PAT and QbD in Formulation Technology Transfer

PAT & QbD Conference,
20th Apr-22

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Lupin Ltd.

Class - C

Topics

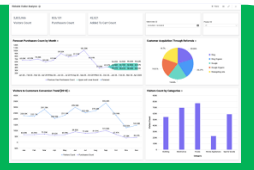
- Pharma 4.0
- Digital Twin in Product Development – case study
- PAT Benefits in Product Transfers
- PAT implementation pathway
- Case studies for
  - NIR for Blend uniformity
  - TMS for Granulation end point
  - DFF for Granulation end point

Pharma 4.0

Transition to Pharma 4.0

	Limited or no automation	Limited or no data Analytics
Current State	Scattered Information	Data only from soft sensors and manual

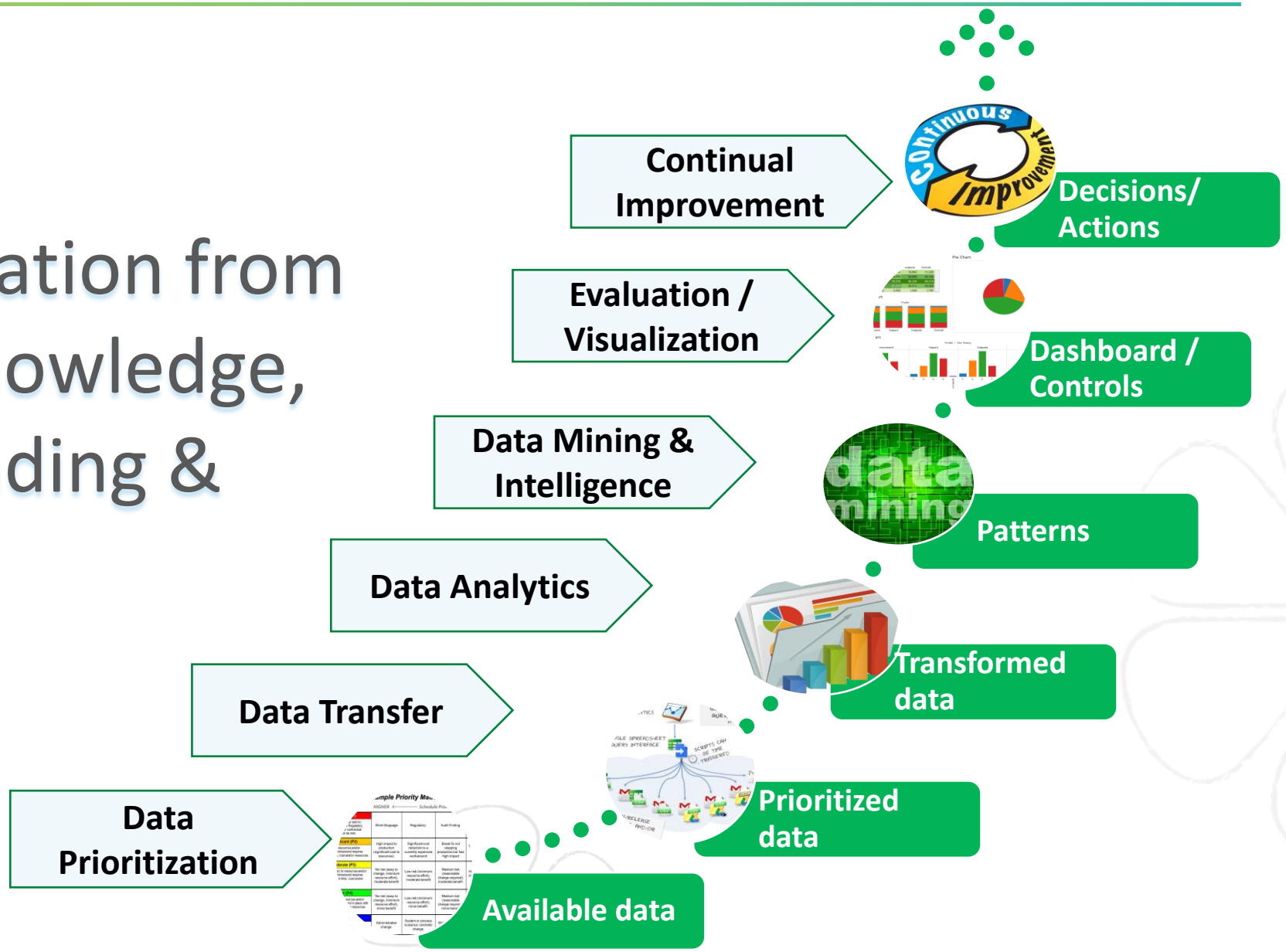
- ✓ No Process automation, Manual APQR
- ✓ End-Product testing & Batch Release
- ✓ Chance for breach of data integrity
- ✓ Preventive maintenance

Future State	Automation 	Quality-Predictive analytics 
	Knowledge Management 	End-to-End Vertical & Horizontal integration 

Pharma 4.0

- ✓ Process automation, Continued Process verification (CPV) and Continuous Process Verification
- ✓ **R**eal **T**ime **R**elease **T**esting & Batch Release
- ✓ Enhanced data integrity
- ✓ Predictive maintenance

Transformation from Data to Knowledge, Understanding & Wisdom



End – to – End Integration

Paper

ERP

MES

DMS file

LIMS HPLC

Pharma 4.0

Maintenance

Logistics

Pharmaceutical Developme

Technology Transfer

Commercial Manufacturin

Product Discontinuation

Across the Product Life cycle

Equipment Data

SCADA

Historian

CAPA

Digital twin in Pharma 4.0

The digital twin technology can be used **to replicate processes in order to collect data to predict how they will perform**. A digital twin is, in essence, a computer program that uses real world data to create simulations that can predict how a product or process will perform.

Computational Fluid Dynamics (CFD) is one of the most popular types of digital twin solution.
Digital twins organize bioprocess development, suggest experimental designs, and manage new knowledge. This drastically cuts process development costs, achieved by combining previous platform knowledge to predict future process results.
Digital twins can save manufacturers millions in a number of aspects, ranging from reducing the number of required process performance qualification (PPQ) runs to setting a robust control strategy.

Reduce **time to market** creating economies of scale and optimum use of resources

Lower costs through reduced waste up to **20% savings**

Ensure high quality of products increase of up to **10% product-margin**

Digital twin in Product development- case study

Digital Twin in Development / Product Design

Service Overview

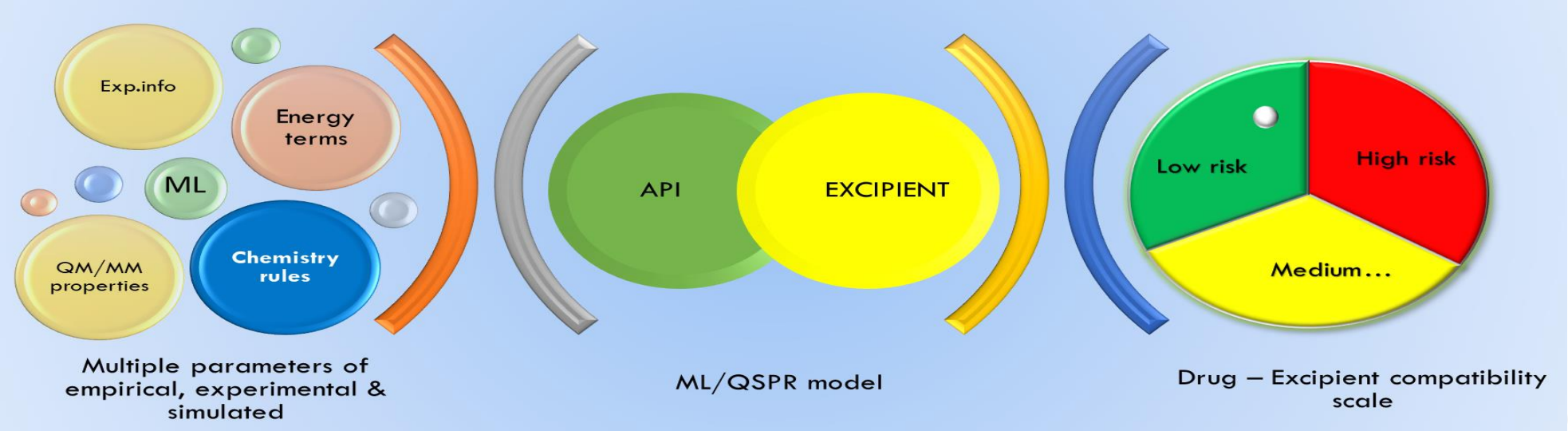
- Physics and Chemistry based modelling to assess the material interaction and material compatibility behavior through simulation modelling
- Solving critical process and formulation challenges occurs during the R&D phase by identifying the late-stage issues at very early stage through the simulation innovation at the interception of science, technology and health systems.

