Application to Process Analytical Technologies (PAT) implementation in GSK

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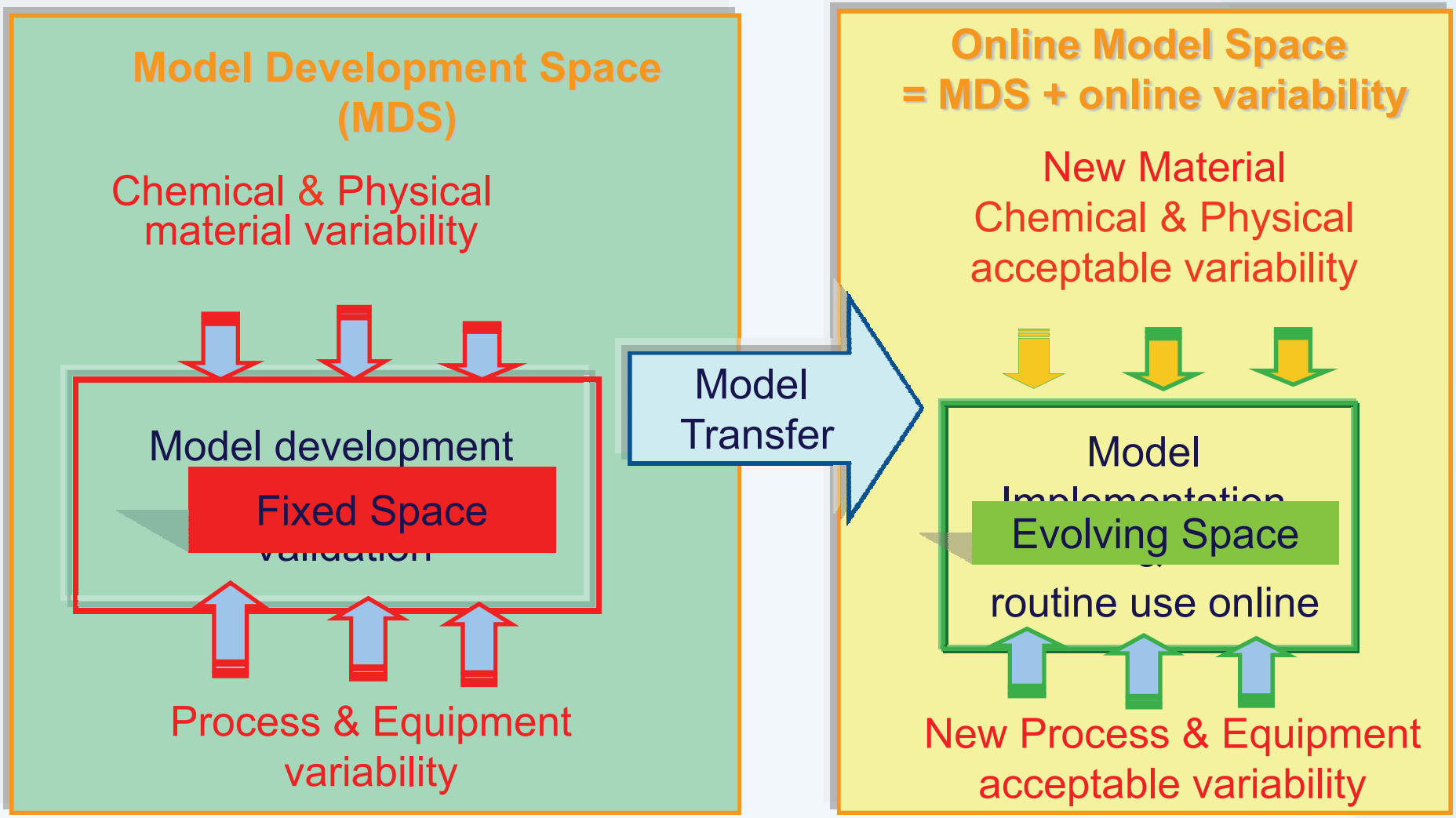
Outline

- Model transfer for Process Analytical Technologies (PAT) applications
  - Quality by Design (QbD) applications
  - Relevant FDA keynotes
- Situations requiring PAT model transfer – When?
- Dynamic Orthogonal Projection (DOP) method for model transfer
- Examples of NIR based PLS Model Transfer between

Model transfer for PAT applications

Quality by Design (QbD) concept

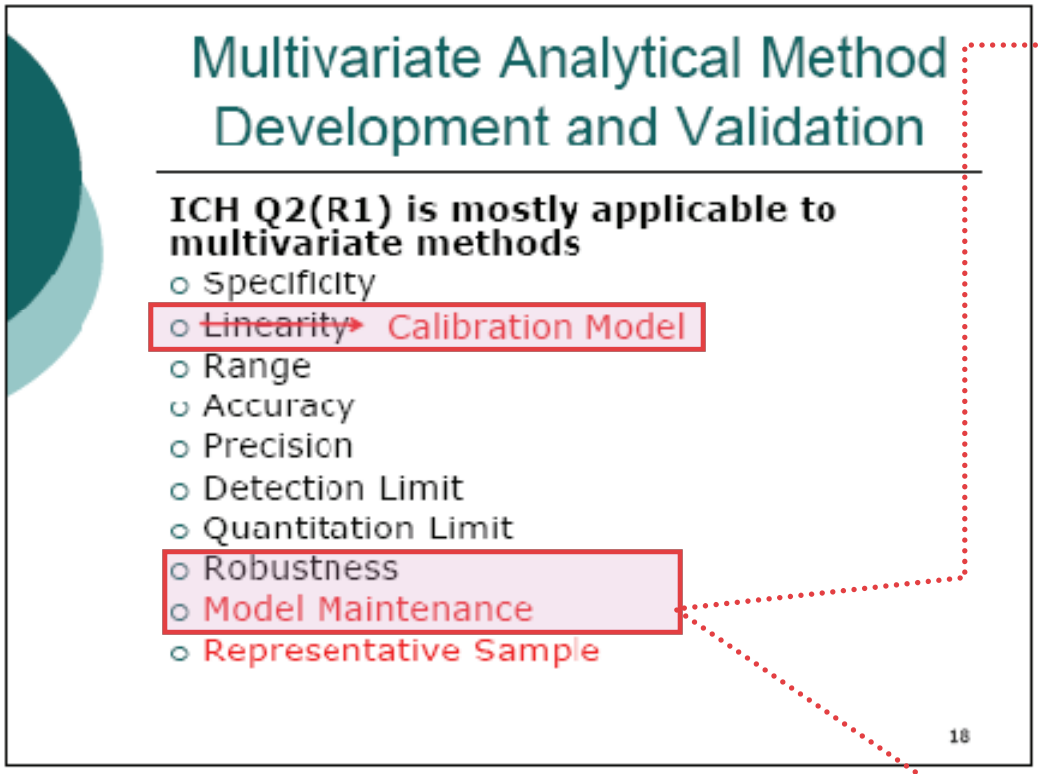


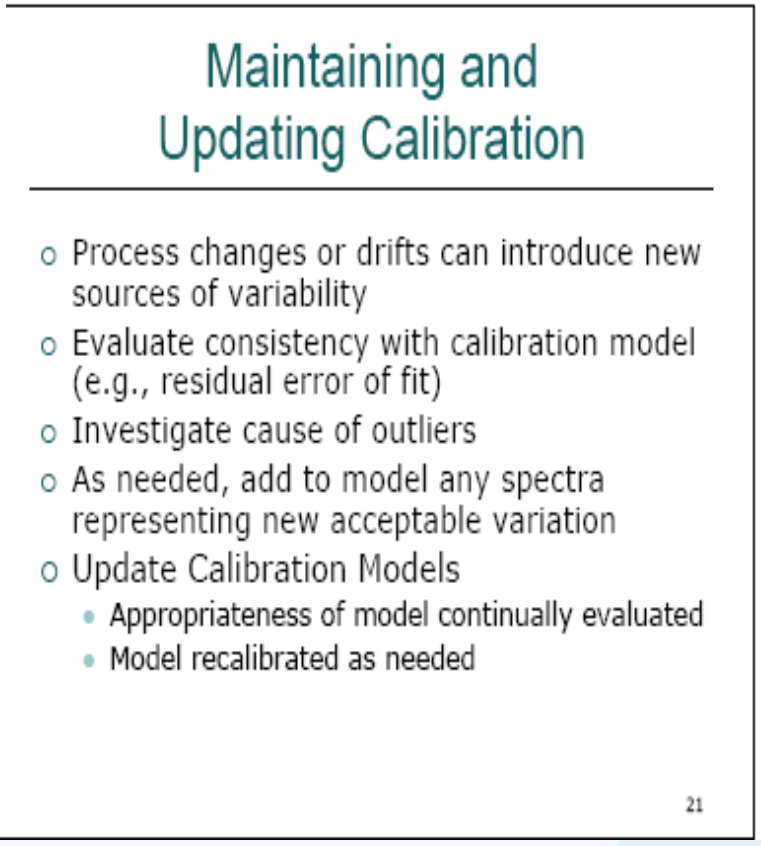
Model **Transfer** = **Maintenance** of the Model Performance by **Updating** it

