PAT Implemented for Continuous Manufacturing

Dr. Mark Smith
Process Analytical Sciences Group
Pfizer Global Supply

Continuous Manufacturing

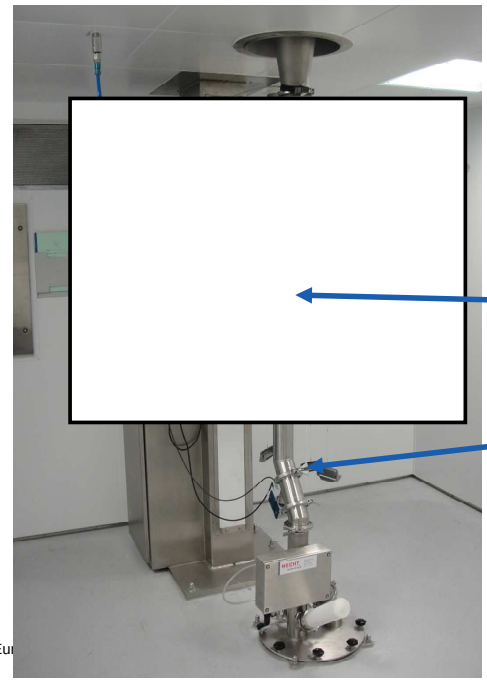
- Continuous manufacturing can provide
  - Increased production with a small equipment footprint
  - Ease of scale-up
  - Lightly attended, flexible manufacturing
- Development of personalized medicine concepts are becoming a reality
  - Will require flexible, low volume, low inventory manufacturing of high value products
- Pressures for local manufacturing
  - Many of the Governments in the emerging markets will insist on local manufacturing
    - ⇨ Continuous processing based on mobile skids is seen as a possible solution

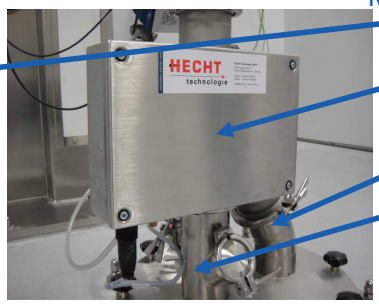
Continuous DP Manufacturing – Direct Compression Tablet

- Three level concept
  - Existing docking stations and tablet press
  - New feeding, dispensing, mixing, and blend transfer
  - Throughput aligned across process
- PAT and process measurements more critical for controlling continuous processes
  - May better facilitate RTRt
    - ⇨ Overall approach to RTRt is similar
- Continuous process must be accompanied by the correct control strategy

Feeding and Dispensing System

PAT Integration





NIR Spectrometer

Continuous Mixer

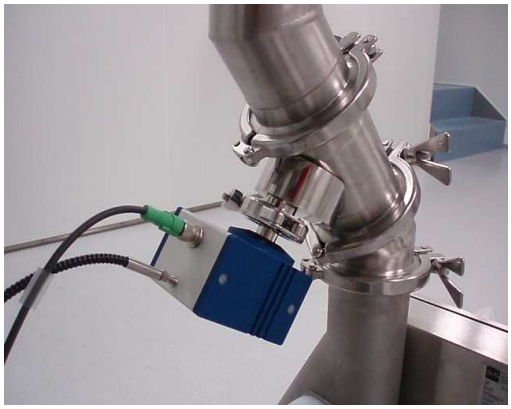
Measuring Point for NIR

Diverter

Bad Channel

Good Channel

PAT Integration

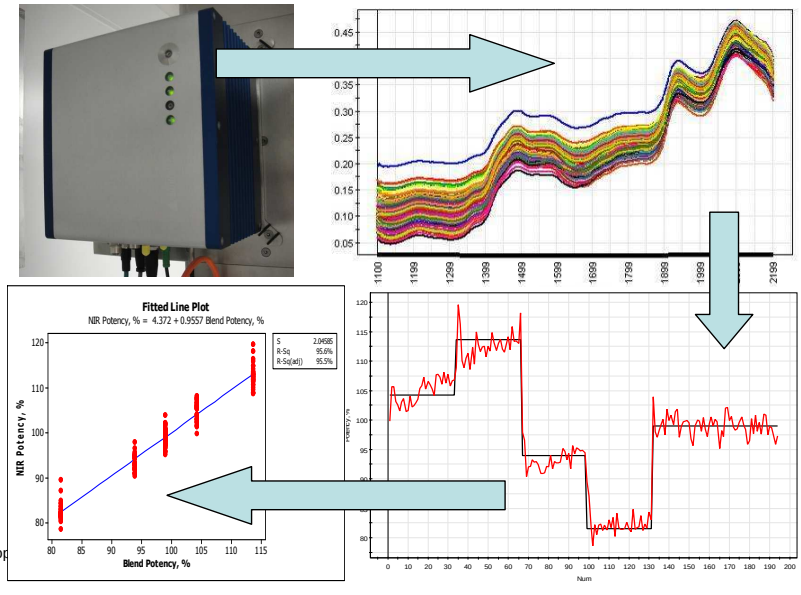


- Interface between PAT and process is critical
  - Ensure good powder contact on probe
    - Minimize impact of dynamic powder flow
    - Avoid segregation potential

