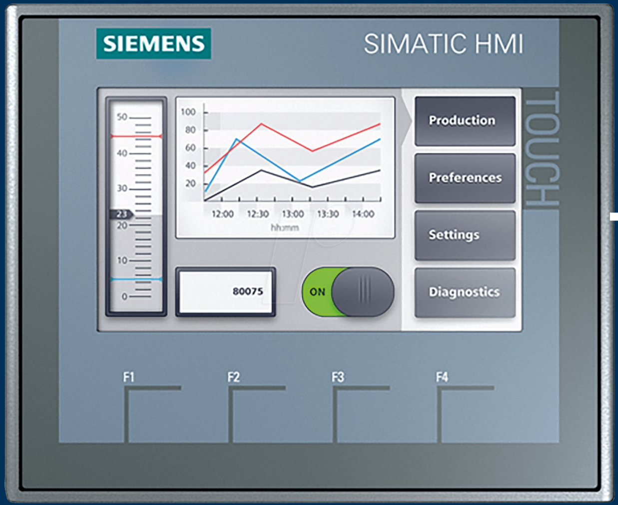
Digital Infrastructure

Implementing Pi Historians

Data Capture

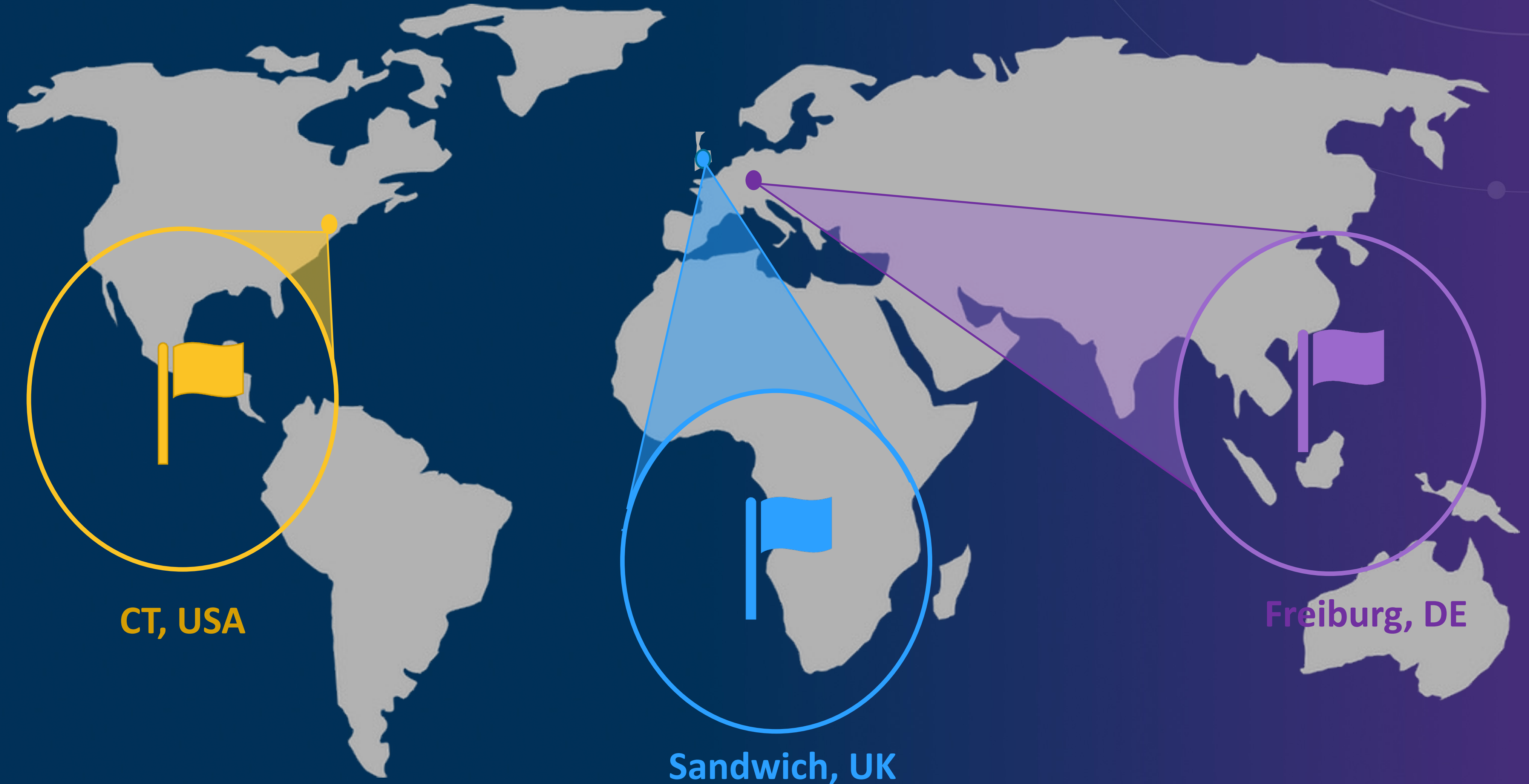
PLC

HMI



PI Historian

Data Availability



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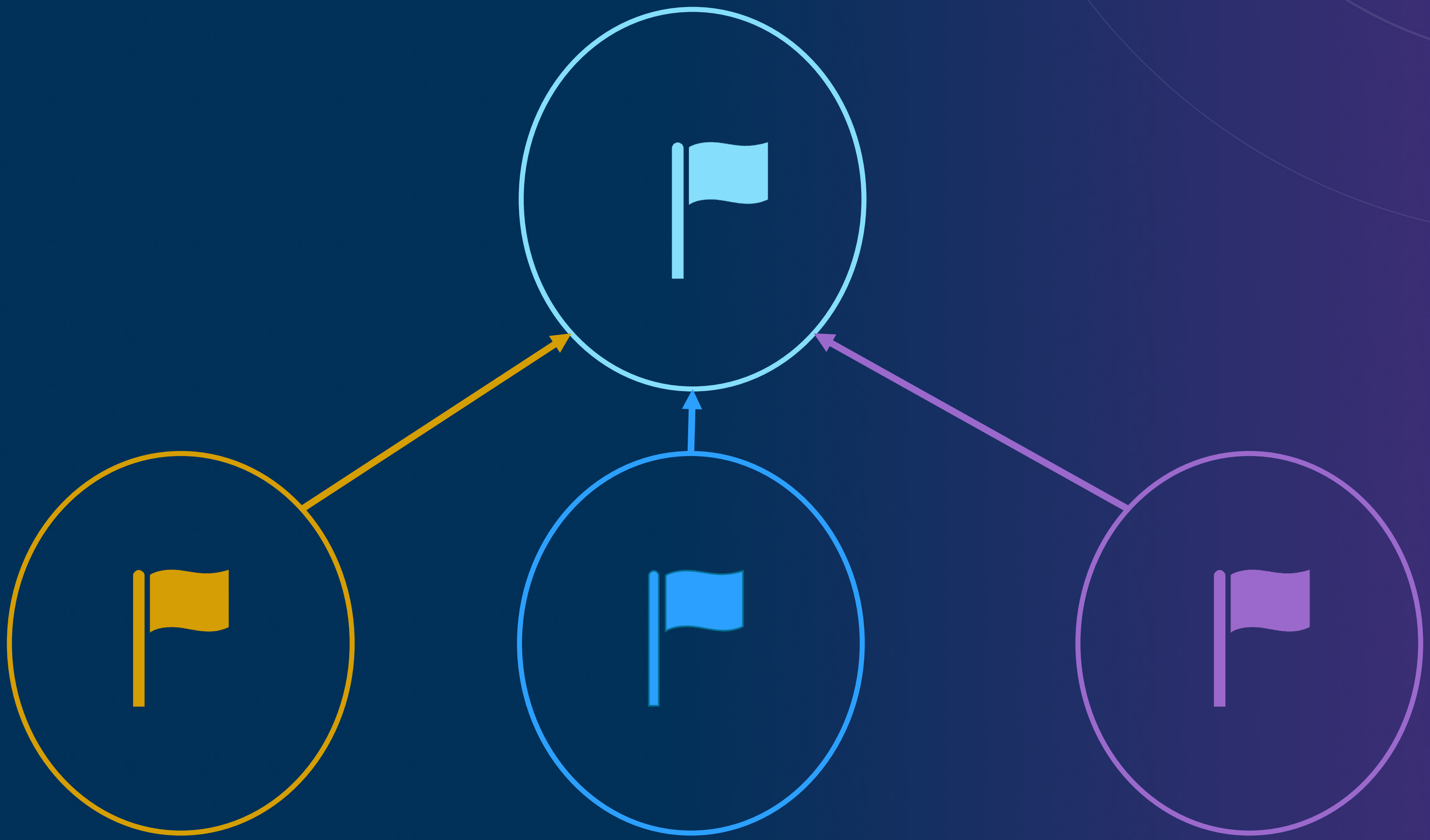
Data Availability



Common Asset Framework

CT, USA

- Batch Data
  - ❑ Product ID
  - ❑ Recipe
- Feeder-0X
  - ❑ Attribute 1
  - ❑ Attribute 2
- CMT-1
  - ❑ Attribute 1
  - ❑ Attribute 2
- Coater-1
  - ❑ Attribute 1
  - ❑ Attribute 2

Sandwich, UK

- Batch Data
  - ❑ Product ID
  - ❑ Recipe
- Feeder-0X
  - ❑ Attribute 1
  - ❑ Attribute 2
- CMT-1
  - ❑ Attribute 1
  - ❑ Attribute 2
- Coater-1
  - ❑ Attribute 1
  - ❑ Attribute 2

Freiburg, DE

- Batch Data
  - ❑ Product ID
  - ❑ Recipe
- Feeder-0X
  - ❑ Attribute 1
  - ❑ Attribute 2
- CMT-1
  - ❑ Attribute 1
  - ❑ Attribute 2
- Coater-1
  - ❑ Attribute 1
  - ❑ Attribute 2

Data Driven Insights

Leveraging Seeq Analytics

Use Case Introduction

CHALLENGE

- **Case 1:** Monitoring of continuous/dynamic processes is limited with the conventional methods
- **Case 2:** Continuous processing consists of several unit operations executing in parallel. Need to identify and respond to observations quickly.
- **Case 3:** Semi-batch processes – large number cycles executed within a single batch. Need to understand process dynamics to ensure a uniform final product.

SOLUTION

- Real time monitoring with predictive modeling
- Pair manufacturing experience with advanced analytics capabilities. Bring the models to the manufacturing floor.
- Standardized views and analytics to interpret large data sets

RESULTS

- Increased understanding. Ability to identify and respond to variability resulting in a higher assurance of quality
- Avoidance of waste and reduction in production down-time.
- Improved monitoring, creation of a data-based control strategy and improved product uniformity

Use Case Introduction

CHALLENGE

SOLUTION

RESULTS

Granulation Monitoring

- Conventional monitoring practices provide limited information
- Controls are set at start-up, but process is continuous/dynamic with variability

Continuous Manufacturing

- Several unit operations running in parallel – if one operation is paused, all are paused.
- Need to identify and address issues quickly

Semi-Batch Process

- Large number cycles executed within a single batch.
- Need to understand process dynamics to ensure a uniform final product.