Model transfer for PAT applications
Relevant FDA keynotes

Moheb Nasr's Slides

Considerations for Analytical Procedures and Control - 2009





FDA Keynotes Speech 2009

Moheb Nasr's Slides (27April2009 AAPS modelling workshop)

Outline

- Quality by Design (QbD)
- Models in a QbD approach
  - Models for design space
  - Models for control strategy and continual improvement
- Concluding comments

Model Maintenance and Update

In a QbD approach, process learning does not stop at product launch

- Design space can be reassessed and updated
- Models that are part of the control strategy may need to be periodically reassessed and updated

HOW can multivariate based regression models used for PAT applications be updated and continuously maintained to accommodate these continued variabilities ?

Model Transfer - When?

- Transfer between PAT instruments
- Transfer between probes
- Transfer after instrument maintenance/ part changes
- Transfer between changes in formulation (e.g. raw material supplier, etc.)
- Transfer between production sites
- Transfer between production scales
- Transfer between production lines within site
- Transfer between changes in process settings (e.g. temperature profile, agitation speed, etc.)

Current Available Solutions for Model Transfer

Model re-development

- Model re-build using current variability from online space
- Model re-build using additional variability in the model online space (DOE)
- Exhaustive Modelling (e.g. parallel sampling, model increment)

☺ Rebuild model against only new current variability

☺ Update the model against new variability using DOE or by merging the model dataset with new data

☹ DOE runs to rebuild the model dataset

☹ Need to measure the source of variability

☹ High Cost, increased time for transfer

Model Correction

- Using Bias/Slope correction method
- Using Transfer Function

☺ Correct for new variability,
Low cost - Practical

☹ When variability disappears, needs to be corrected again

☹ Need the use of standard samples

Model Update and Robustness maintenance

- Using Dynamic Orthogonal Projection (DOP) method

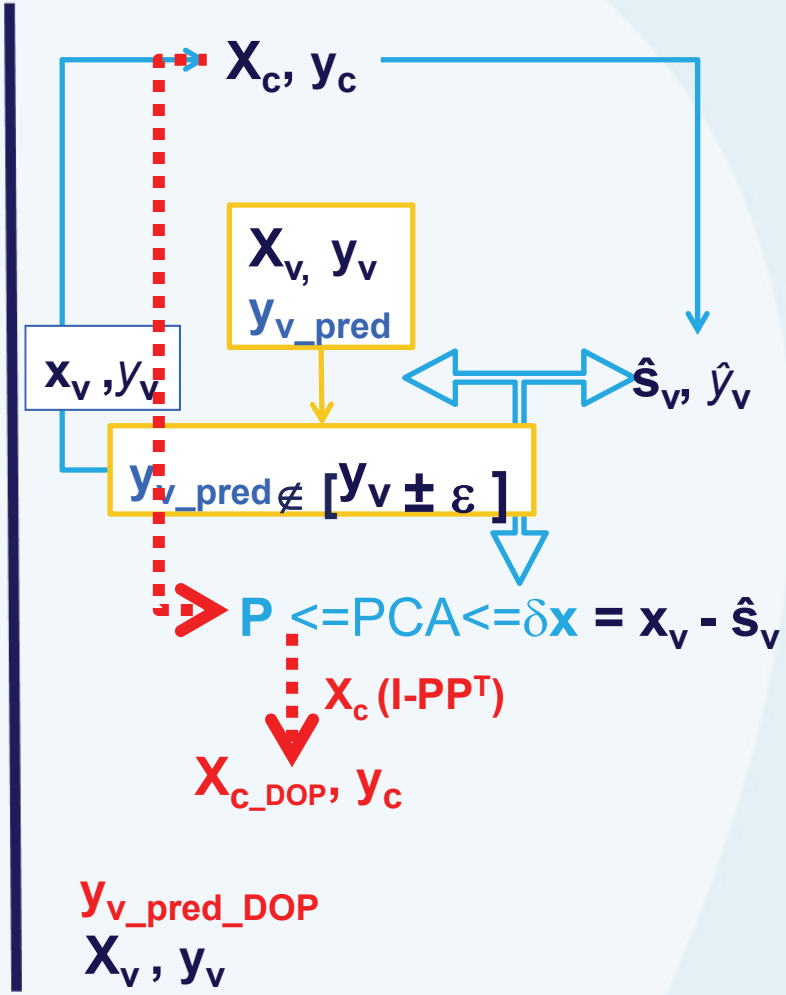
☺ Update the model against new variability using few samples

☺ Low cost and time to transfer – more practical for online use

Dynamic Orthogonal Projection (DOP) method

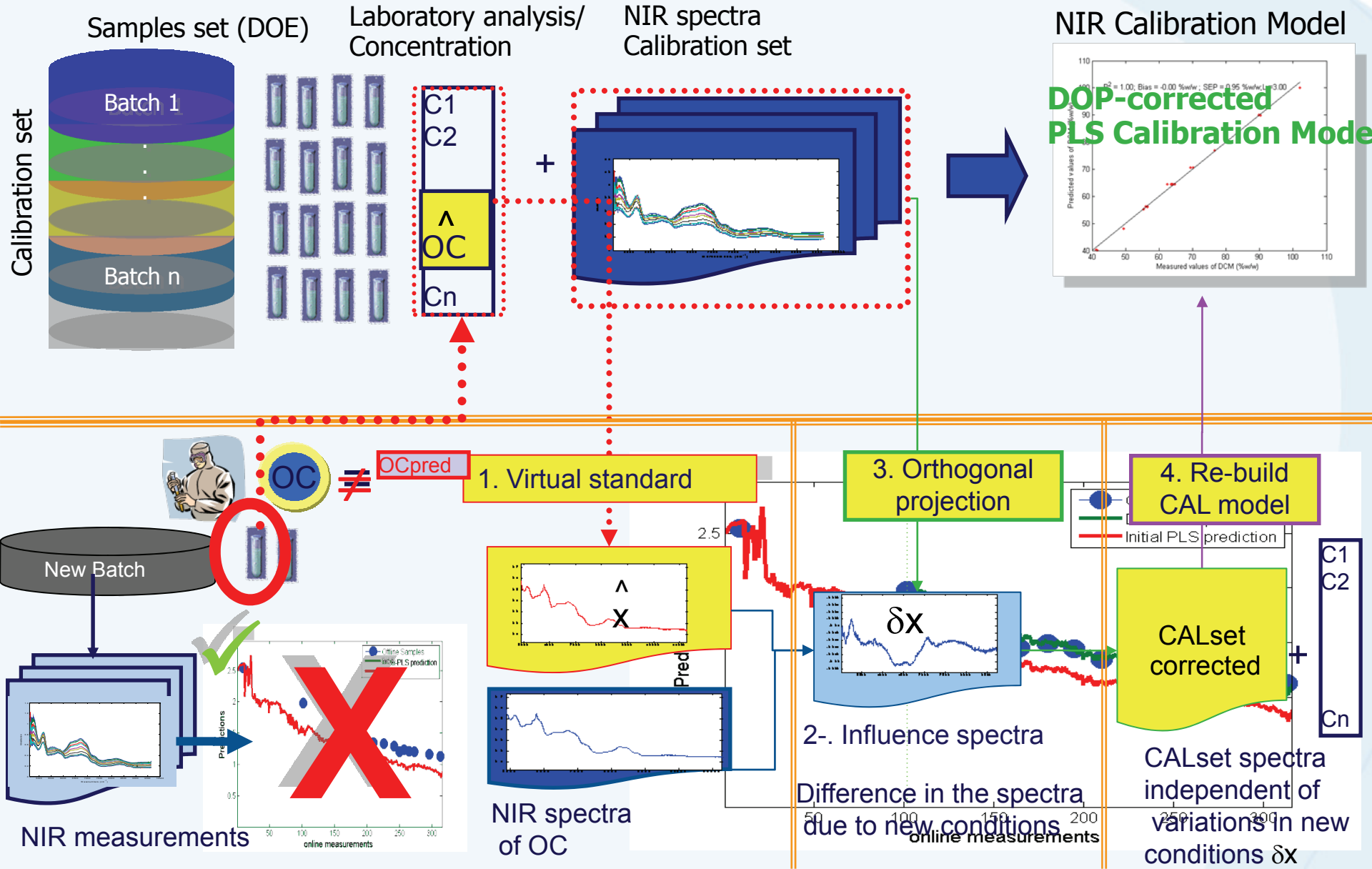
Step 1:	Calibration Set (Spectra, Attribute) CALset
Step 2:	Validation set collected under the new conditions (Spectra, Attribute) VALset
Step 3:	Use 1 sample of the VALset for DOP† correction of the CALset spectra from the effect of new conditions
Step 4:	Re-Compute the model using the corrected CALset spectra
Step 5:	Validate the model using the VALset