Tablet Press

NIR Blend Potency

- Method developed using a combination of pre-blend and dynamic batches across the range 85 – 115% LC



Process Parameters Determining Potency and CU

- In a typical batch solid drug product process:
  - Primary Blend Potency (CU) = f weighing + mixing
- In a batch process weighing and mixing are a one time event
- In a continuous process, weighing and mixing operation is repeated many ten's of thousands of times
  - Operation is time variant in nature
- For a continuous process, the material flow can be considered a stream of "micro batches", each having a discrete potency and CU.
- Sampling of a continuous process should take into account the rate at which "micro batches" are flowing from the system.
- Sampling should be time variant, and match material throughput

Sample Size Calculation

- The sample size that is measured by NIR depends on
  - Probe spot size
  - Penetration Depth of light
  - Powder Density
- A single measurement may be much less than a unit dose

Sample that probe sees

Example:

Acquisition time is 20ms

Probe spot diameter is 2mm

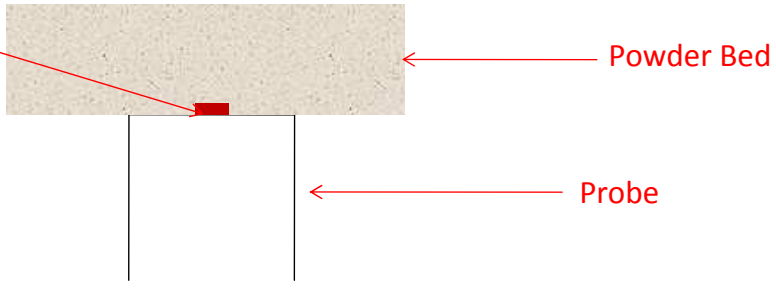
Depth of penetration is 0.5mm

Powder density is 0.7mg/mm^3

M = p (d/2)2DH

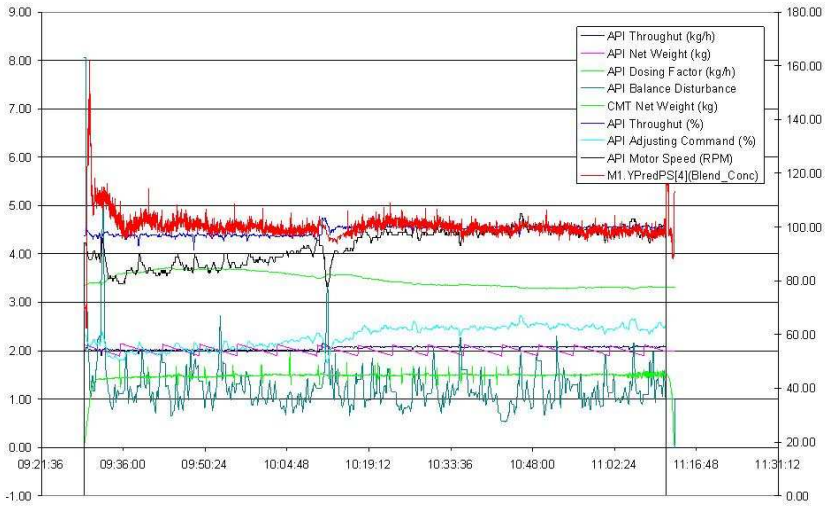
M = 1.1mg/scan

Therefore co-add scans for "unit dose"



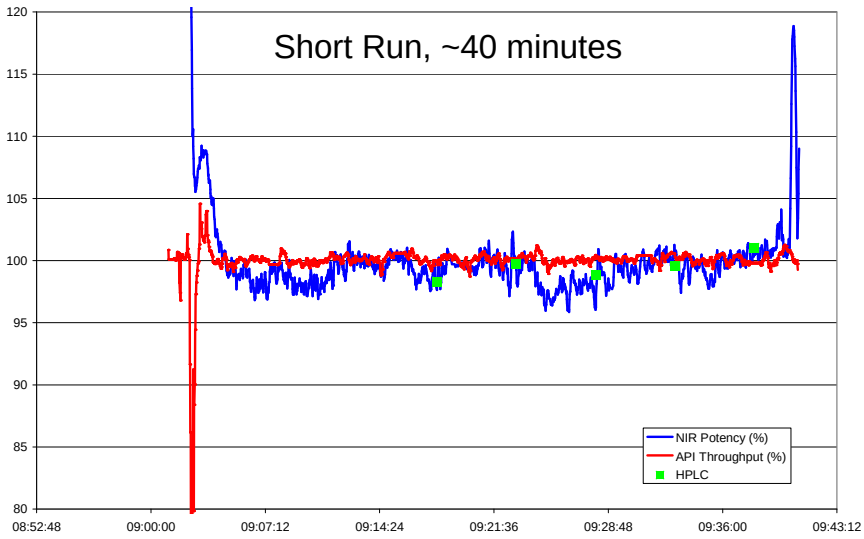
Steady-State

- Based on combination of process and measured parameters
  - Throughput ~60 kg/hour (300,000 tablets/hour)