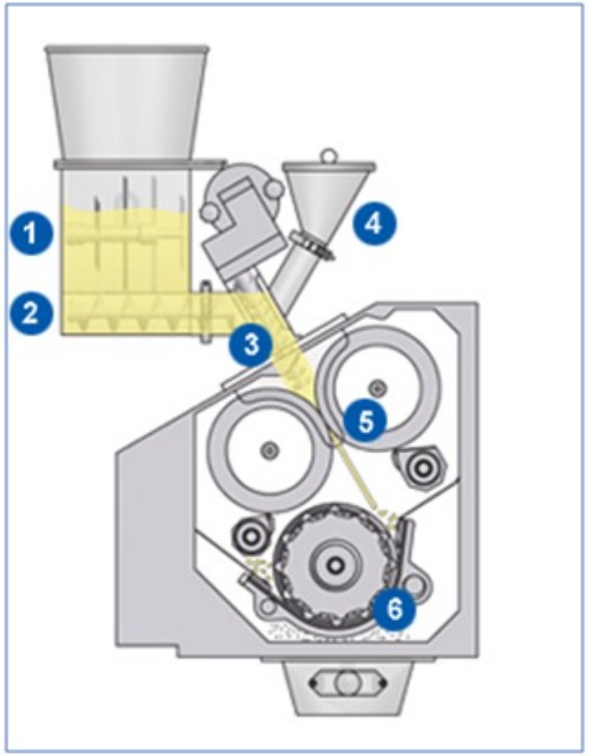
Case 1: Granulation Monitoring

- Dry granulation or roller compaction creates larger granules from a powder blend

- Controlled force is applied to the powder blend to create ribbons of material, which are then milled to target size

- Key process parameters
  - **Force:** Nominal mechanical force applied between two rollers
  - **Gap:** Minimum distance between the two press rollers
    - Machines using a floating gap system adapt powder feed rate to maintain ideal gap settings
  - **Solid Fraction (SF):** Relative density of the output material, important in achieving optimal tablet properties

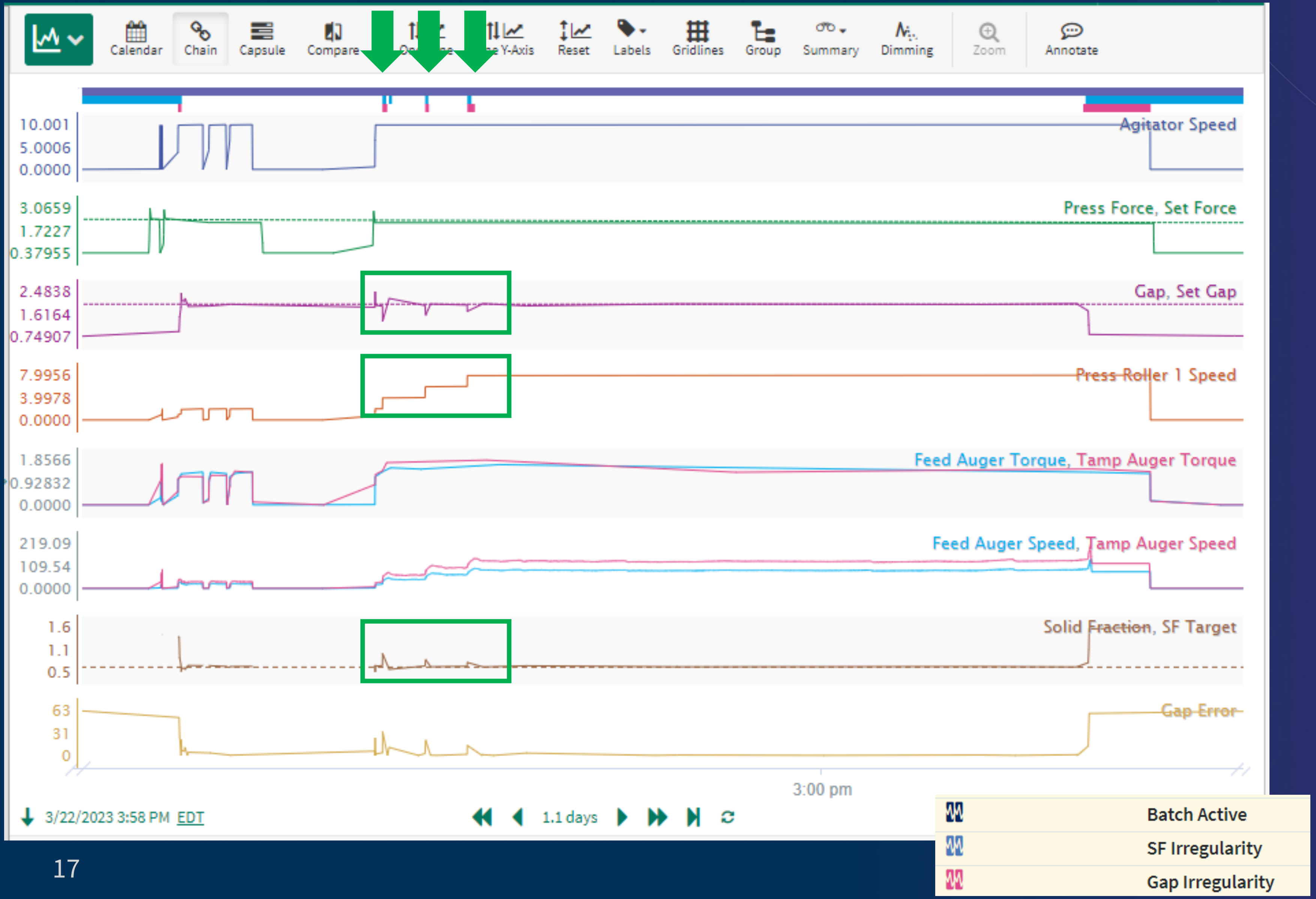
- **Challenge**
  - Monitoring of continuous/dynamic processes is limited with the conventional methods



The Gerteis® roller compaction process showing: (1) Inlet funnel with agitator, (2) Feed auger, (3) Tamp auger, (4) Small quantity inlet funnel, (5) Press rollers with ribbon, (6) Rotor with desired granules

Case 1: Granulation Monitoring

Solution: Utilize real time modeling for granulation performance. Identify irregularities.