Solution Overview

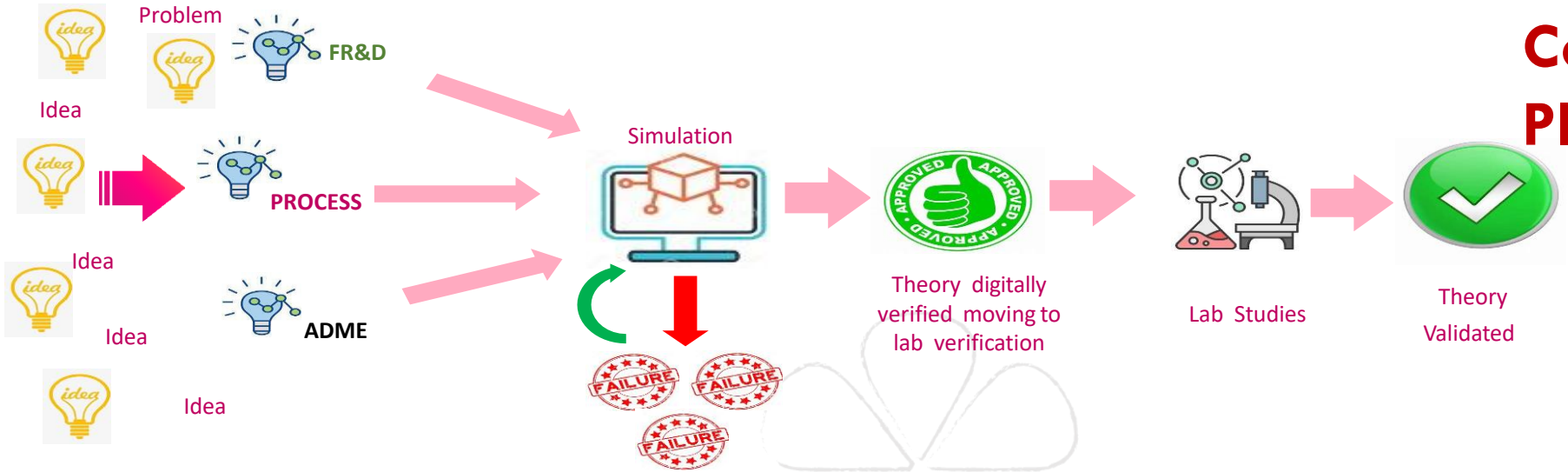
- Chemistry based Insilco modelling and simulation provides deep insights of the material and their compatibility in the formulation. These rationale studies can be established during early stages of drug development by not having actual materials & lab experimentation
- Formulations can be screened and rule out basis can be established before any clinical trials preventing from randomized trails
- Rationale selection of excipients through these simulation models helps give better bioavailability and manufacturability by not affecting the stability of core drug
- During large scale batch manufacturing, issues in every unit operation of tableting can be optimized through simulation studies. Right Processing Conditions and Critical Process Parameters are key which affects manufacturing outcome

Courtesy- PharmaDem

Digital Twin in Development / Product Design



Future R&D : Model driven digital formulation design



In silico Excipient Compatibility - Platform

Courtesy- PharmaDem

Digital Twin in Development / Product Design

- Selection of compatible excipients to API
- Optimisation of excipients concentrations to reduce the incompatibility effect
- Estimation of API behaviour in formulation conditions.
- Change of dose/strength impact on API stability

Courtesy- PharmaDem

Modelling & Simulation – Case Study

Case study on API Excipient compatibility studies using virtual simulation.

1. API-Excipients 50:50% compatibility results
2. API-Formulation dry state compatibility study
3. API-Formulation wet state compatibility study
4. Report document

Problem statement- There is a failure in stability at long term conditions in one strength but not the other. (Both are look alike formulation)

Courtesy- PharmaDem

Modelling & Simulation Case study

Strength	125mg/5ml	250mg/5ml
	mg/5mL	mg/5mL
API	128.125	256.25
Xanthan Gum USNF	6	6
Guar gum USNF	2.25	2.25
Sodium Benzoate USNF	10	10
Sodium Citrate USP	9	9
Citric Acid USP	5	5
Flavour Strawberry IH	25	25
Colloidal Silicon Dioxide USNF	15	15
Sucrose USNF**	3049.625	2921.5

Current Stability data:

125mg/5mL

Initial	
Day 0th	**Day 10th**
101.5 %	99.3 %
18 Month	
Day 0th	**Day 10th**
95.1 %	89.7 %

250mg/5mL

Initial	
Day 0th	**Day 10th**
102.5%	101.2%
18 Month	
Day 0th	**Day 10th**
97.3%	95.3%

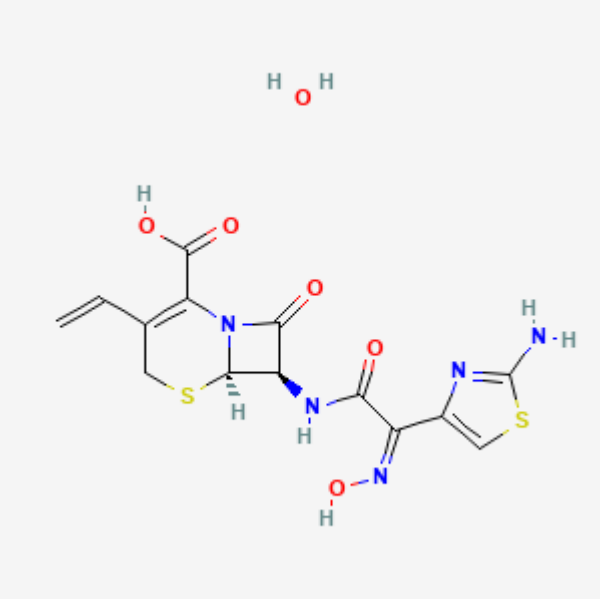
- **89% Assay means there is 11% loss of API in 125mg dose**
- **~5% loss API is there for 250mg dose strength**

- Both formulations are similar except change in sucrose percentage.
- **250mg dose is stable where as 125mg is not stable at 18 months, WHY?**

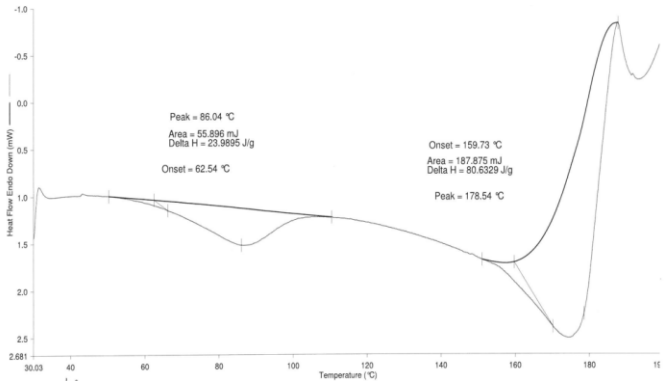
Courtesy- PharmaDem

API Information

Structure



Solid state



ΔH= 80.63 j/g
MP=178.5C

Solubility

pH dependent solubility (mg/mL)

Water	0.6067
0.1N HCl	5.0009
pH 3.0 acetate buffer	1.244
pH 4.5 acetate buffer	3.7131
pH 6.5 phosphate buffer	6.252
pH 7.5 phosphate buffer	16.3365

Known excipients compatibility:

Compatibility study data not available.

Courtesy- PharmaDem

Modelling & Simulation – Case study

API-Excipient 50:50% Compatibility Study @ 25C

SUBSTRATE	SCORE	DESCRIPTION
Sodium citrate dihydrate		Highly incompatible
Sodium benzoate		Highly incompatible
Guar gum		Highly incompatible
Xanthum gum		Incompatible
Sucrose		Incompatible
Silicon dioxide		Compatible
API		Reference
Strawberry flavour		Compatible
Citric acid		Compatible

- *Sucrose and Xanthum gum are found to be Incompatible excipients. Both of them together making up to 92% in formulations*

API-Formulation Dry State Compatibility Study @ 25C

Substrate	SCORE	DESCRIPTION
Citric acid		Highly incompatible
Sodium benzoate		Highly incompatible
API		Reference
Sodium citrate dihydrate		Incompatible
Guar gum		
Sucrose		
Xanthum gum		Compatible
Silicon dioxide		Compatible
Strawberry flavour		Compatible

- *Sucrose effect is diluted to some extent.*
- *Still Sucrose found to be non-compatible with API even in formulation, which is making ~93% mass fraction in 125mg/ml formulation*
- *Change in API concentration, inter excipient interactions could bring the change*

Courtesy- PharmaDem

Modelling & Simulation – Case study

API-Formulation wet state Compatibility Study @ 25C

SUBSTRATE	SCORE	DESCRIPTION
Citric acid		Highly incompatible
Sodium benzoate		Highly incompatible
Water		Highly incompatible
Sodium citrate dihydrate		Incompatible
API		Reference
Guar gum		
Sucrose		
Xanthum gum		Compatible
Silicon dioxide		Compatible
Strawberry Flavour		Compatible

- *Sucrose effect is further diluted when added 50ml of water.*
- *Still Sucrose found to be in yellow zone with API in formulation*
- *Which means weak interactions are persisting between API- and sucrose in presence of water.*

Courtesy- PharmaDem

Modelling & Simulation – Case study

API-Formulation Dry state @ 25C (250 mg)

SUBSTRATE	SCORE	DESCRIPTION
Citric acid		Highly incompatible
Sodium benzoate		Highly incompatible
Sodium citrate dihydrate		Incompatible
API		Incompatible
Guar gum		
Xanthum_gum		
Sucrose		
Silicon dioxide		Compatible
Strawberry Flavour		Compatible

- *Reduction of sucrose concentration has diluted in compatibility with API*
- *Still Sucrose found to be in yellow zone with API in formulation*
- *Weak interactions are persisting between API- and sucrose in presence of water.*

API-Formulation wet State @ 25C (250 mg)

SUBSTRATE	SCORE	DESCRIPTION
Citric acid		Highly incompatible
Sodium benzoate		Highly incompatible
Water		Incompatible
Sodium citrate dihydrate		Incompatible
API		Incompatible
Guar gum		
Xanthum gum		
Sucrose		Compatible
Silicon dioxide		Compatible
Strawberry Flavour		Compatible

- *Sucrose effect is diluted to some extent.*
- *Still Sucrose found to be non-compatible with API even in formulation, which is making ~93% mass fraction in 125mg/ml formulation*
- *Change in API concentration, inter excipient interactions could bring the change*