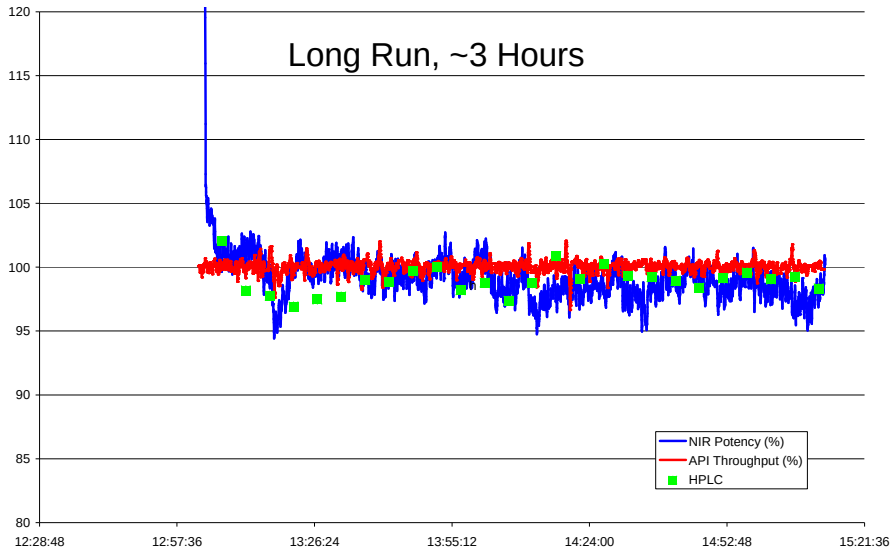
NIR Blend Potency

- Independent runs performed, with comparison to tablet data



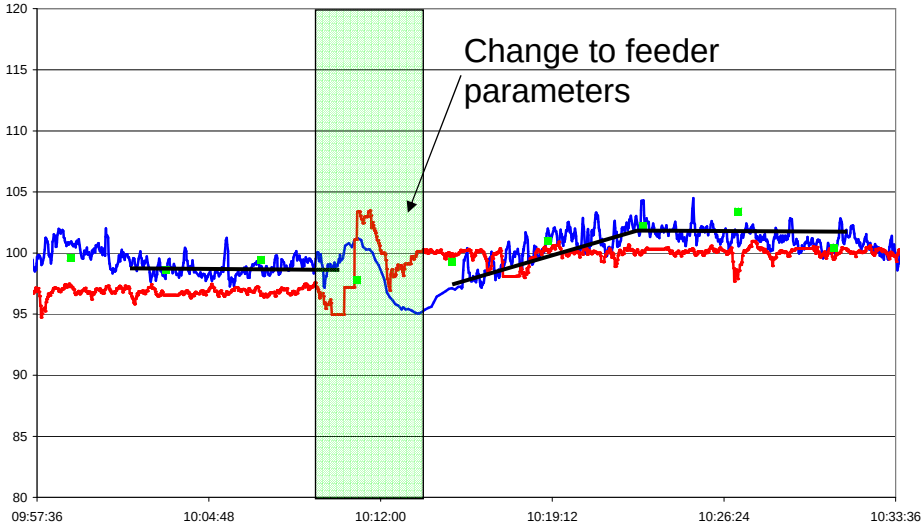
NIR Blend Potency

- Independent runs performed with comparison to tablet data



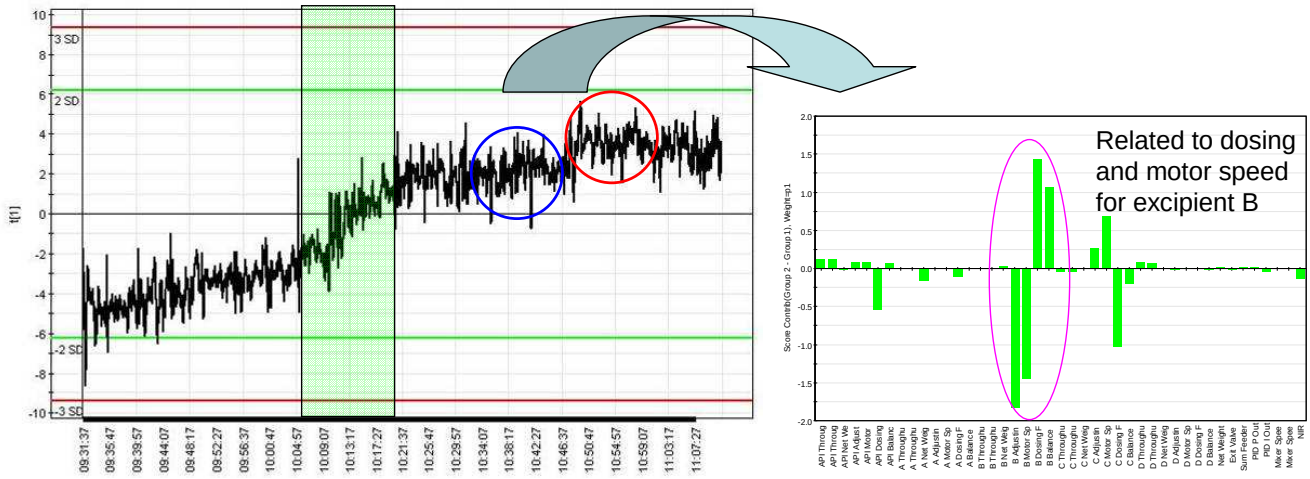
Artificial Potency Ramp

- Small ramp (~3%) introduced through API feeder
  - Indication of residence times and effect of disturbances