Model transfer and Update using DOP



†*M. Zeaiter, , J.M. Roger and V. Bellon-Maurel, Dynamic orthogonal projection. A new method to maintain the on-line robustness of multivariate calibrations. Application to NIR-based monitoring of wine fermentations Chemometrics and Intelligent Laboratory Systems, volume 80, Issue 2, 15 February 2006, Pages 227-235*

DOP Step 3 and 4 : How does it work?



Examples of Applications

Application 1:

DRYING monitoring

Transfer of NIR model between Production Lines and NIR Instruments

J. REVEL,
Flamel Technologies, France

R. Davenport,
GSK Primary Supplies, Dartford, UK

Application 2:

DISTILLATION Monitoring

Transfer between Sites (NIR Instrument & production scale)

Application 1

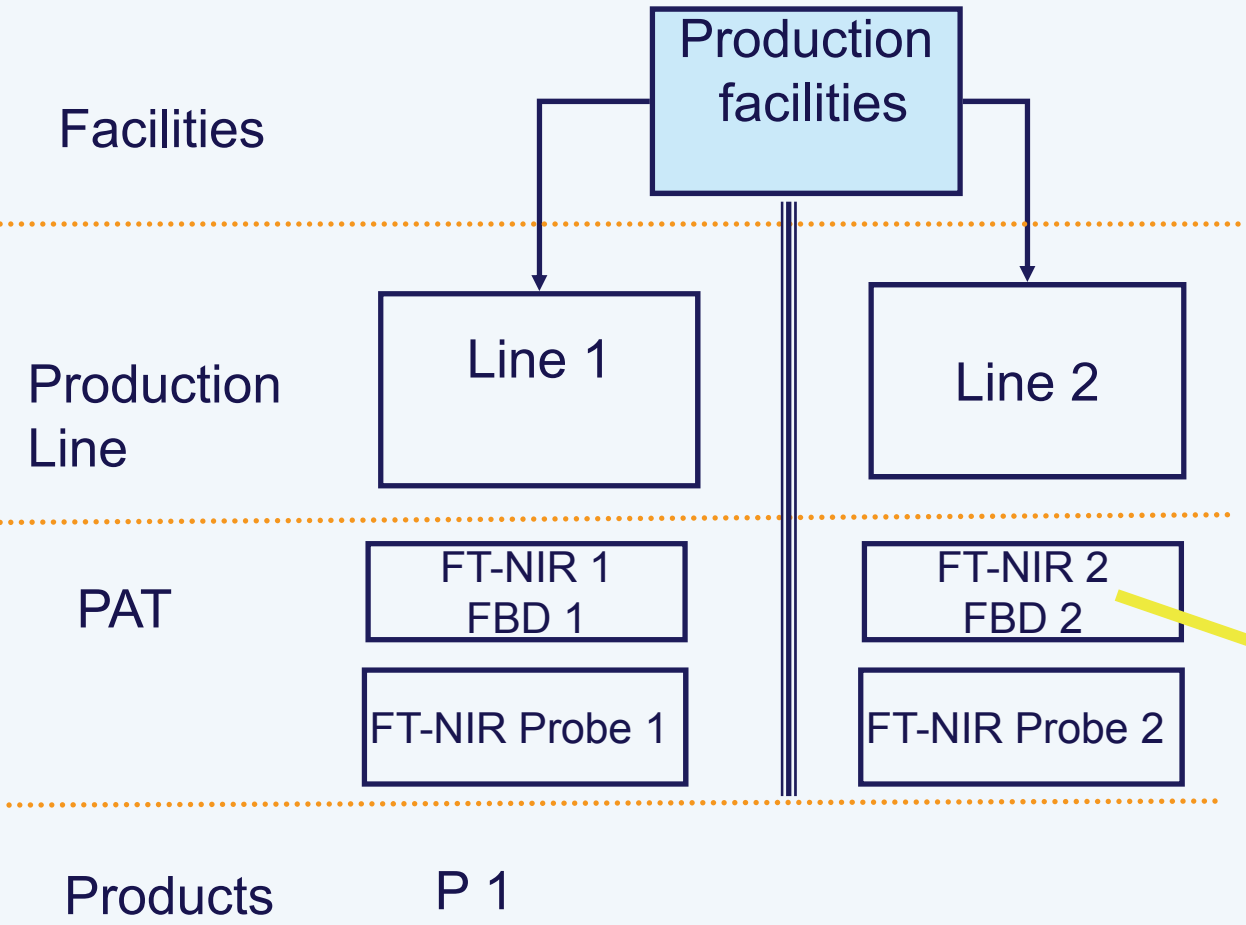
DRYING Monitoring

Results presented from the collaboration work with Ondalys 2008/2009

Transfer between

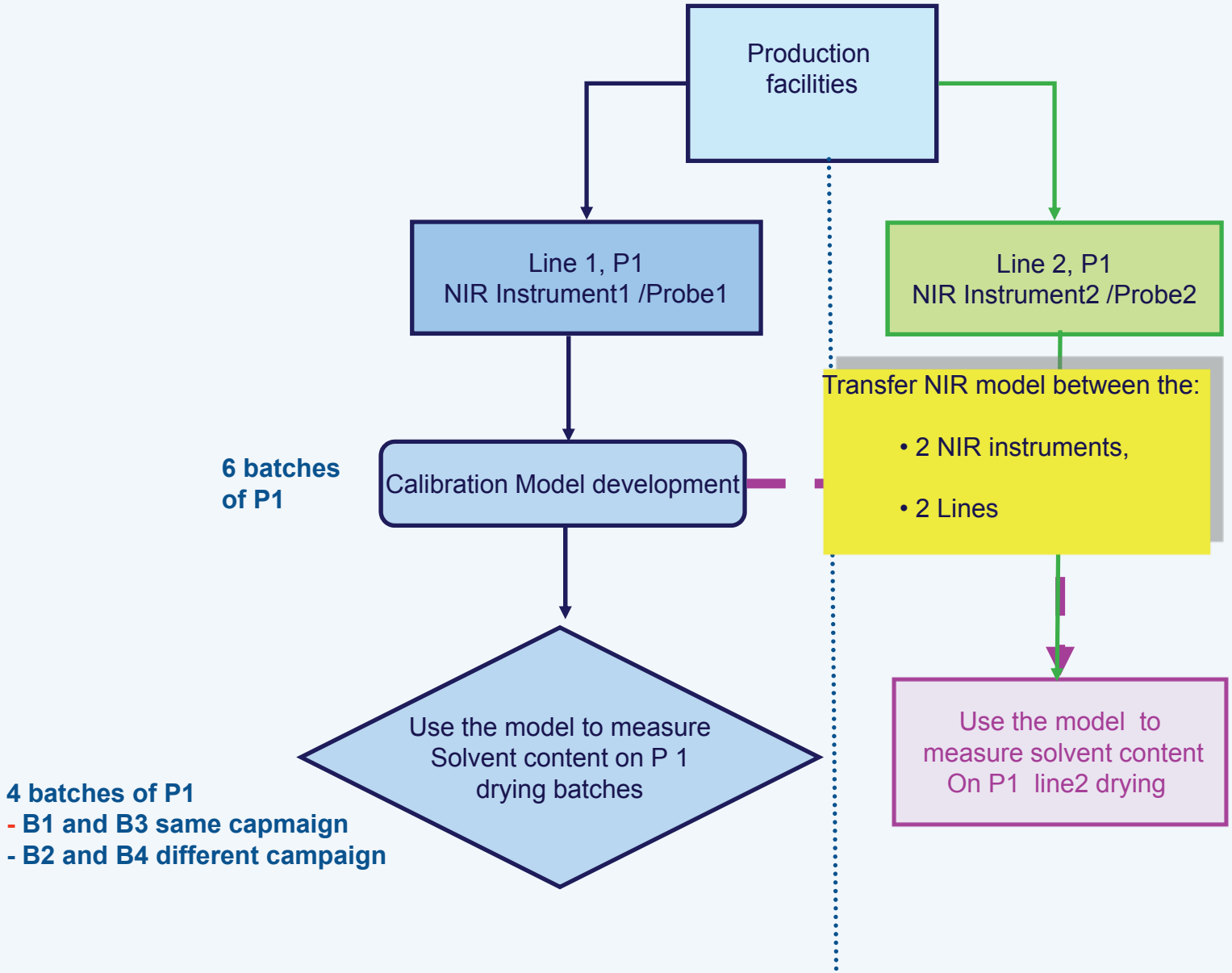
- NIR Instrument
- Production lines

Monitoring solvent level during the drying process using NIR spectroscopy Multivariate Calibration Model (PLS)

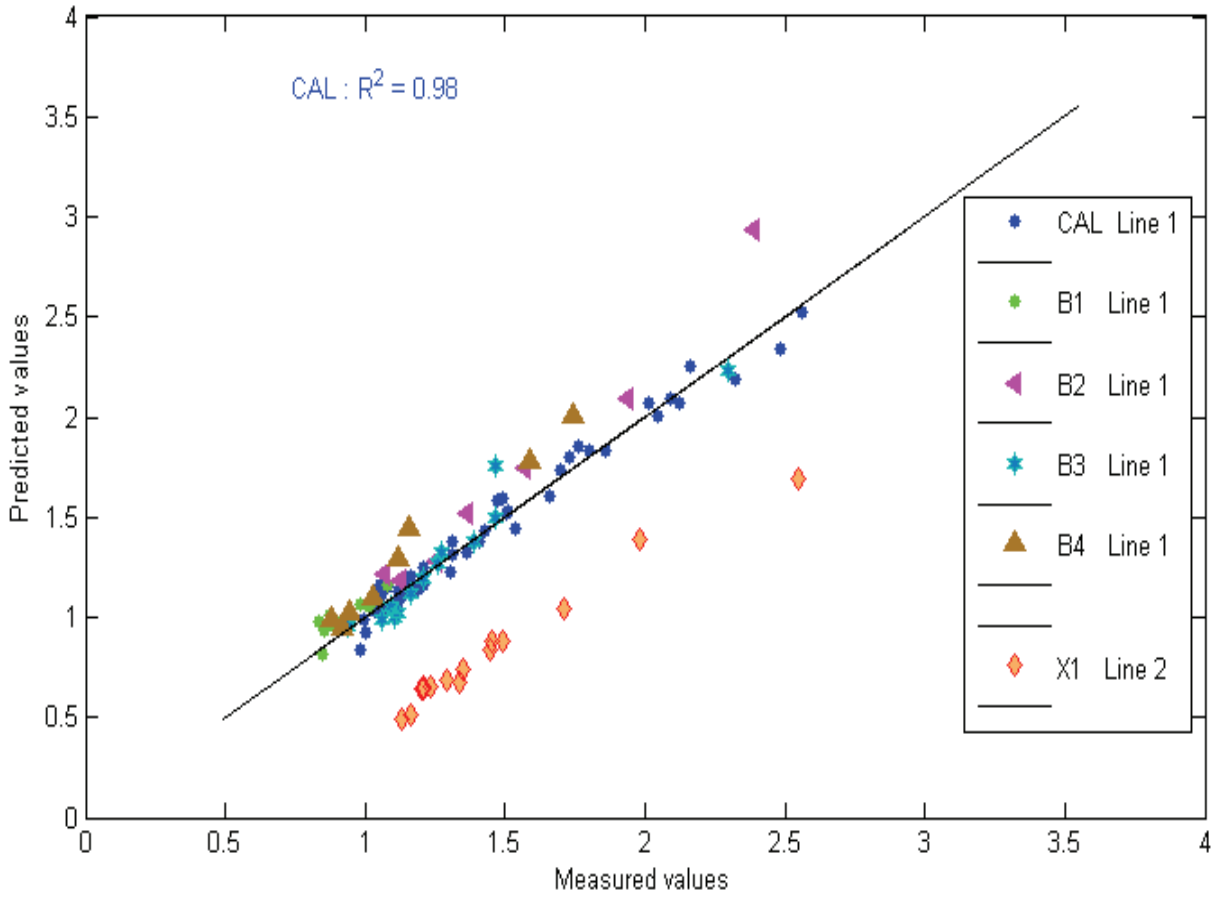


Production Line

Transfer the PLS model between 2 NIR Instruments and production lines



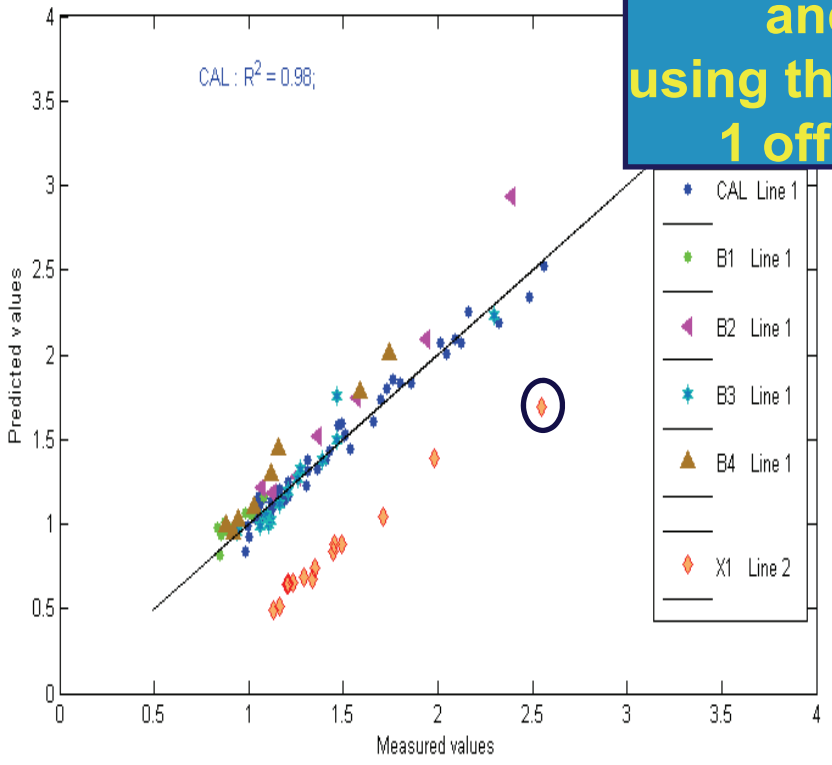
Use the calibration model to predict new batches