Courtesy- PharmaDem

Learnings

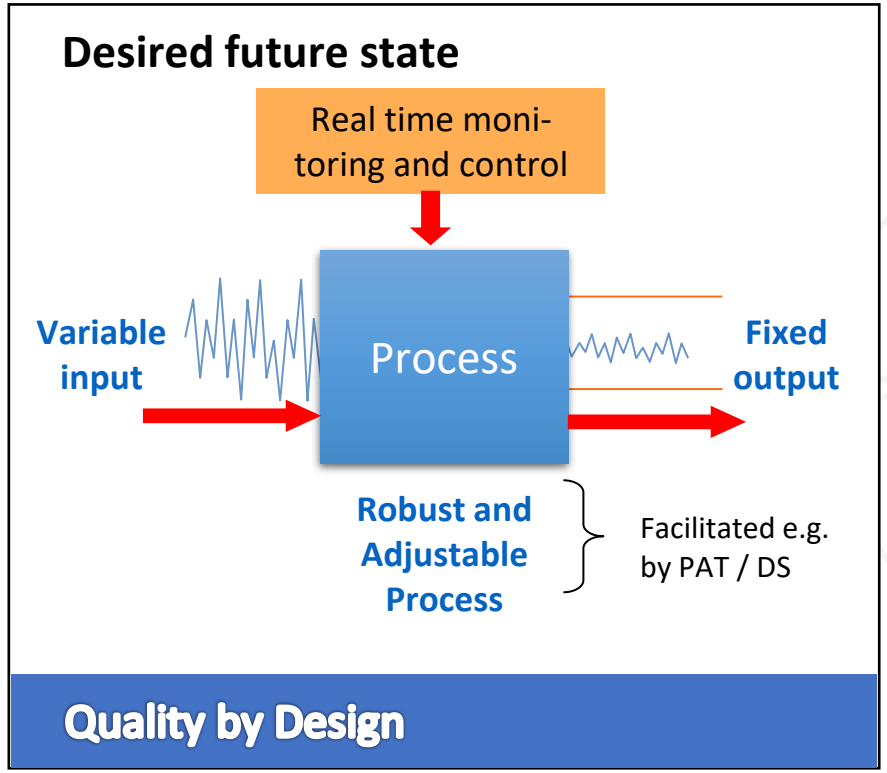
- Many incompatible excipients are used in formulations.
- API alone is very stable in gas phase or in water
- ~90% used Sucrose, 6% used Xantham gum are incompatible with API
- 125 mg has 93% sucrose which is leading to failure in stability
- Where as 250mg dose has reduced 89% of sucrose which diluted the impact of sucrose by 4% leading to reasonable stability at 250mg. But may not stay long for the stability as the difference is minimal.
- Additions of new excipients could improve the stability the API significantly.

Courtesy- PharmaDem

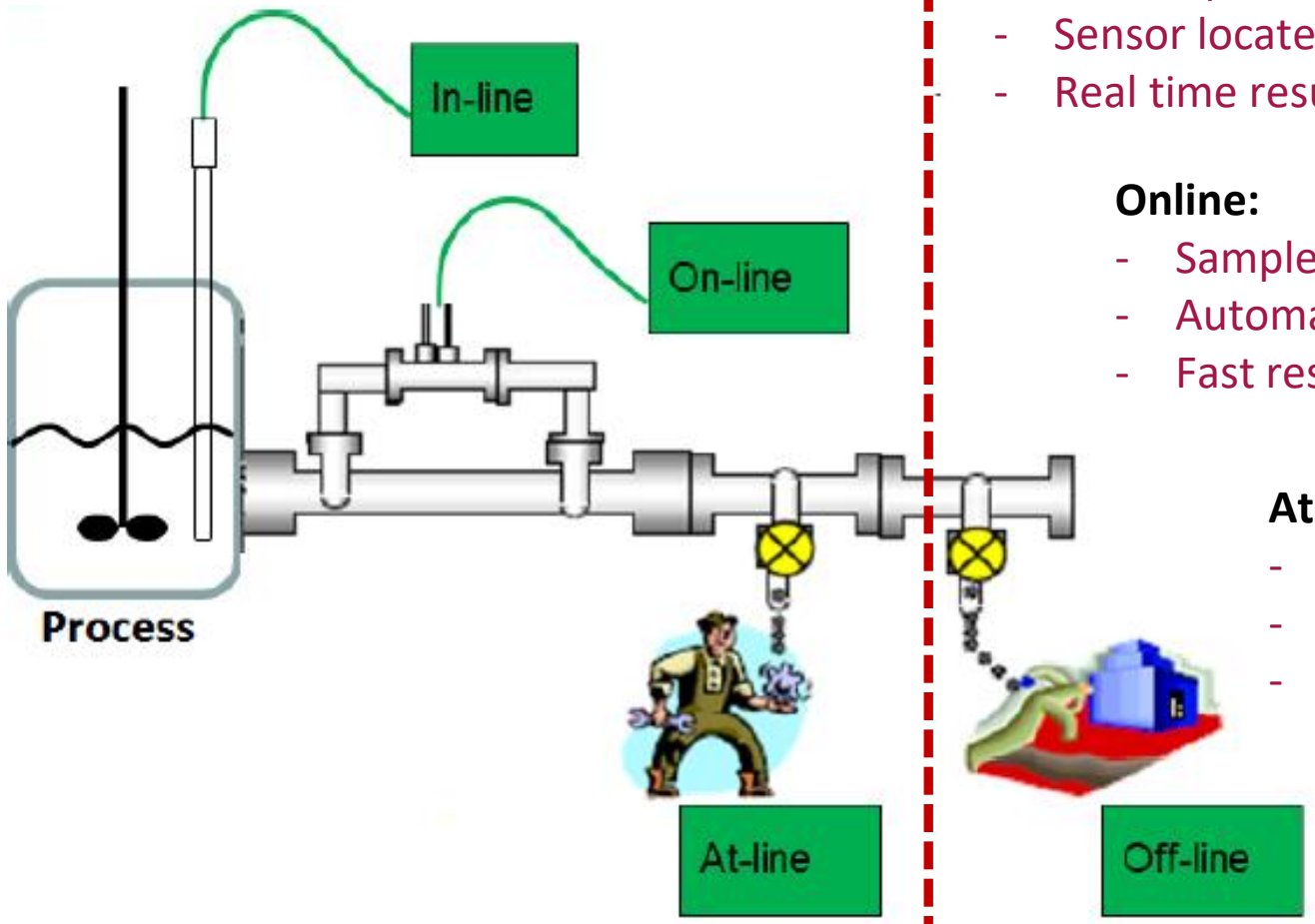
PAT benefits in Product transfers

Use of PAT to Achieve RFT Benefits

- Ability to accommodate expected range of variability in input materials and processes
- Allow process flexibility with the end in mind (Real time data evaluation)
  - Real time data with feed back / feed forward ability to adjust the processes
  - Rapid QbD development with minimal experiment
  - Robust scale up/ tech transfer
- Process trending over time / batches to identify subtle changes
- Net reduction in failure rates.
- Improve assurance of quality & compliance
- Reduce / Eliminate deviations
- Reduce costs (reworks, resample, retesting, etc)



Measurement types



Inline:
- No Sample collection required
- Sensor located within the equipment
- Real time results, fast response time

Online:
- Sample collection via bypass line
- Automated sample preparation / Analysis
- Fast response time & high frequency of analysis

PAT

At line:
- Manual Sample collection during operation
- Automated Analysis at shop floor
- Rapid results & medium frequency of analysis

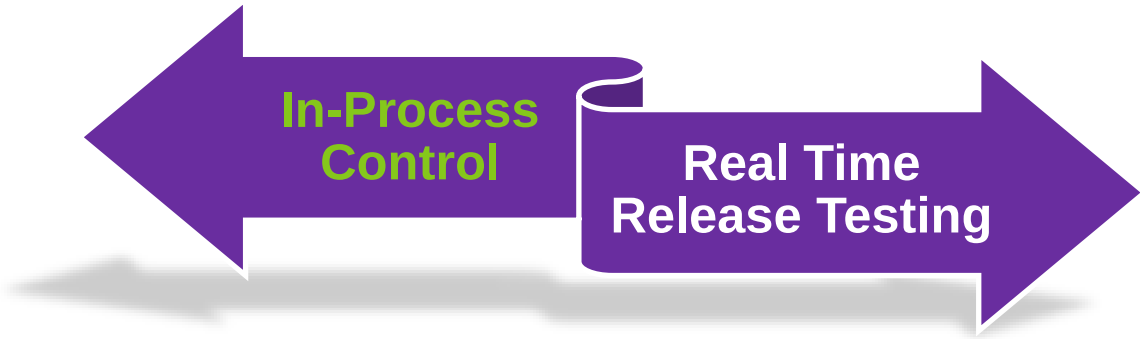
Offline:
- Manual Sample collection during operation
- Transport of sample to Laboratory
- Slow response time and low frequency of analysis

Manufacturing shop floor

QC Lab

PAT for IPC's & RTRT

•**Both IPCs and RTRT are based on PAT measurements of in-process materials**



•In-Process Control Measurements

- Analysis of in-process materials to assess material against in-process action and warning limits for conformance /non-conformance
  - Results can result in action to adjust the process
  - Non-conforming results initiate segregation of the in-process material from the process. OOS procedures are then followed.