Multivariate Condition Monitoring

- >50 parameters related to dosing, feeding, mixing of all raw materials monitored simultaneously
  - Identify deviations from normal operation



Release Approaches for a Continuous Process

- Enhanced understanding of product performance can justify the use of surrogate tests or support real-time release in lieu of end-product testing. For example, **disintegration could serve as a surrogate for dissolution** for fast-disintegrating solid forms with highly soluble drug substances. Unit dose uniformity performed in-process (e.g., **using weight variation coupled with near infrared (NIR) assay**) can enable real-time release and provide an increased level of quality assurance compared to the traditional end-product testing using compendial content uniformity standards.

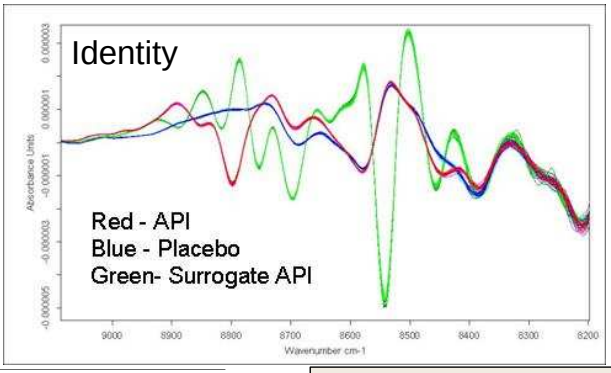
  Q8(R1) Pharmaceutical Development Revision 1

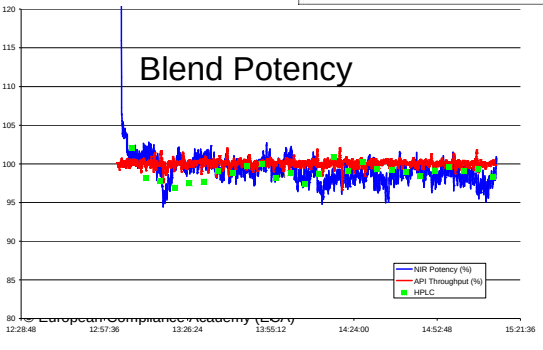
RTRt Strategy

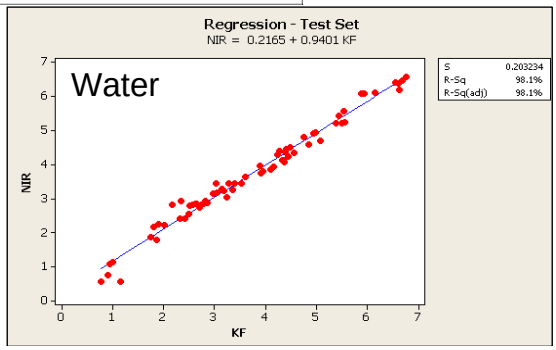
- Continuous blend monitoring forms critical element of release

Current QC Methods for Release	Intended Methods for Release	Step
Appearance (visual)	Appearance (visual)	Tablet
Identity (HPLC)	Identity (Offline NIR)	Tablet
Assay on Tablet (HPLC)	Assay on Blend (Online NIR)	Blend
Content Uniformity (HPLC)	Content Uniformity (Online Blend NIR & Checkmaster)	Tablet
Impurities (HPLC)	Only EOSL - due to high capability for low impurity residues	Tablet
Dissolution (Dissolution Tester)	Disintegration (Disintegration Tester)	Tablet
Water Determination (KF Method)	Water Determination (Offline NIR)	Tablet
Microbiology (on a regular basis)	Microbiology (no changes - on a regular basis)	Tablet