Key Input Parameters

- Roller gap
- Press force
- Roller speed

Calculated Values

- Solid Fraction (SF)
- SF Error
- Gap Error

Key Insights

- Real-time granulation performance, predicted deviation from setpoints

Example Use Case

- Identify SF and Gap irregularities during manufacture, stop process and troubleshoot
- Process improvement, refine setpoints for future batches

Result

✓ Reduced startup time
✓ Material savings

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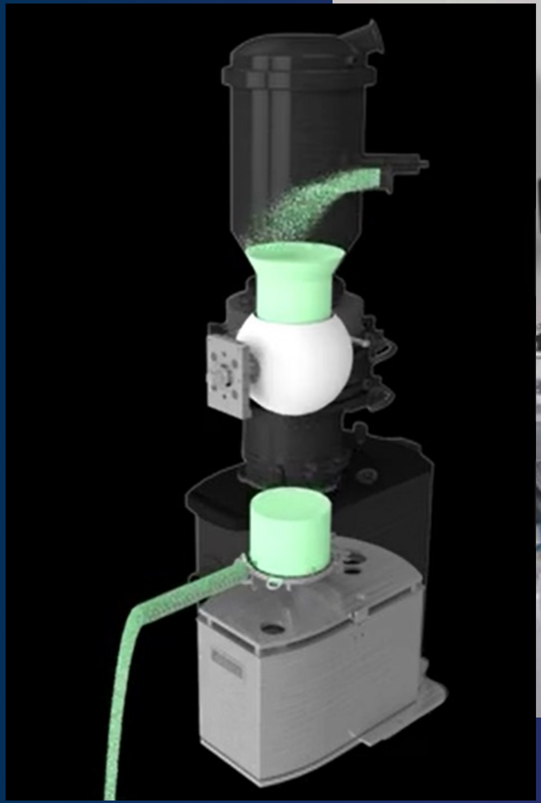
Case 2: Continuous Manufacturing

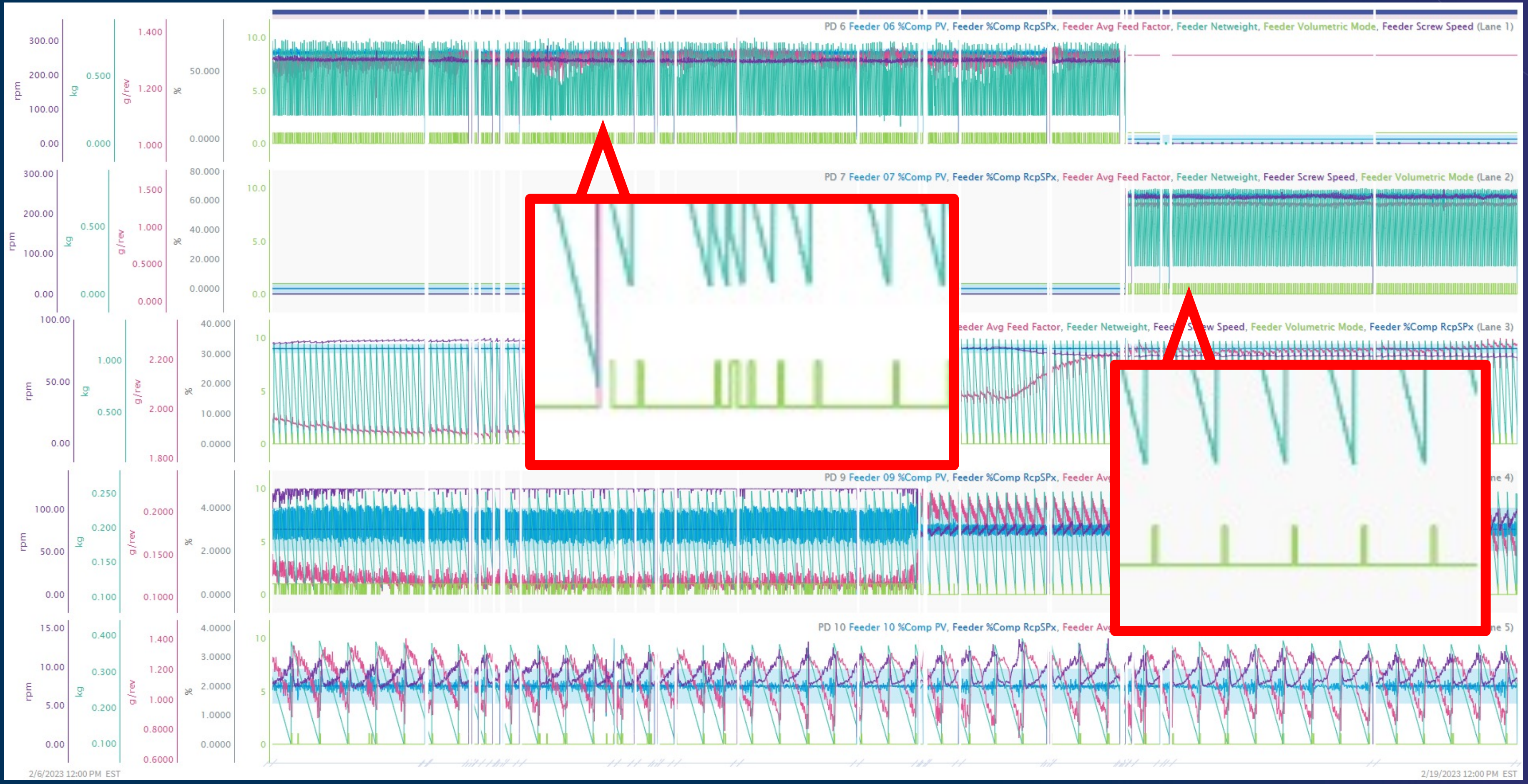
- ❑ Continuous feeders are used in PCMM manufacturing to feed powders into the system at a fixed rate
- ❑ Powder inputs are then mixed in a continuous blender and compressed into tablets
- ❑ Feeder performance is a key component in meeting target tablet composition
- ❑ **Challenge**
  - ❖ Continuous processing consists of several unit operations executing in parallel. Need to identify and respond to observations quickly.