•RTRT

- Analysis of up-stream in-process materials to assess the **batch** as a whole against the release specifications for end product
- Only material passing all IPCs are included in the batch and the batch analysis for release

PAT implementation Pathway

PAT Progression in Product Lifecycle

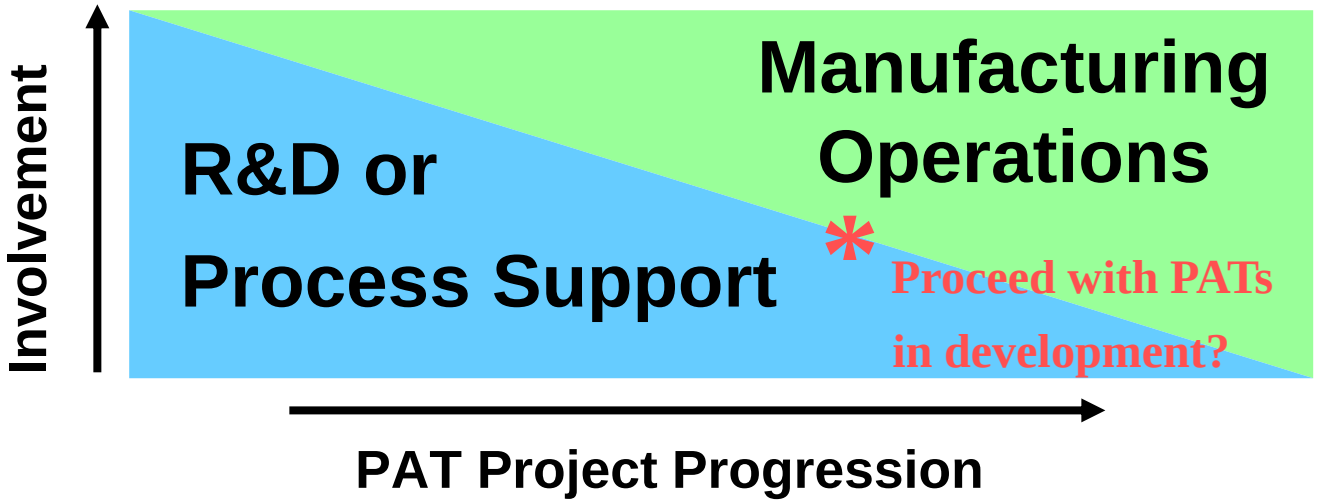
"Early PAT"

- Used to determine CPP's

"Late PAT"

- Used to control the process
- Requires formal validation

RFT



Improved quality.

Improved safety.

Cost savings.

Process Control

Process Knowledge

Well Controlled Process

Fundamental Goals

PAT system- Product qualification

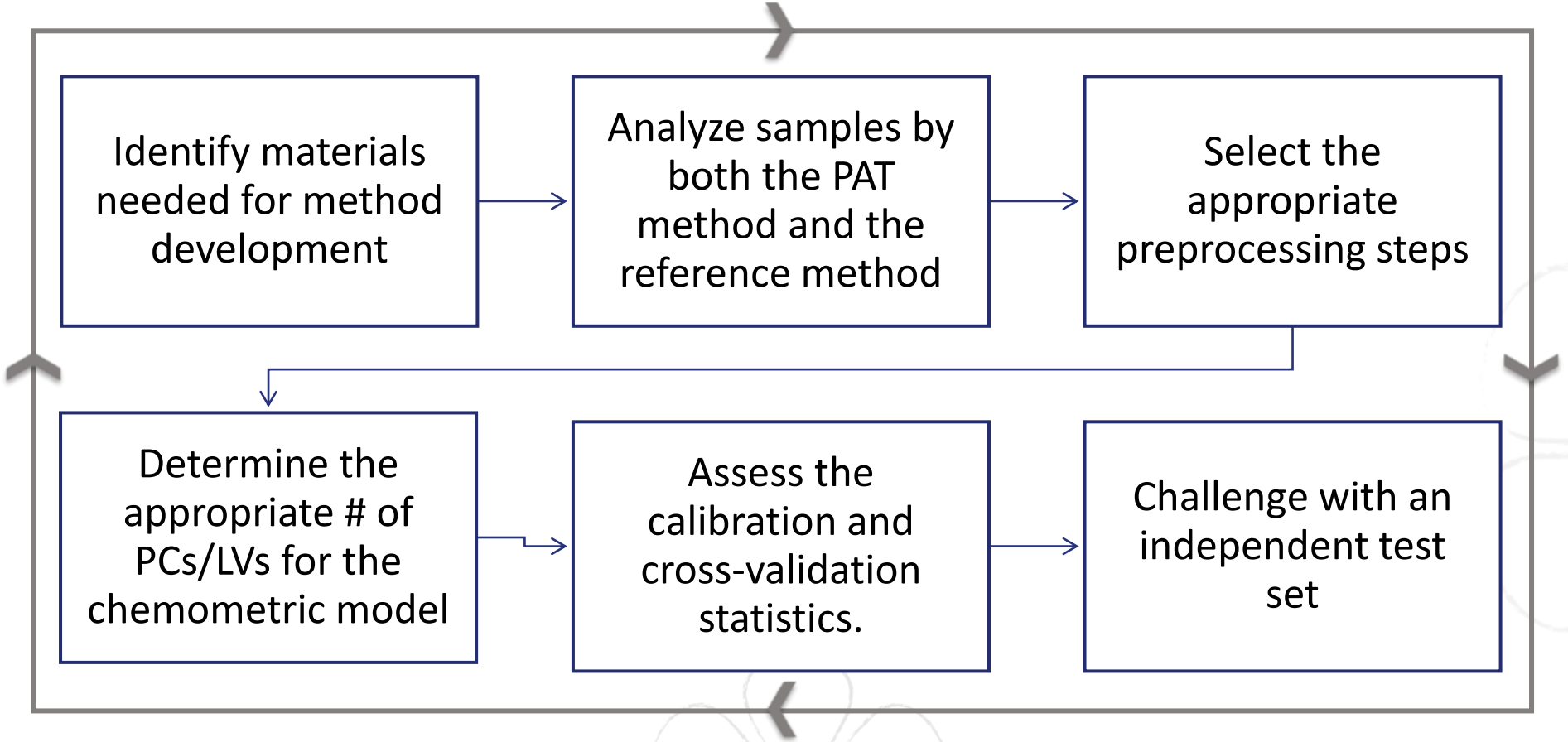
- PAT System Qualification and Method Validation should be based on intended use of data.

Three Levels	Quality Impact
1. Development or Proof of Concept	No Impact
2. Information Only	Indirect Impact
3. Release Decisions	Direct Impact

- Validation or Commissioning and Qualification must conform to applicable:
  - Corporate Quality Standards
  - Site Procedures

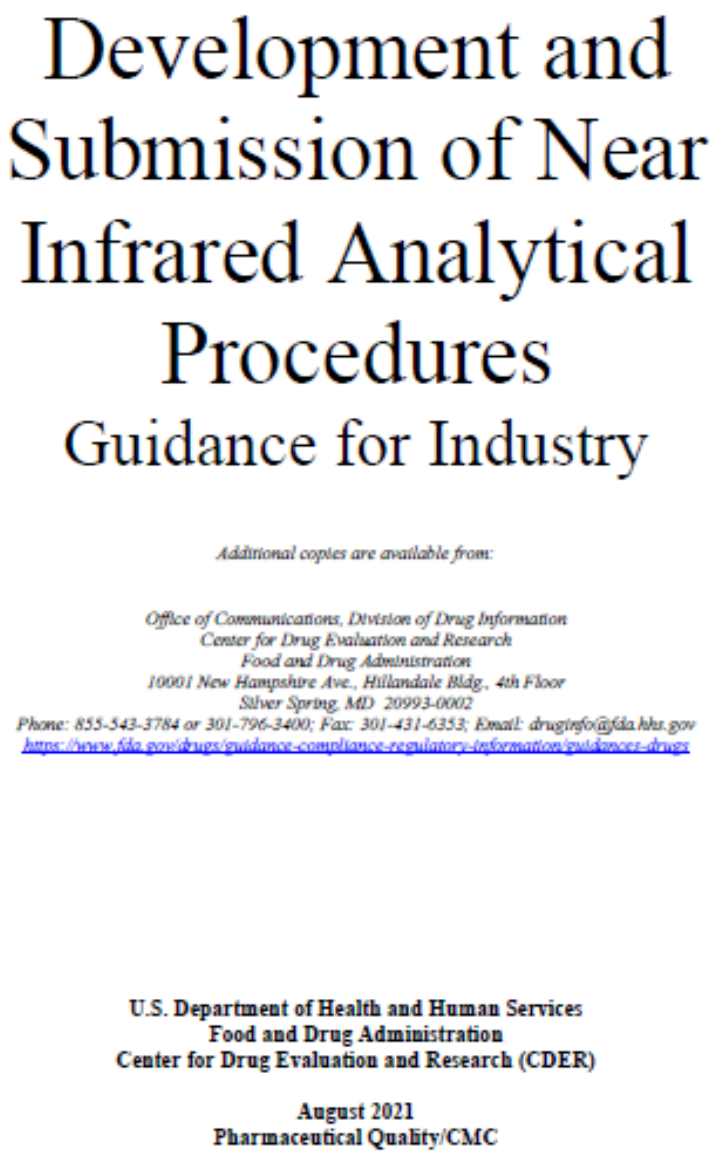
PAT system- Product qualification

1. Define data acquisition parameters that ensure high quality data collection across manufacturing process range
2. Develop the data processing method



Iterative Process

FDA Guidance - NIR



Development and Submission of Near Infrared Analytical Procedures

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2021
Pharmaceutical Quality/CMC

Final Guidance

Minimum Data Requirement for *"Prior Approval Supplement":*

1. Method Validation: Covering accuracy, precision, specificity, linearity, range, detection and quantitation limits, and robustness.
2. Method Equivalency: Comparative Data of Traditional Blend Uniformity Analysis Vs NIR End Point Criteria.
3. Method Development Report
4. Analytical Test Procedure /STP
5. Qualification and Requalification Plan

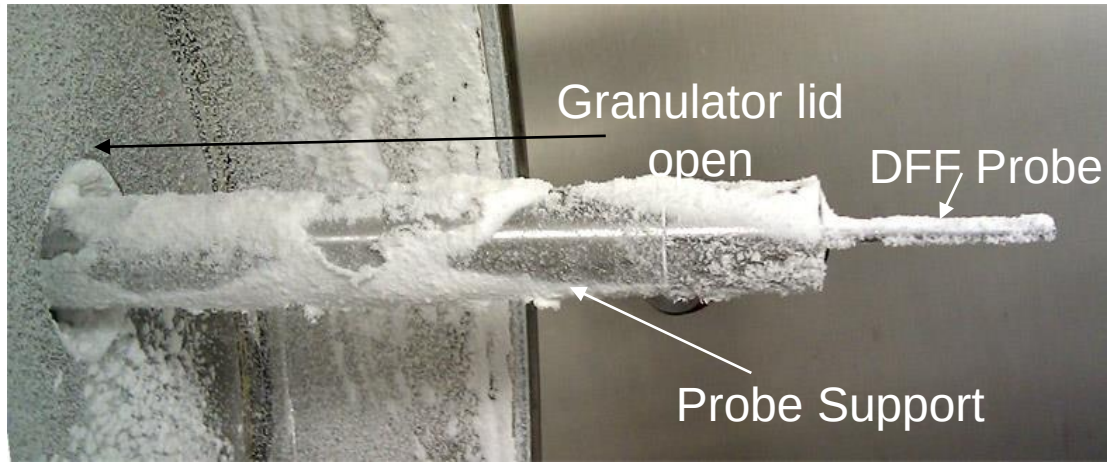
FDA may inspect the facility before approval of first supplemental application.