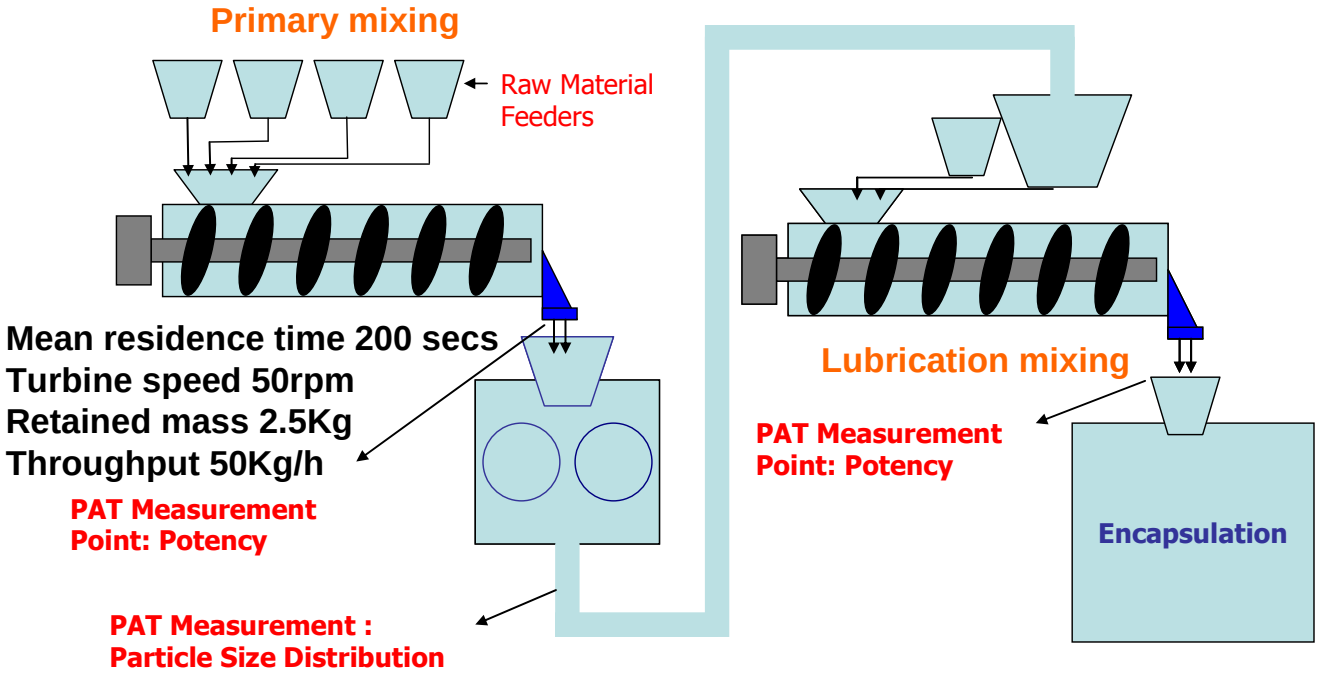
RTRt Methods



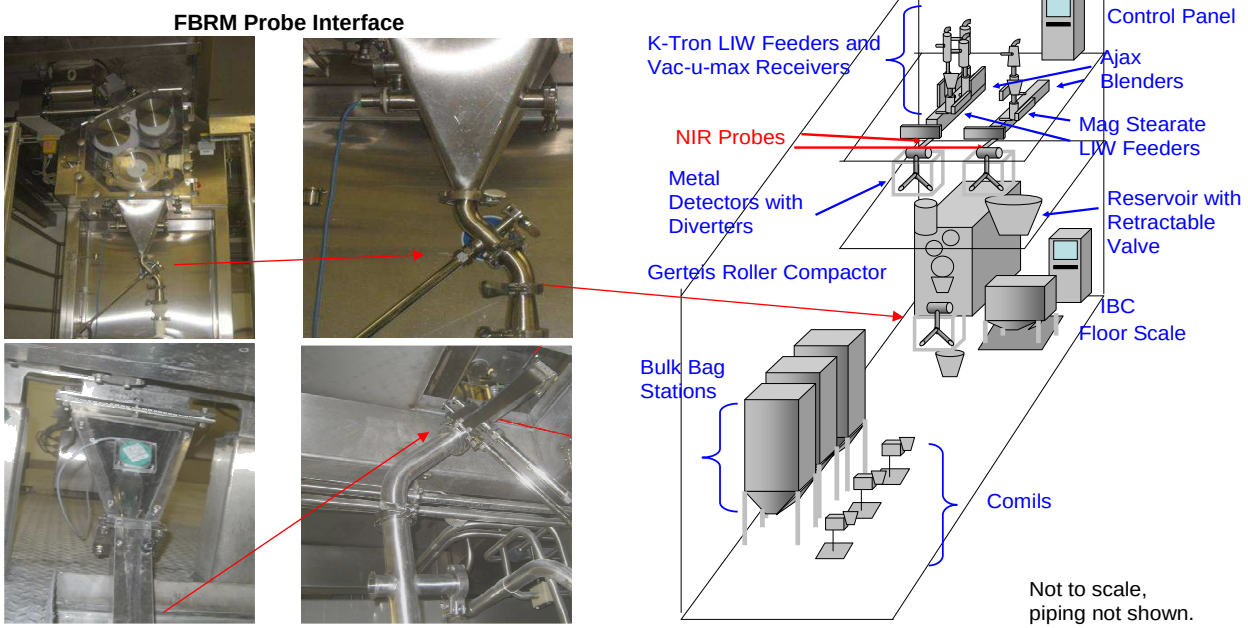




Continuous Dry Granulation

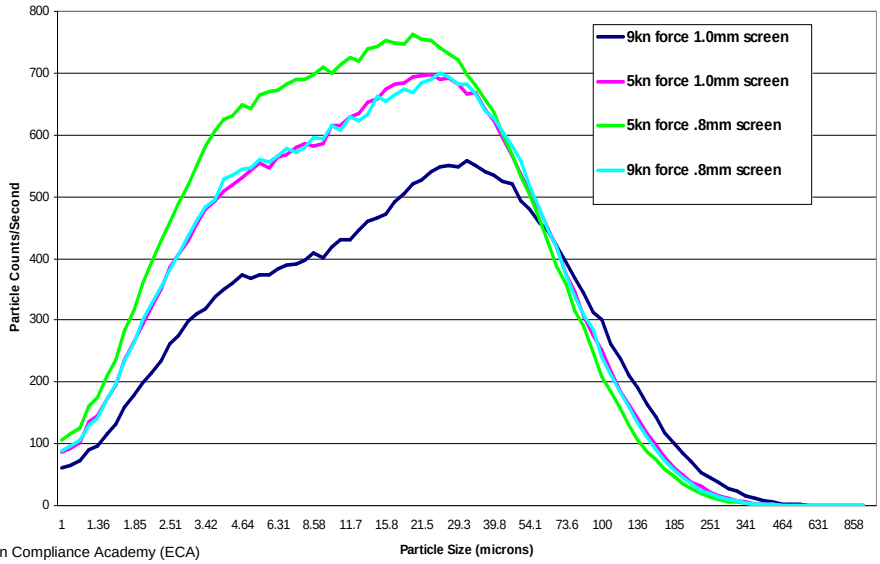


Continuous Dry Granulation



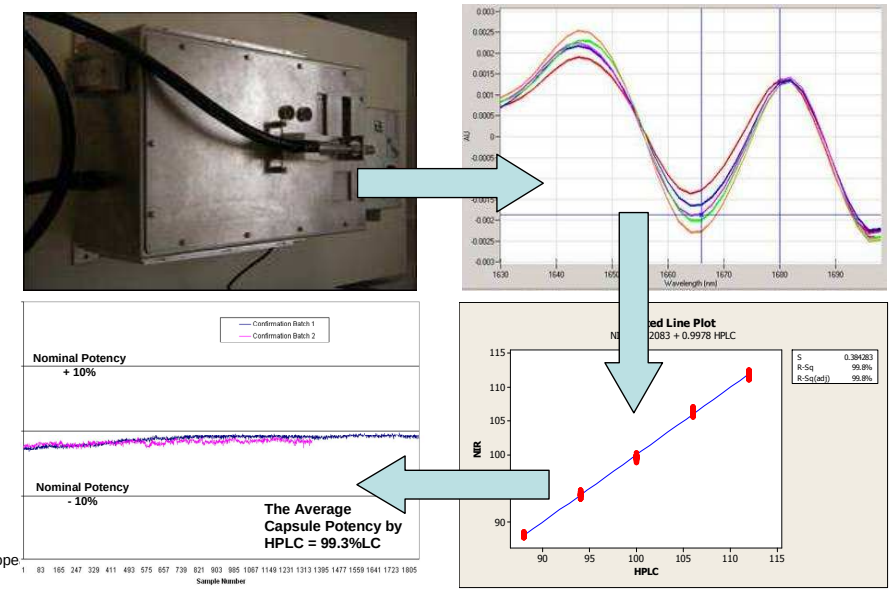
Granule PSD at different processing conditions