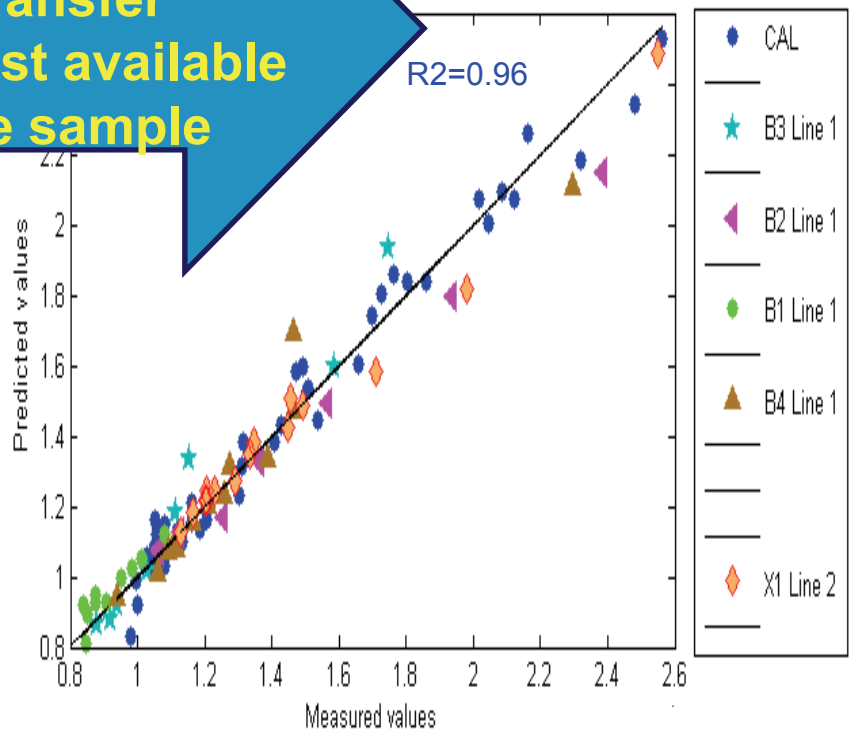


- Same Campaign, Line and NIR instrument (B1 and B3)
- New Campaign (B2 and B4)
- New line and new NIR instrument X1

Transfer of the model to predict on line 2 using DOP method

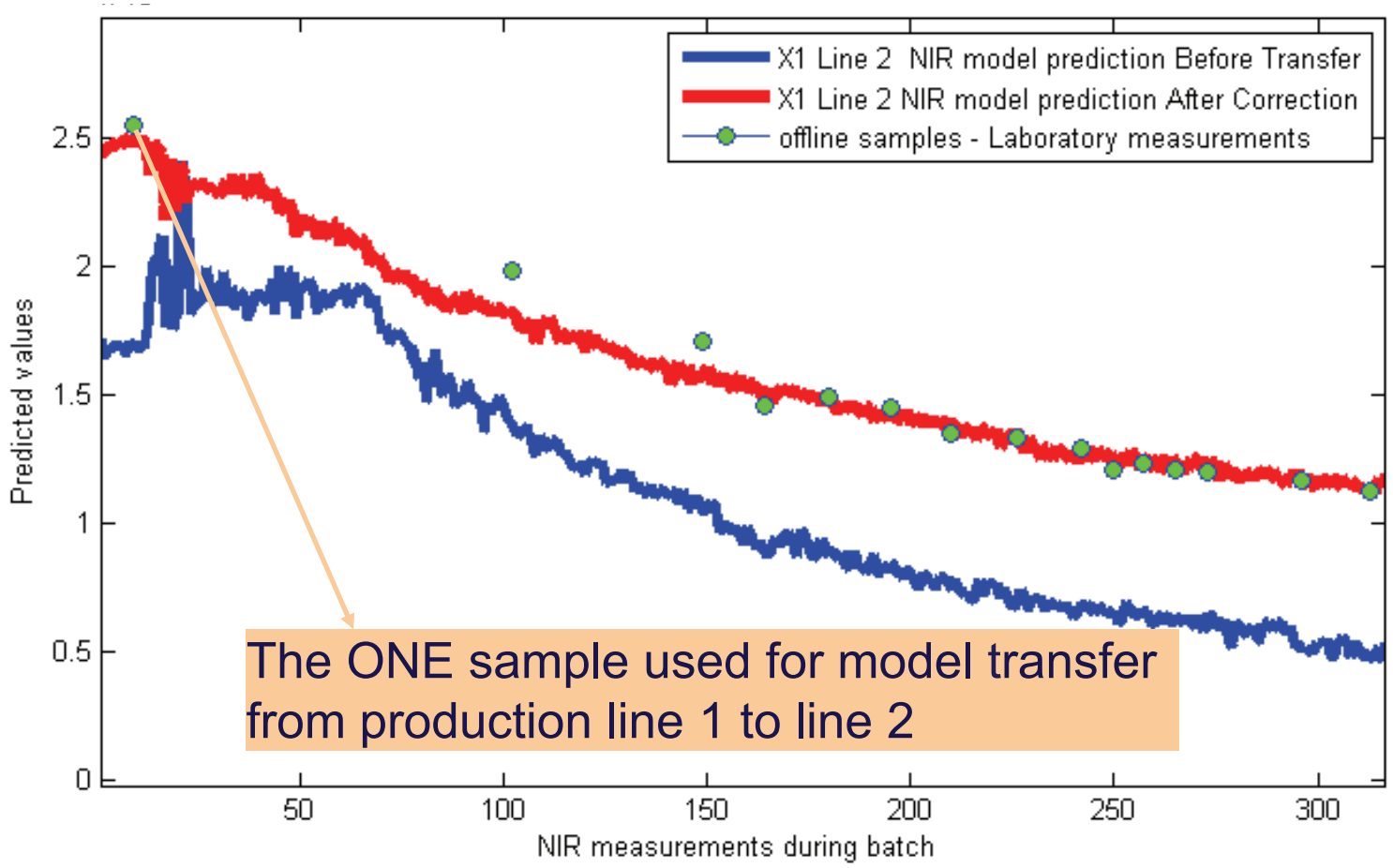
Model Update and transfer using the 1st available 1 offline sample