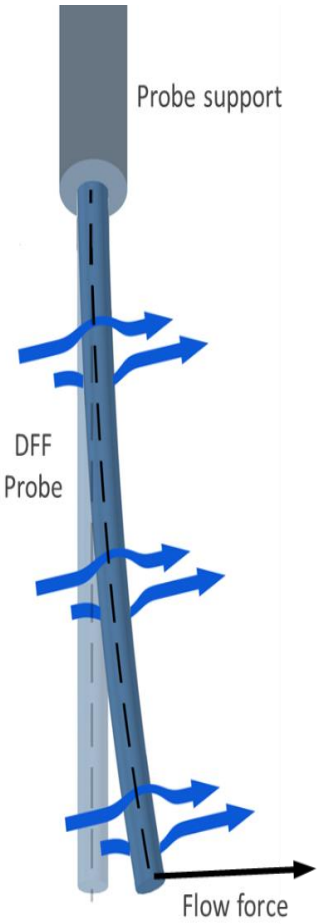
LUPIN

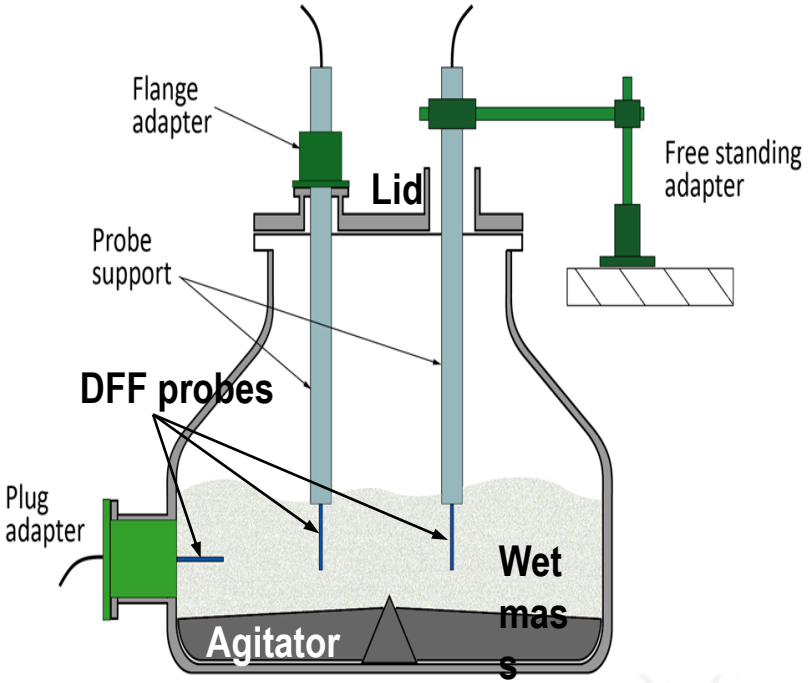
Case studies

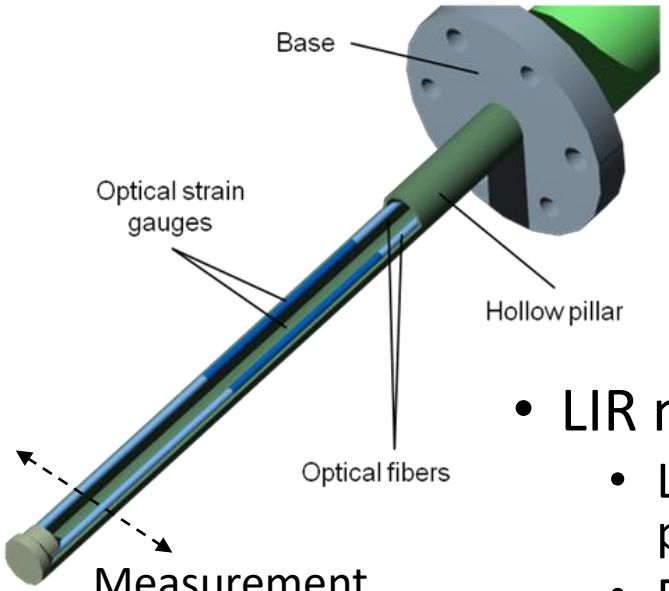
- DFF (Drag Force Flow Sensor)
- NIR (Near Infra Red)
- TMS (Torque Monitoring System)

DFF Sensor - POC









- LIR measures
  - Local Flow Force - FPM – 500 times per second
  - Flow uniformity (tackiness) – PCF
  - Local Temperature