- An understanding of the impact of processing conditions
  - Potential for control to ensure consistent output



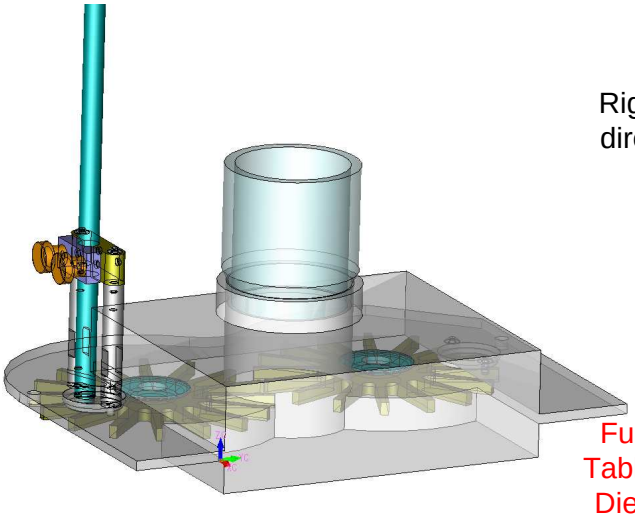
NIR Blend Potency

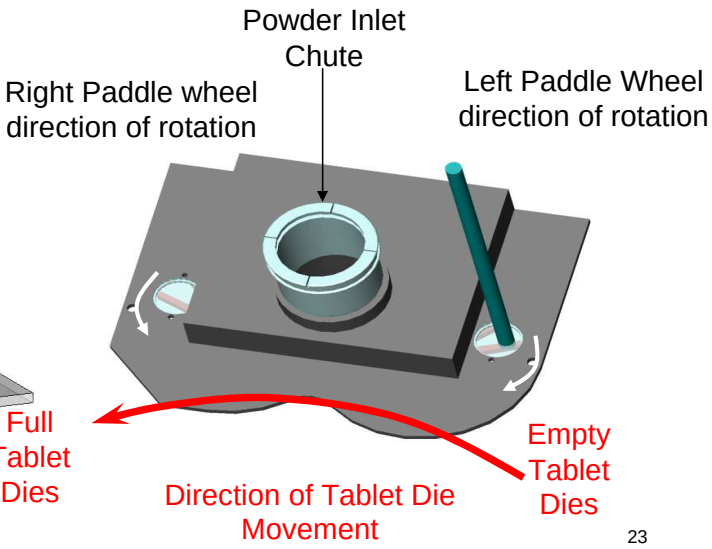
- Method developed using a combination of pre-blend and dynamic batches across the range 88 – 112% LC