Kreiser MJ, Wabel C, Wagner KG. Impact of Vertical Blender Unit Parameters on Subsequent Process Parameters and Tablet Properties in a Continuous Direct Compression Line. Pharmaceutics. 2022; 14(2):278. https://doi.org/10.3390/pharmaceutics14020278

Case 2: Continuous Manufacturing

Solution: Pair manufacturing experience with advanced analytics capabilities. Bring the models to the manufacturing floor.



15 Feb 2023, 14:35:00	Stop	Valve-TU6 failed to open	42012	Blender2	False
15 Feb 2023, 14:35:15	Stop	PD6 - in volumetric mode	42050	Blender2	False

Key Input Parameters

- % Composition
- Feed Factor
- Feeder Netweight
- Volumetric Mode
- Screw Speed

Key Insights

- Monitor feeder performance throughout batch based on key parameters

Example Use Case

- Erratic feeder behavior; inconsistent volumetric mode spikes (Top-ups not occurring successfully)
- Checked equipment set-up, identified loose bolt preventing actuation. Swapped equipment and opened work order to repair bolt.

Results

✓ Resolve system alarms
✓ Material savings

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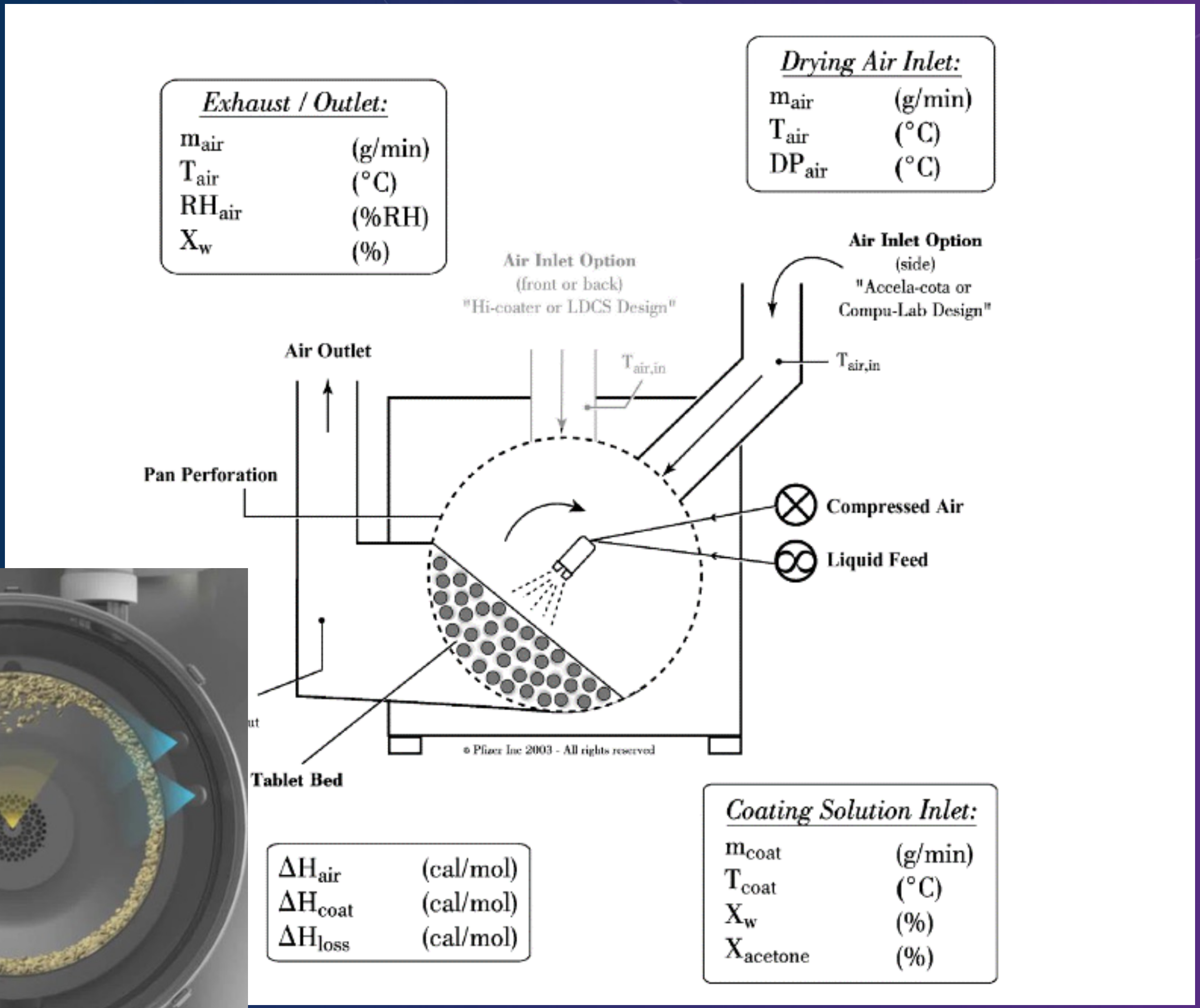
Case 2: Continuous Manufacturing – Film Coating

- Film coatings are applied to compressed tablets for aesthetic and functional reasons
- Process conditions for this unit operation may vary greatly with tablet properties, formulation changes, and scale-up
- Thermodynamic modeling enables process optimization for coating parameters such as temperature, air flow, and humidity



- Challenge
  - Continuous processing consists of several unit operations executing in parallel. Need to identify and respond to observations quickly.

am Ende MT, Berchielli A. A thermodynamic model for organic and aqueous tablet film coating. Pharm Dev Technol. 2005;10(1):47-58. doi: 10.1081/pdt-35915. PMID: 15776813.