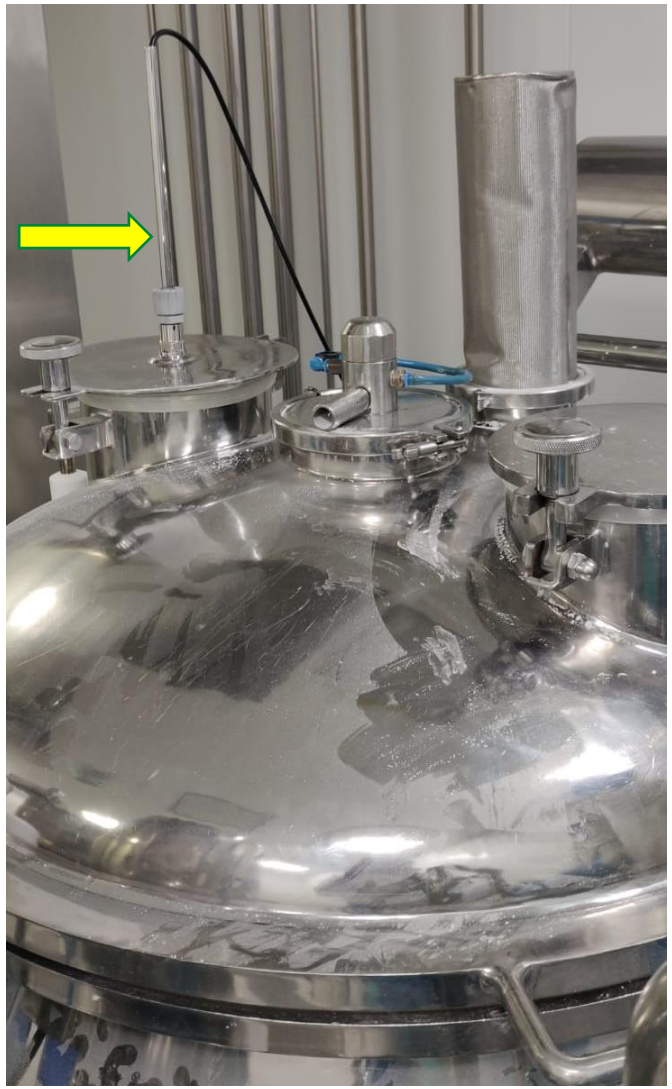
A thin (1-4 mm) cylindrical pin

No moving parts

Minute pin deflection measured

Deflection is related to drag (shear) force

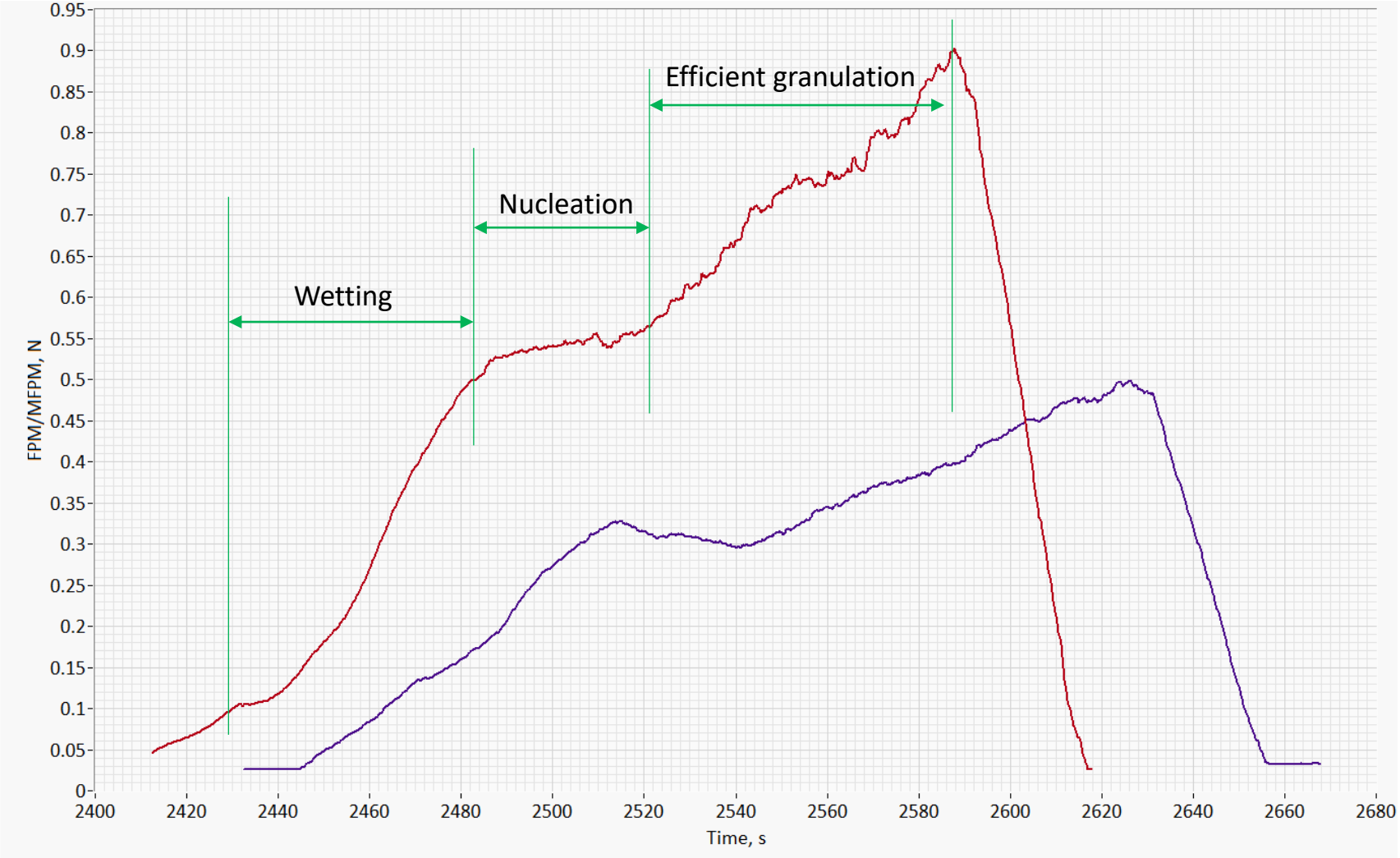
DFF Sensor - POC



Lupin Demo 12/3/22 probe installation- Nagpur

Equipment: 400 Ltrs RMG

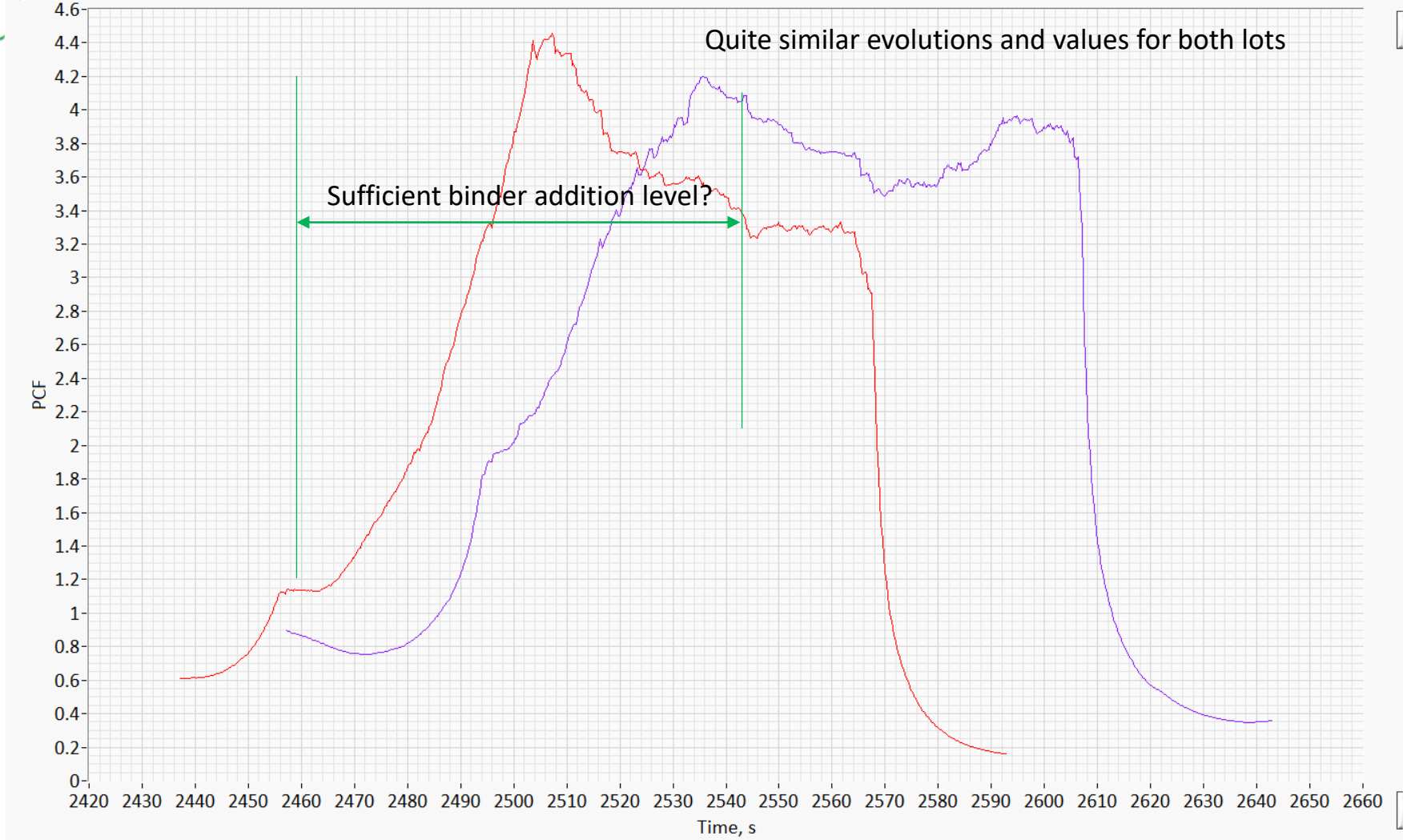
DFF Sensor - POC



Both evolutions are very similar to each other. Granulation stages are identifiable.

MFPM (array size 100), binder addition: Lot 1 (red) and Lot 2 (violet)

DFF Sensor - POC



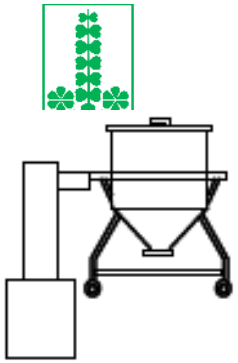
Both evolutions are very similar to each other. Granulation stages are identifiable.

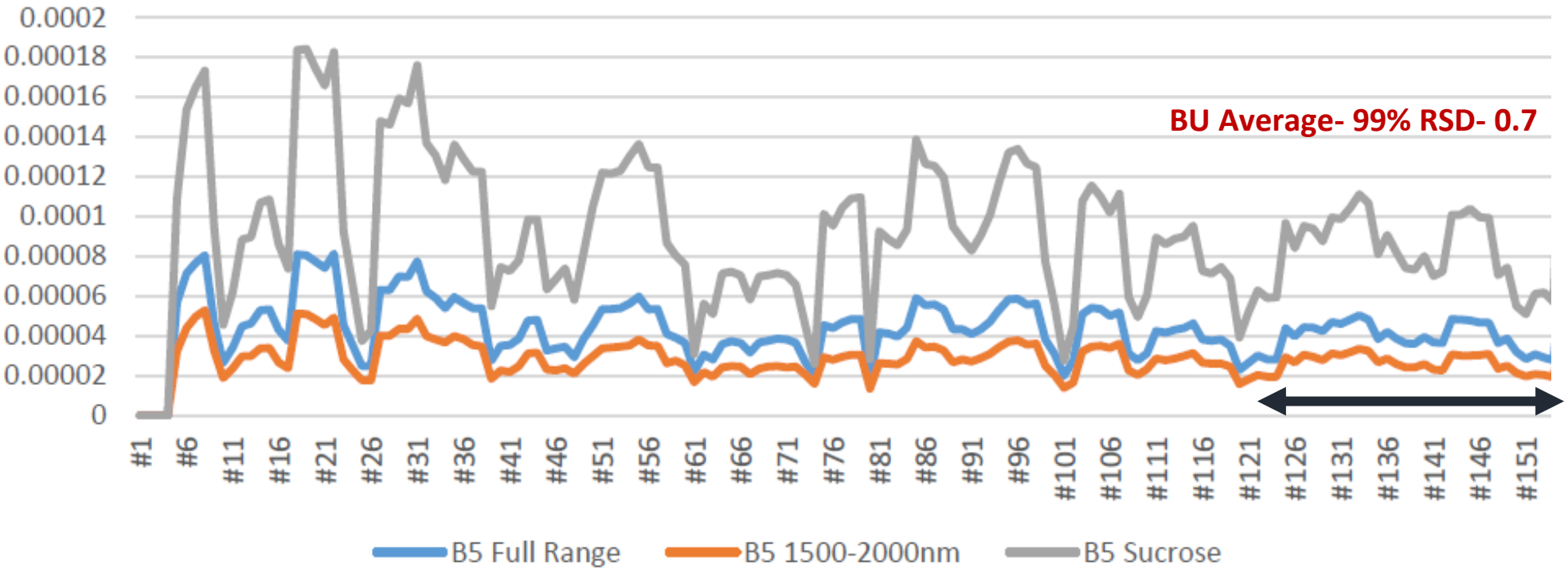
PCF (array size 300), binder addition: Lot 1 (red) and Lot 2 (violet)