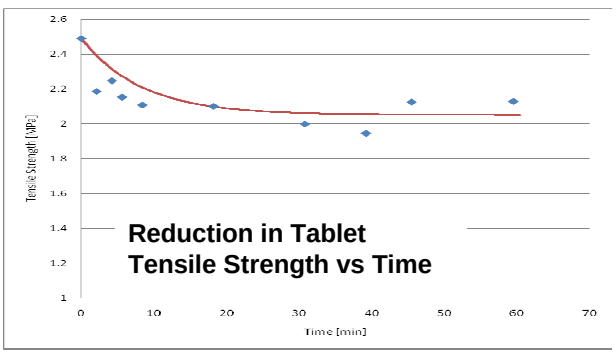
Tablet Feed-frame Monitoring

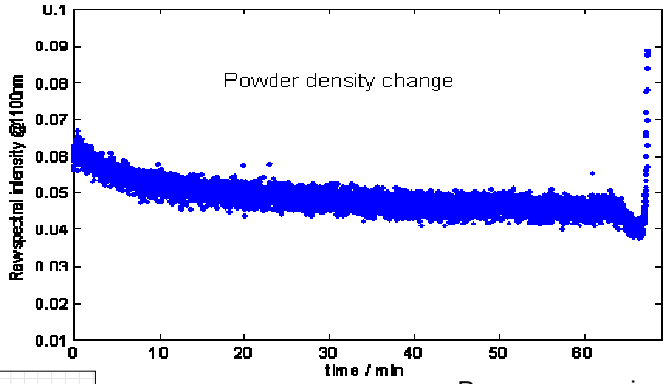
- PAT applied for monitoring blend in the feed-frame / encapsultor
  - Unit operation that is already continuous (semi-continuous)

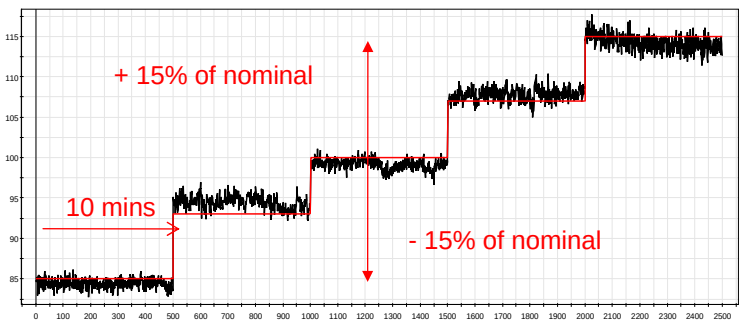


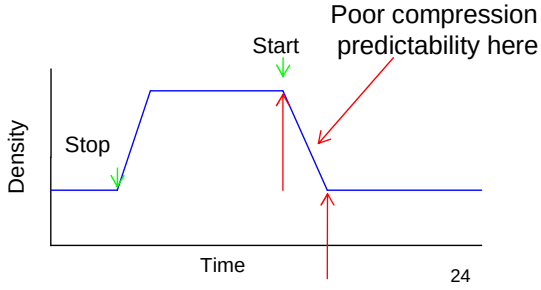


Tablet Feed-frame Monitoring





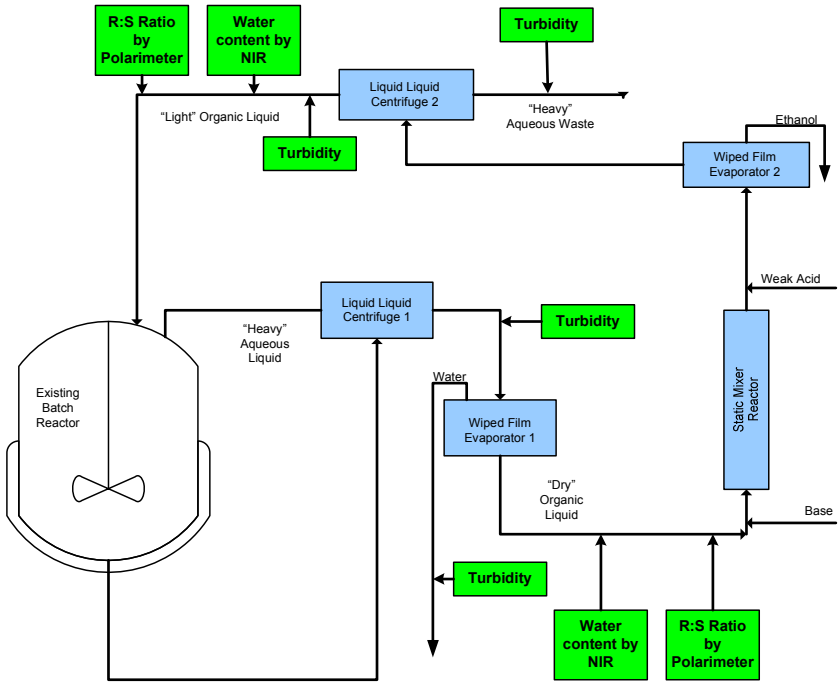




Potential Benefits

- Increased process understanding of blending and compression process
- Understand and monitor feed-frame function
- Ability to detect segregation during powder transfer from IBC to the tablet press
- Applicable to both Batch and Continuous Processes
- Integration of PAT signal and tablet press weight control signal into compression machine logic
  - Advanced Process Control
- Opportunity to implement as part of RTRt paradigm