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Case 2: Continuous Film Coating

Solution: Pair manufacturing experience with advanced analytics capabilities. Bring the models to the manufacturing floor.

Key Input Parameters

- Inlet / Exhaust air temperatures
- Pressure

Calculated Values

- Thermodynamic model
- Heat requirements
- Ideal inlet temperature required, +/- 10% range

Key Insights

- Thermodynamic model for continuous film coating; predict ideal parameter range

Example Use Case

- Predict and set inlet temperature parameters prior to CFC batch
- Avoid coating defects due to incomplete drying or drying too quickly

Results

✓ Reduce experimentation required to optimize process parameters
✓ Time and material savings

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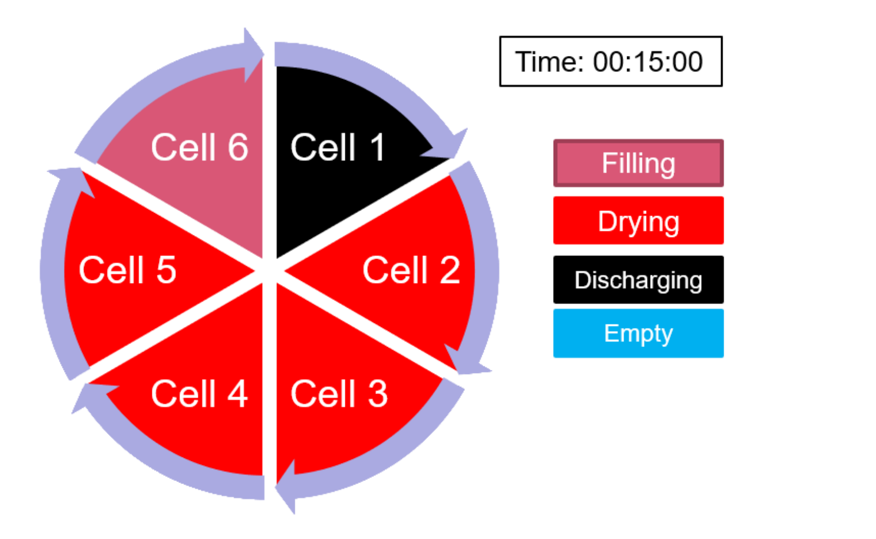
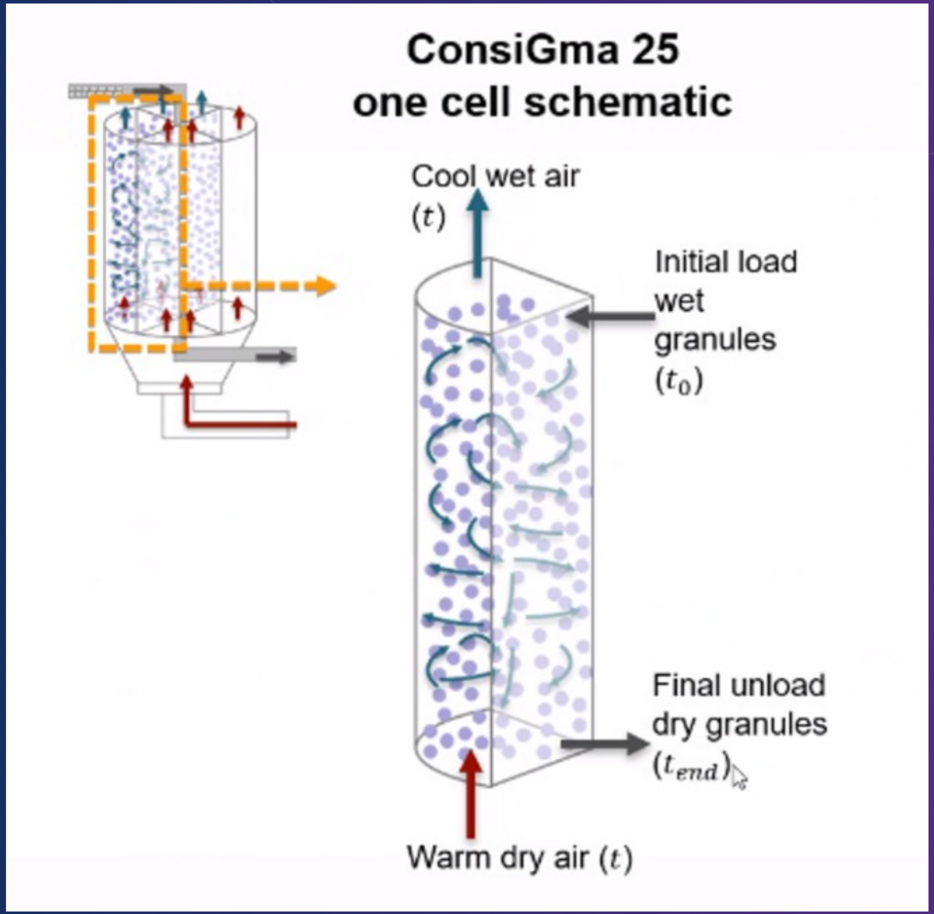
Case 3: Continuous Wet Granulation

- Wet granulation is a process used to improve compressibility and flowability of materials prior to compression
- Unit operation consists of Feeding, Blending, Liquid Addition, Granulation, Drying, Milling, Compression
- The ConsiGma six-cell fluid bed dryer dries wet granules in a continuous drying cycle
- **Challenge** a large number cycles are executed within a single batch. Need to understand process dynamics to ensure a uniform final product.