Conclusions

- LIR adequately described all four stages of the process as well as idle times
- Granulation process during binder addition was found to consist of reliably identifiable sub-stages almost identical for two lots
- Kneading stages for both lots were found to be extremely short (several revolutions) that lead to the conclusion that the wet mass has densified during the long delay between binder addition and kneading stages, and the kneading stage was limited to heating of the motor at high load
- Based on the process fingerprint (FPM+PCF), recommendations about dry powder mixing cycle length and amount of binder addition were given
- During overall process monitoring, difference in total process timing was detected, as well as startup and shutoff vessel motion

NIR – Blend Uniformity

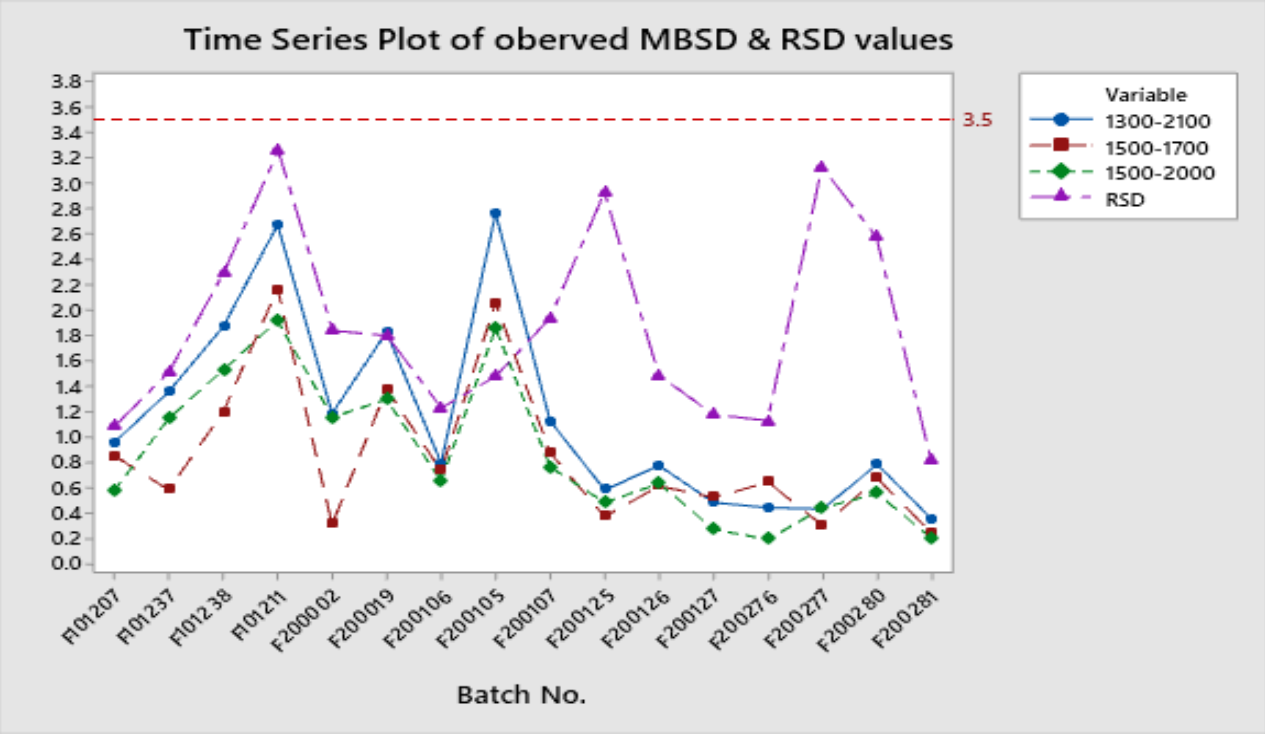


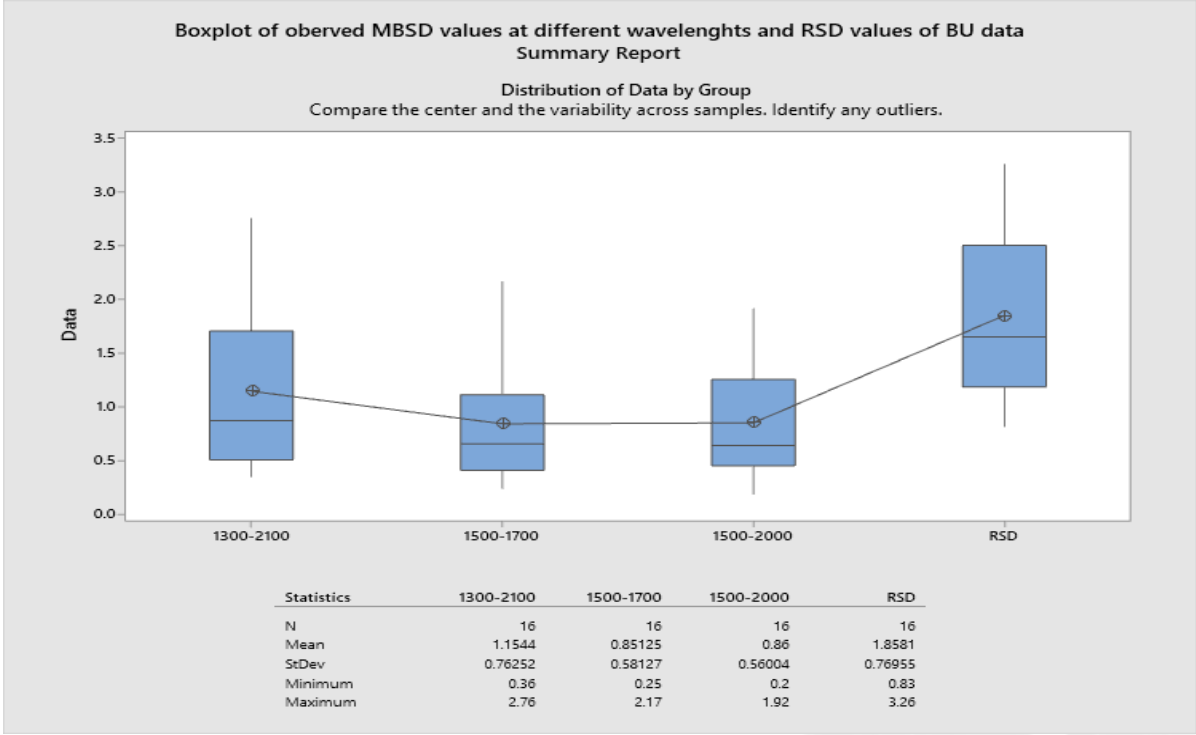


MBSD range for last 15 rotations

	B5 Full Range	B5 1500-2000nm	B5 Sucrose
Min	2.77	1.92	5.08
Max	4.84	3.08	10.37
Delta	2.07	1.16	5.29

NIR – Blend Uniformity





Inference:

RSD values obtained by chemical analysis are always at higher side as compared with MBSD values obtained though NIR analysis except in batch no. F200105.

Inference:

Variability (by Std. Deviation) represented by observed MBSD values at wavelength 1300-2100 are matching with the RSD values obtained by chemical analysis.

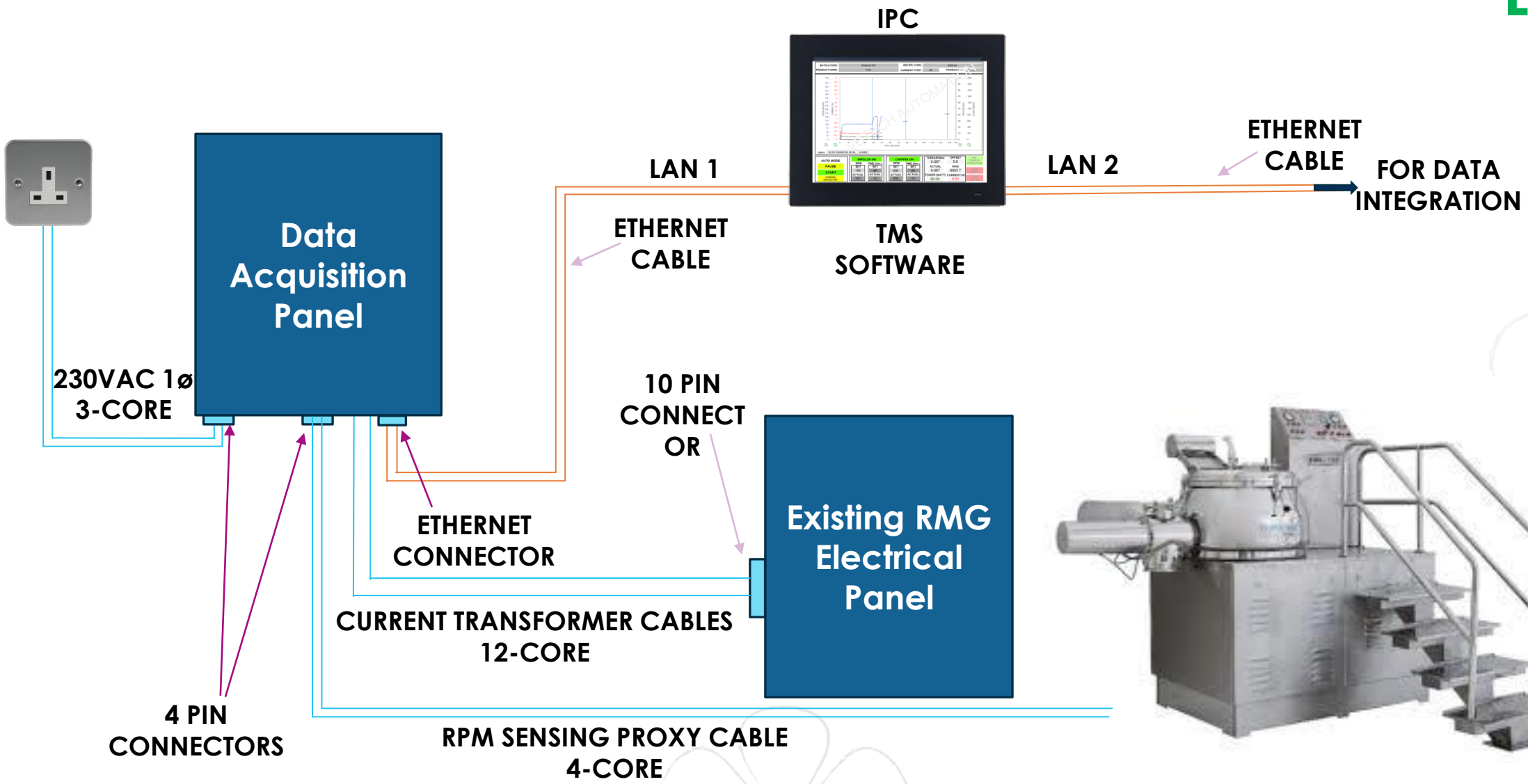
❖ PAT NIR Recommendation for RA filing -

Based upon the data NIR study can be implemented in future commercial batches of the said product for monitoring of blend uniformity instead of blend uniformity testing by chemical analysis after required regulatory filing and approval.