Continuous API Manufacturing – Hybrid Process



In-line Turbidity

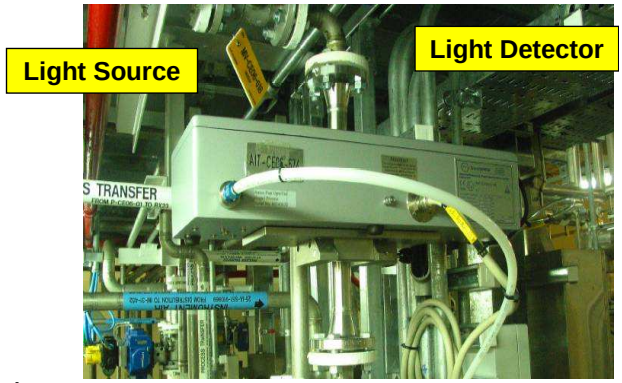
- Used to measure the turbidity of organic phase leaving the separator
  - Control destination of organic stream
- Used to measure the turbidity of the organic and aqueous phase leaving the separator
  - Monitor performance of separator
- Automatic process control

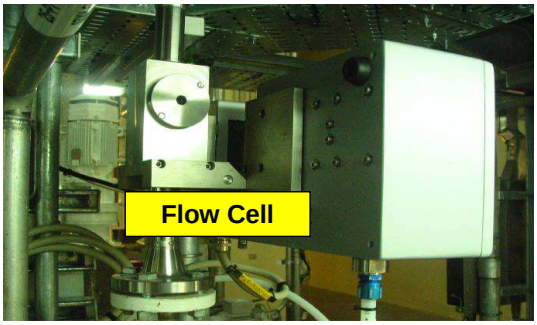
Water and Ethanol Monitoring

- Process downstream sensitive to both water and ethanol content
- Measurement of water and ethanol level using NIR
  - Method qualified and used for control of process

Polarimetry

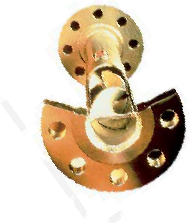
- Assessment of reaction rate
- Measurement of optical rotation of input and output streams
  - Accurately determine feed stream concentration
  - Correlation demonstrated between enantiomeric composition and optical rotation
    - ⇨ Applied for process monitoring

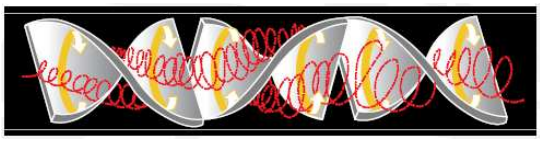




Continuous Liquid Manufacturing

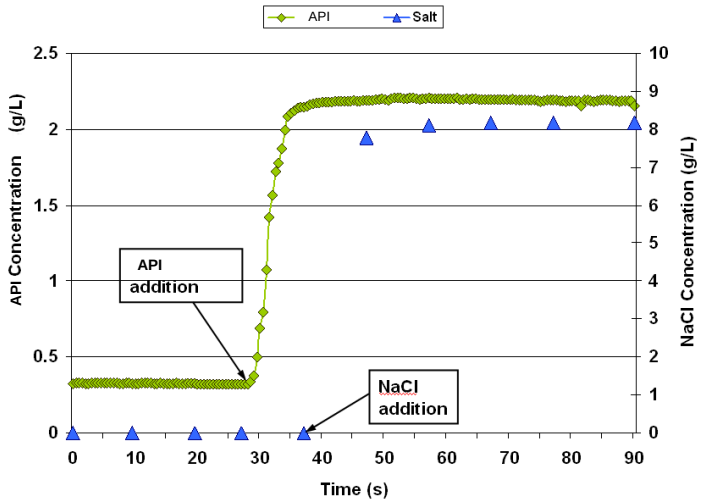
- Applications include
  - Coating applications
  - Solutions/suspensions for aseptic fill/finish
- Production Technology
  - Mixers
    - ⇨ High Shear mixers (Particle size reduction and dissolution)
    - ⇨ Static Mixers (dissolution)
  - Powder dispenser (Loss in weight feeders)
  - May other operations already continuous
    - ⇨ e.g. Filling





PAT for Continuous Liquids Manufacturing

- UV spectroscopy for monitoring API addition/mixing
- Conductivity for monitoring salt addition



Summary

- A number of unit operations are already continuous / semi-continuous by their nature, others require new equipment and investment
- A suitable control and release strategy (often incorporating PAT) must be established
  - Including back-up strategies
- PAT is critical for monitoring and controlling continuous processes
  - Potential for time variant events
- PAT method development must take into account the dynamic nature of the process (e.g. probe design and sampling)
- An enhanced understanding of material characteristics required
  - e.g. flow characteristics and cohesive properties
- Continuous systems must be capable for multiple products / volumes

Acknowledgements

- Process Analytical Sciences Group
- Pfizer Manufacturing Sites
  - PGS Illertisen
  - PGS Caguas
  - PGS Singapore
- PPD Freiburg
- Global Manufacturing Services
  - GAPT
  - TSO
- GCMC
- WRD
- Many other highly engaged colleagues!