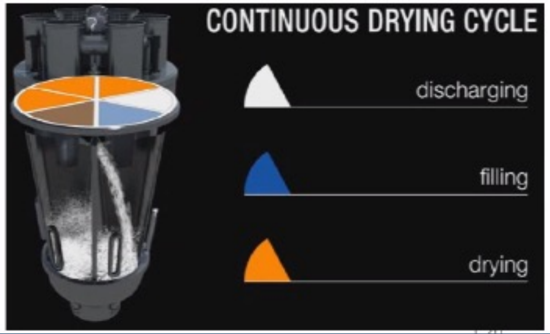


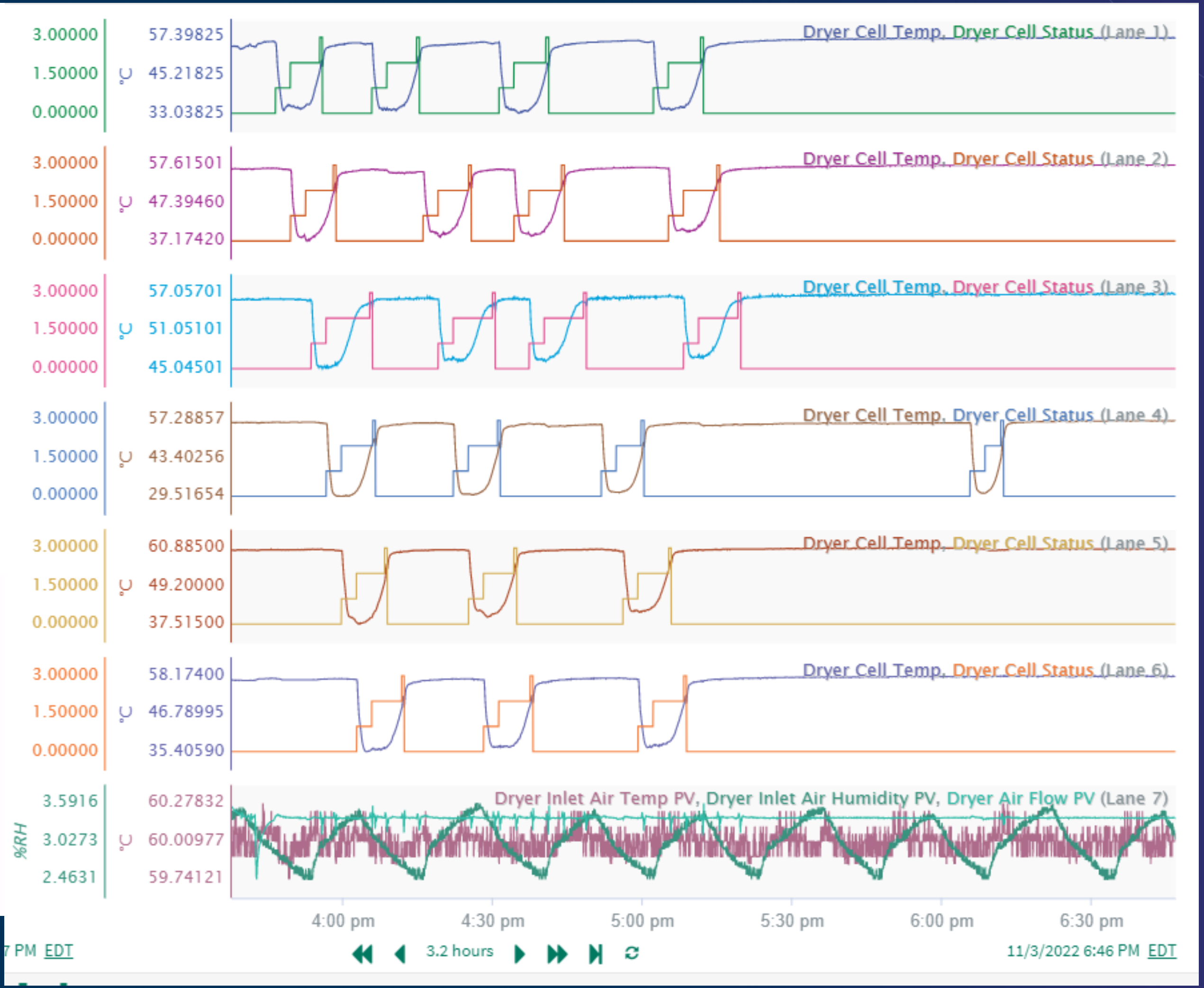


Case 3: Continuous Wet Granulation

Solution: Standardized views and analytics to interpret large data sets

Name	Avg
Dryer Cell Temp	48.77232 °C
Dryer Cell Temp	50.47650 °C
Dryer Cell Temp	51.43891 °C
Dryer Cell Temp	49.74909 °C
Dryer Cell Temp	54.69636 °C
Dryer Cell Temp	51.37872 °C
Dryer Inlet Air Temp PV	57.62966 °C
Dryer Inlet Air Humidity PV	4.3523
Dryer Air Flow PV	341.72382 m³/h





Key Input Parameters

- Dryer cell temperature
- Dryer cell status
- Inlet temp / humidity
- Air flow

Calculated Values

- Average batch values

Key Insights

- Batch performance
- Variation across dryer cells

Example Use Case

- Identify variation across dryer cells, optimize drying parameters such as Drying Time and Delta T