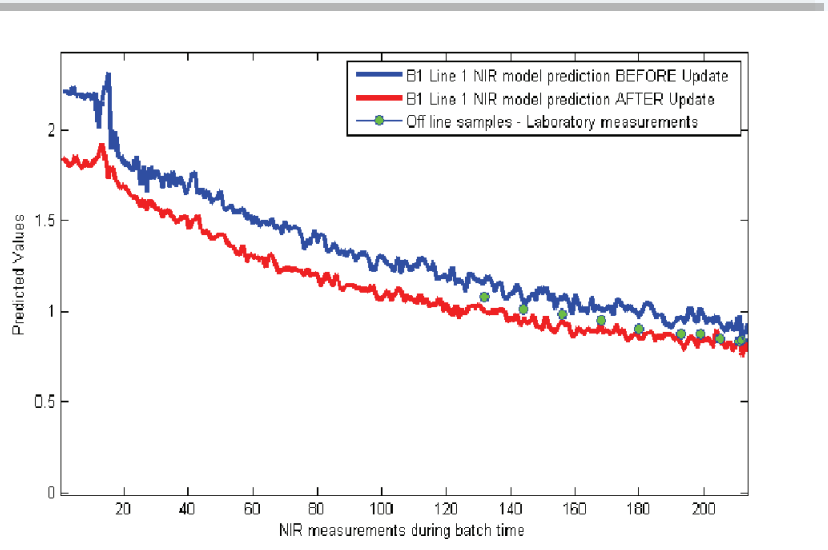
- New line and new NIR instrument X1

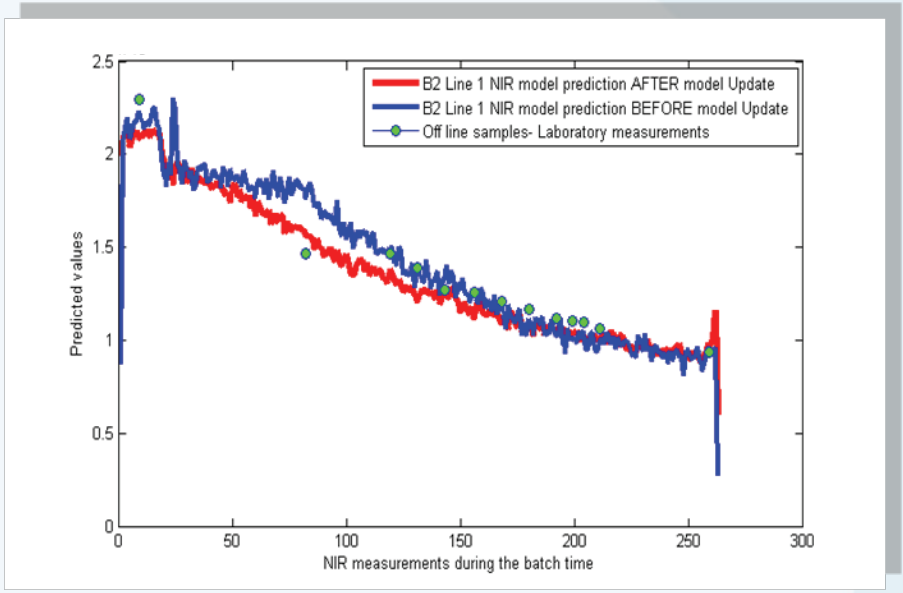
Model Transfer between production lines and NIR instruments using the first Offline sample on batch X1 line 2

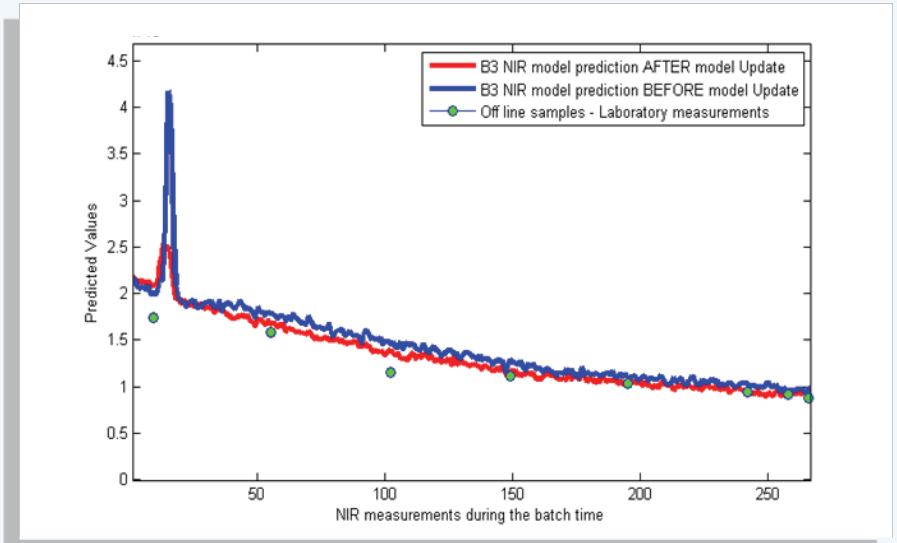


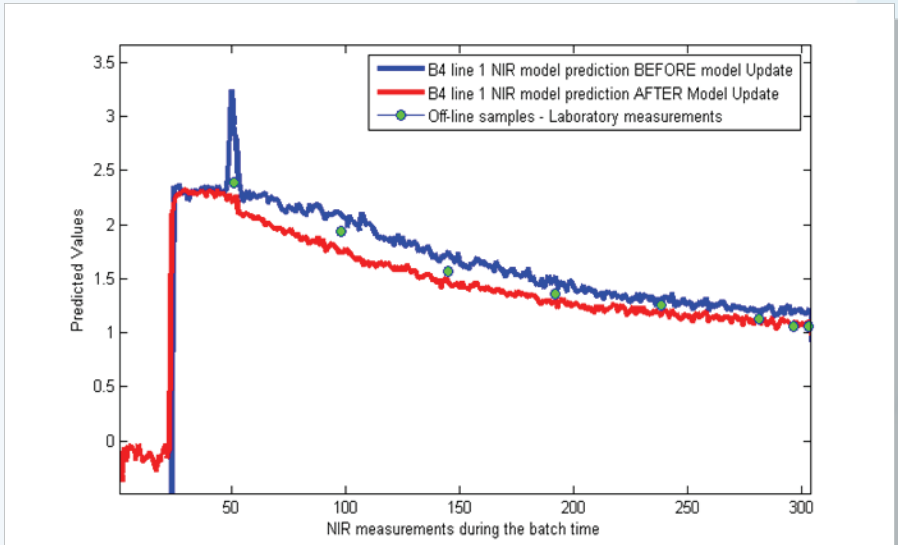
Model performance maintained on both Line 1 and Line 2 after Model transfer

NIR model transferred used again on batches from Line 1 to check if the model performance is maintained