Following recommendation is provided for future commercial batches using NIR spectrum.

- NIR study to be performed with wavelength range of 1300-2100nm.
- Batches where observed MBSD values is less than 2.8 to be considered uniform and to be proceed for next stage without chemical testing.
- Blend uniformity sampling and testing to be performed in the batches where observed MBSD value is more than 2.8 and batches to be further processed for powder filling stage after getting the blend uniformity results within the limit as per approved in-process specification.

TMS - Architecture



Direct Torque Measurement

In this method it requires installation of strain gauges on the coupling between the motor and impeller shaft. Since the shaft is rotating, a device called a slip ring is used to transmit the signal to the stationary data acquisition system.

Calculated Torque Measurement

In this method it calculate torque from two variable parameters in real time mode. **Impeller RPM** as well as **Motor active power consumption**. Below is the formula applicable to measure the torque.

$$\text{Torque (Nm)} = \frac{60 \times \text{Power (kW)}}{2\pi \times \text{Speed (Rpm)}}$$

In Above formula…

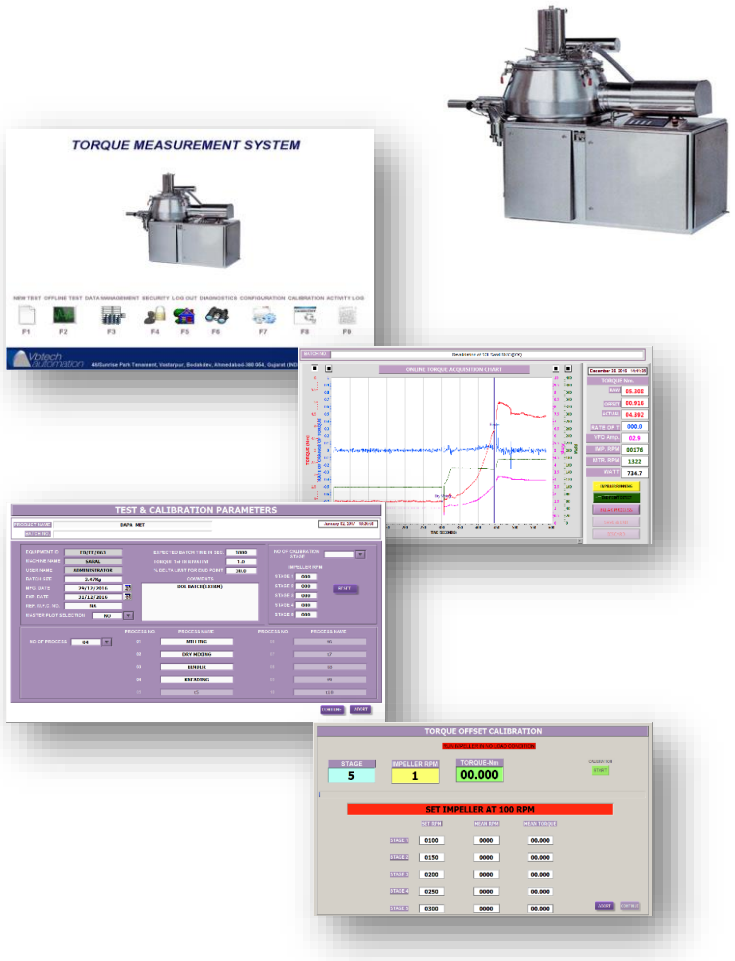
@ RPM measured by RPM sensor Mounted in front of Impeller shaft

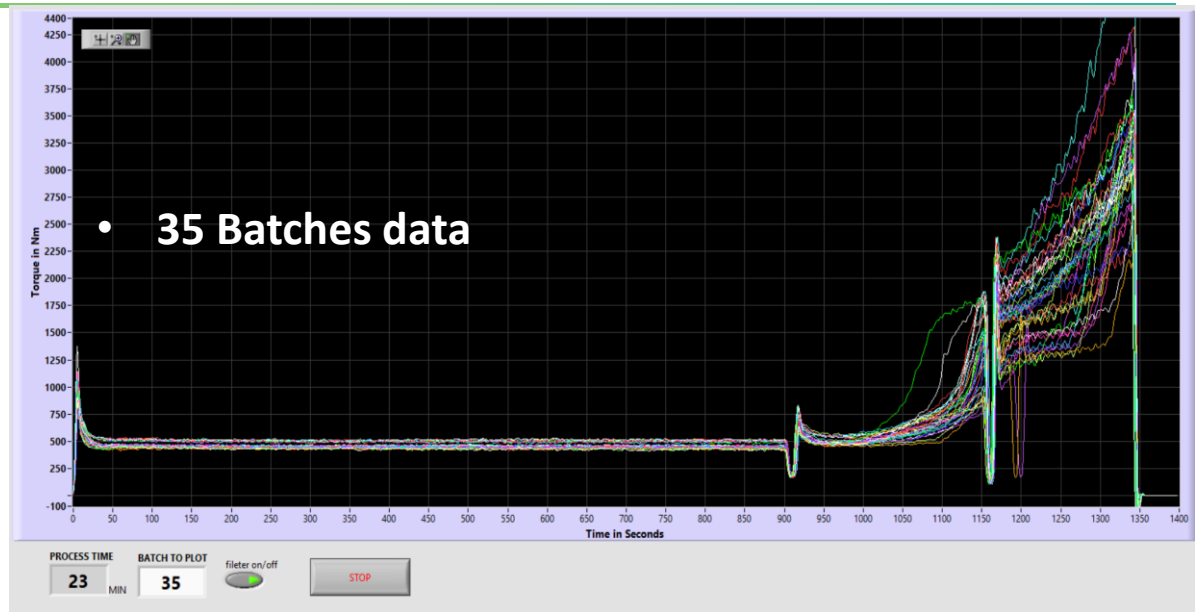
@ Active Power measured by Power transducer **(Active power is a product of current, voltage, and the power factor)**

@ 60 is the time constant

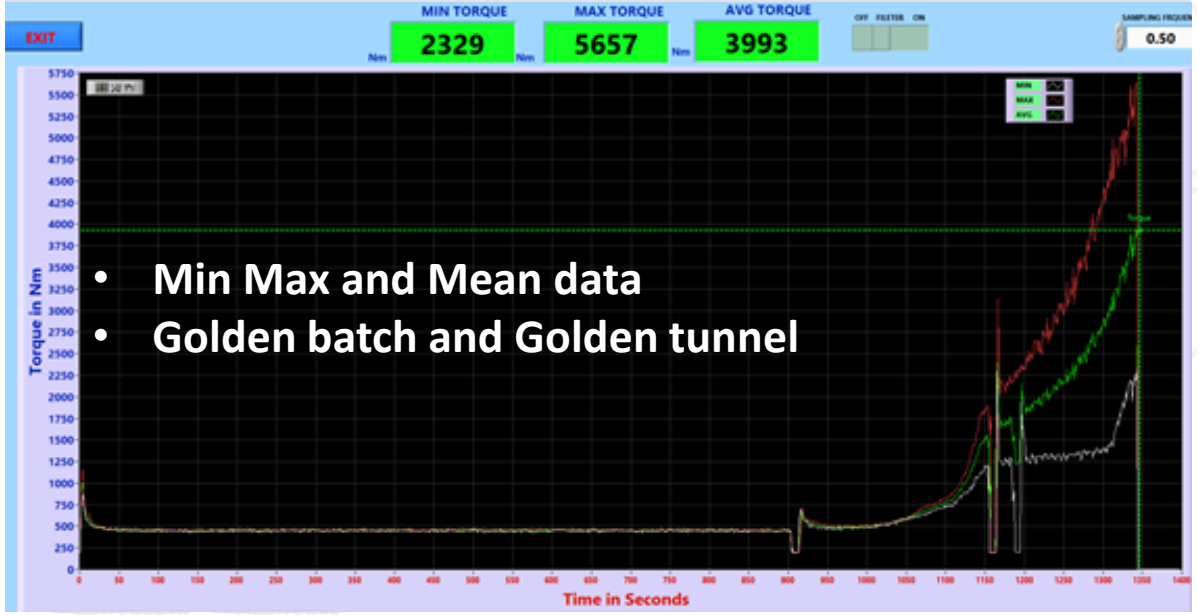
@ 2π is the radius constant

Torque Measurement System (TMS) Implementation





- 35 Batches data



- Min Max and Mean data
- Golden batch and Golden tunnel

THANK YOU

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