Results

✓ Material savings, avoid rejected material

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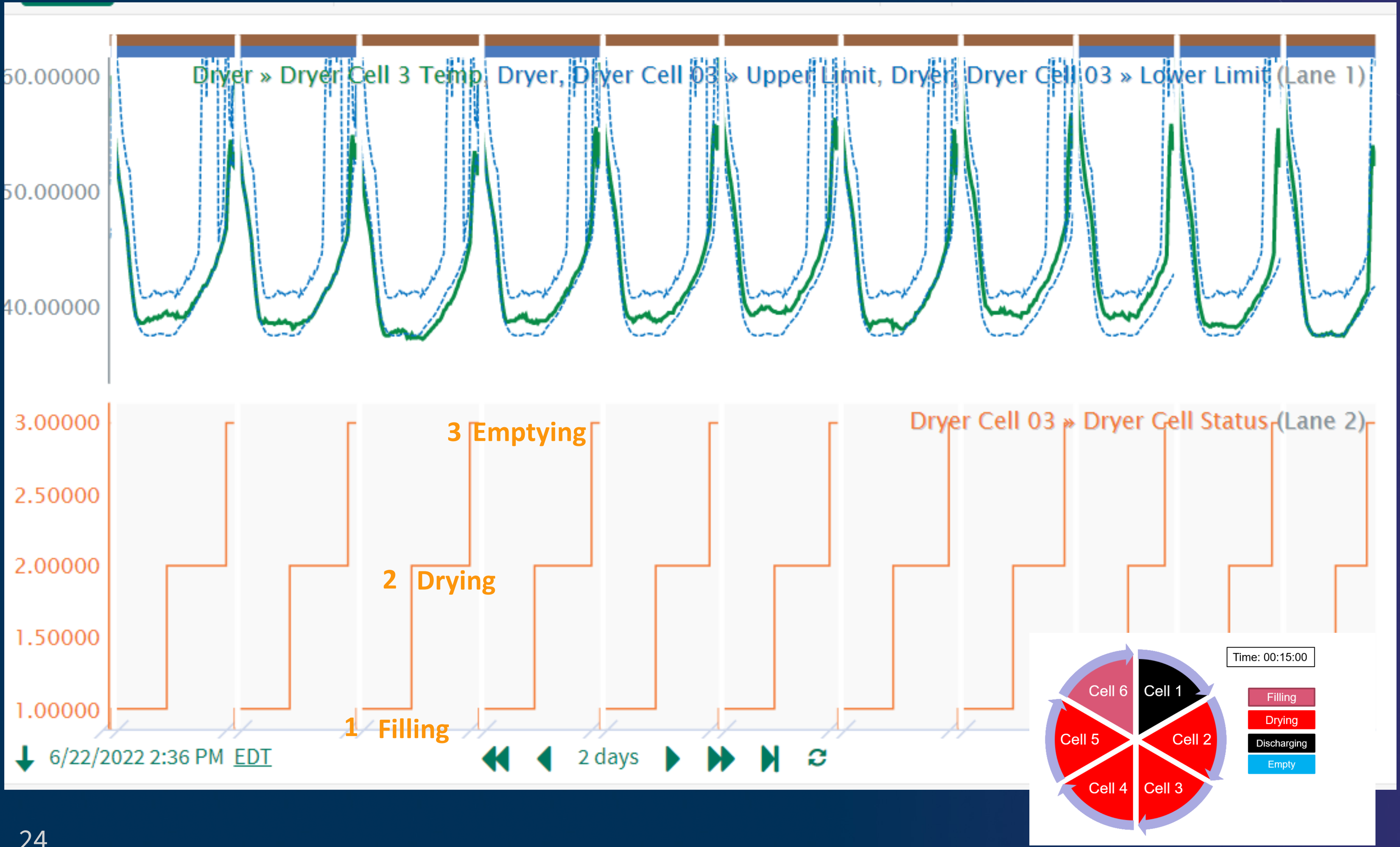
Case 3: Continuous Wet Granulation

Solution: Standardized views and analytics to interpret large data sets



Key Input Parameters

- Dryer cell temperature
- Dryer cell cycle phase

Calculated Values

- Temperature bounds based on "Golden Profile" data set

Key Insights

- Process variation in dryer phase temperature profile, process anomalies, temperature excursions

Example Use Case

- Detect process anomalies during manufacturing, identify and resolve process errors

Considerations

- Variation in Golden Profile data set; requires future refinement to more accurately bound ideal temperature profile

Impact

✓ Material savings

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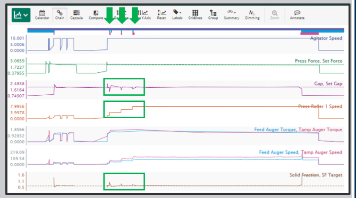
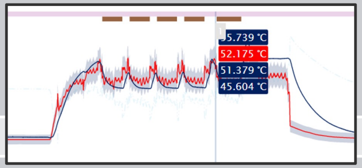
Use Case Summary

	Granulation Monitoring	Continuous Manufacturing	Semi-Batch Process
CHALLENGE	• Conventional monitoring practices provide limited information • Controls are set at start-up, but process is continuous/dynamic with variability	• Several unit operations running in parallel – if one operation is paused, all are paused. • Need to identify and address issues quickly	• large number cycles executed within a single batch. • Need to understand process dynamics to ensure a uniform final product.
SOLUTION	• Utilize real time modeling for granulation performance. Identify irregularities.	• Pair manufacturing experience with advanced analytics capabilities. Bring the models to the manufacturing floor.	• Standardized views and analytics to interpret large data sets
RESULTS	• Captured and responded to variability. Material savings and higher assurance of quality	• Avoided material waste and reduced production down-time.	• Improved monitoring, created a data-based control strategy and improved product uniformity





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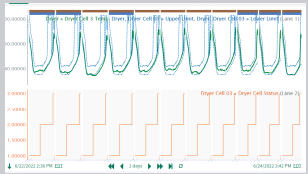

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Thank you

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