Application 2

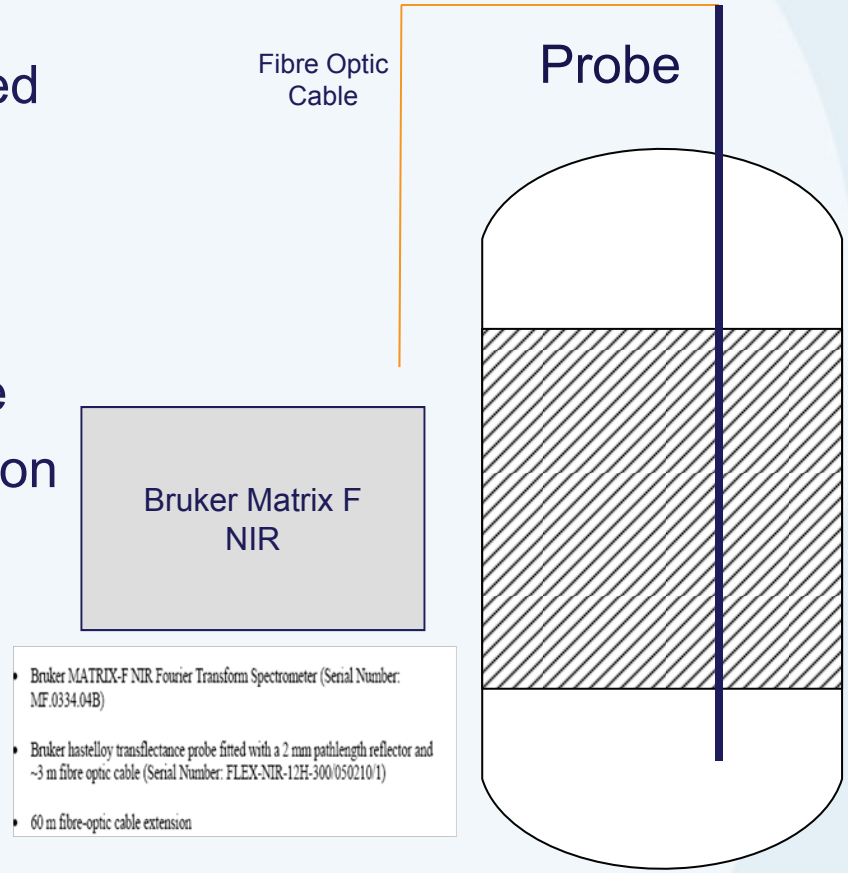
DISTILLATION Monitoring

Transfer between Sites

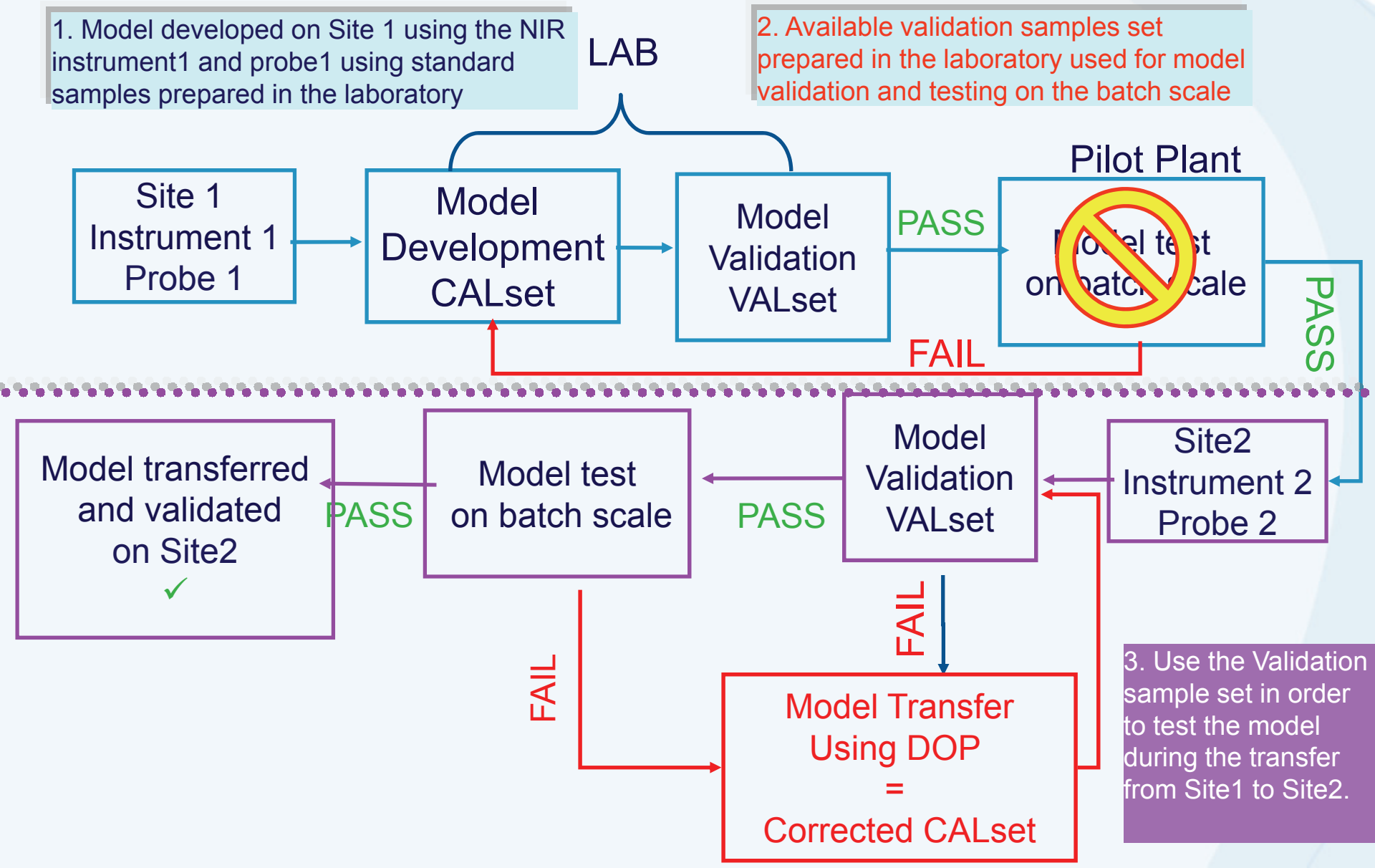
- NIR Instrument
- Production scale

DISTILLATION Monitoring using NIR – Model transfer between sites (NIR Instrument & production scale)

- Concentration is critical to manufacturability.
- NIR advantage is that it could be used to determine solvent concentration during vacuum distillation process
- 3 components mixture with presence of water at the beginning of the distillation
- Water was not taken into account in the calibration model design



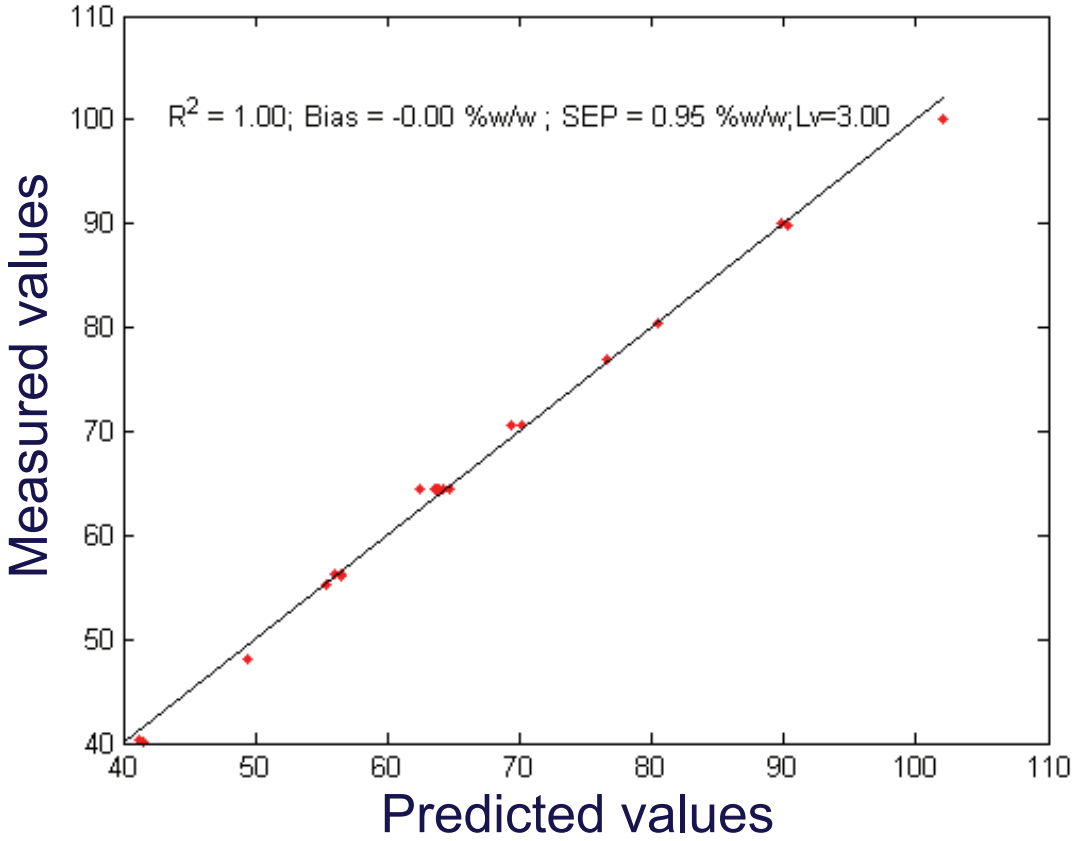
NIR calibration model development and transfer approach used for distillation monitoring



NIR model development for distillation monitoring

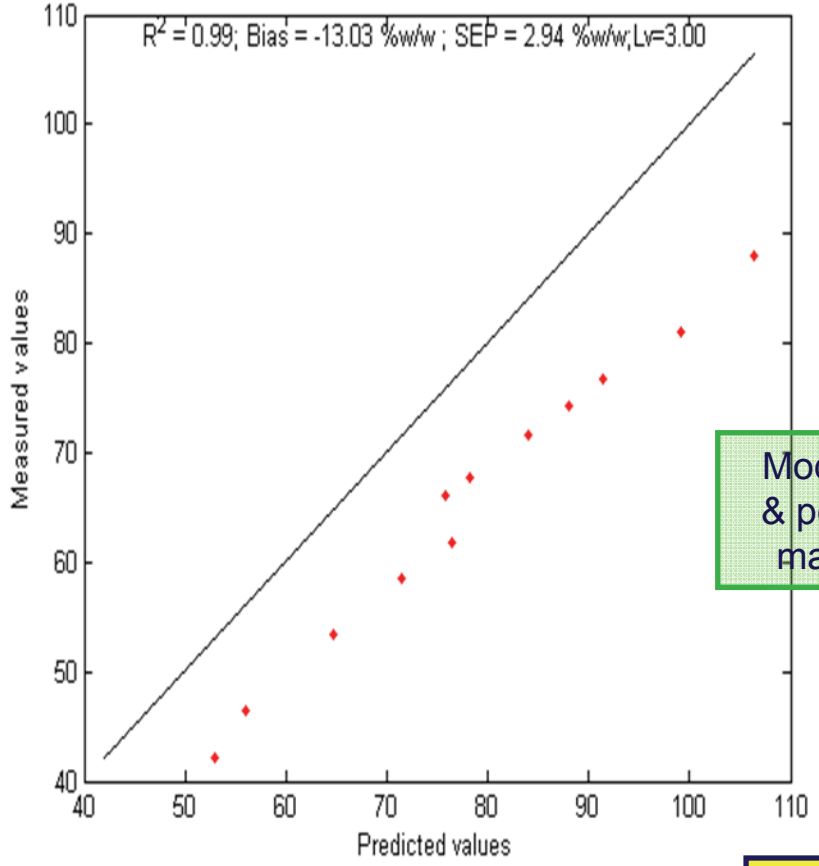
NIR data preprocessing:
- Variable selection : 4500-12000 cm^{-1}

Model:
- PLS model
- Cross validation (LOO)
- 3 Latent variable
- R2=1
- SECV= 0.95%w/w



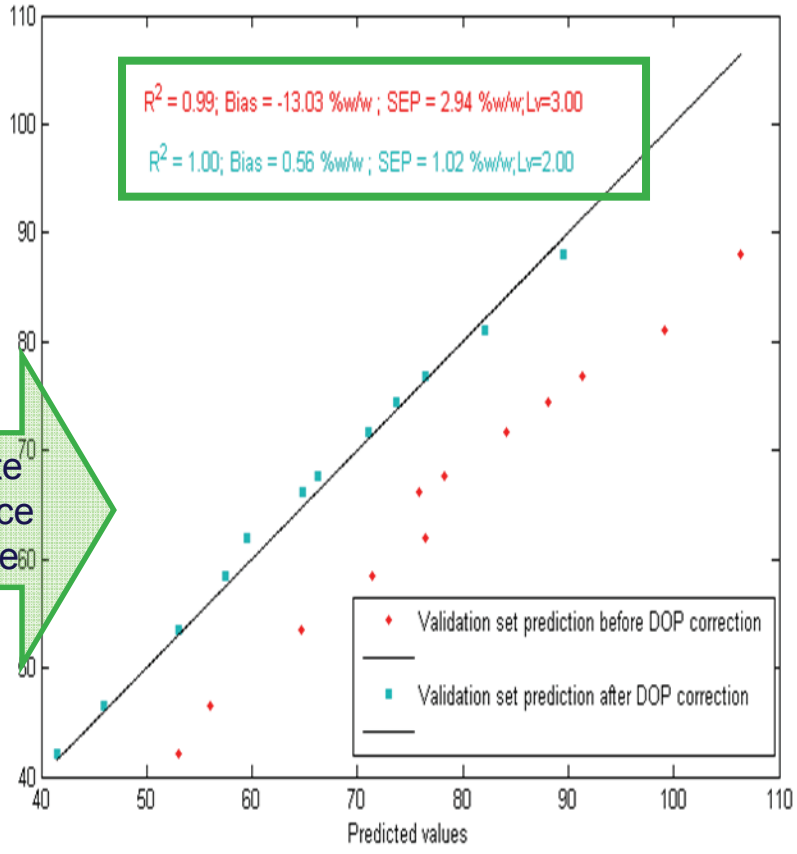
Transfer the model from instrument 1/probe 1 to Instrument 2/probe 2

Model used on Instrument 2 to predict VALTest



Model Update & performance maintenance

Model Transferred used on Instrument 2 to predict VALTest



DOP correction using only the first sample of the validation set measured on instrument 2

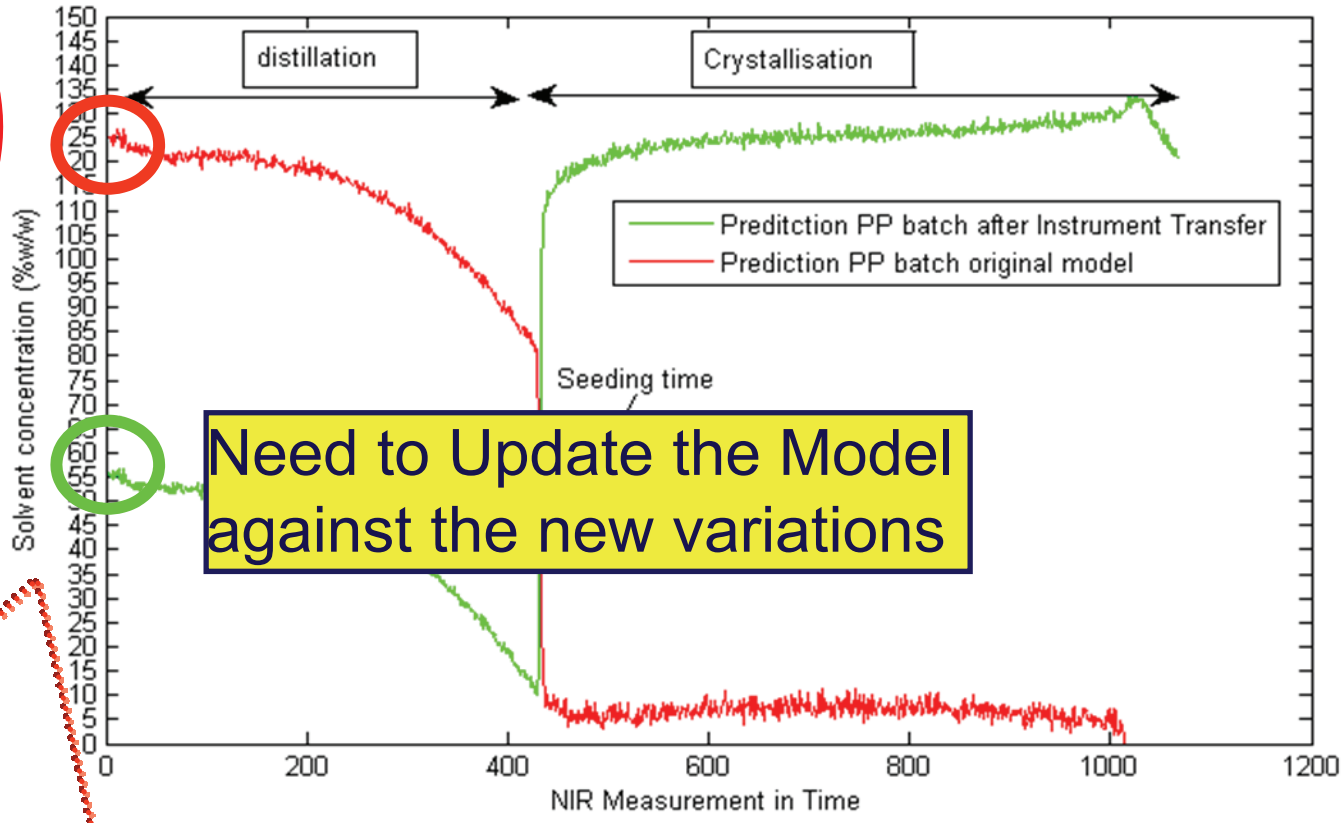
Use the Original and Updated model to monitor the distillation batch PP1

New Variations:

- Scale change
- Presence of water

at the beginning of the process

the start of the distillation ~86%w/w

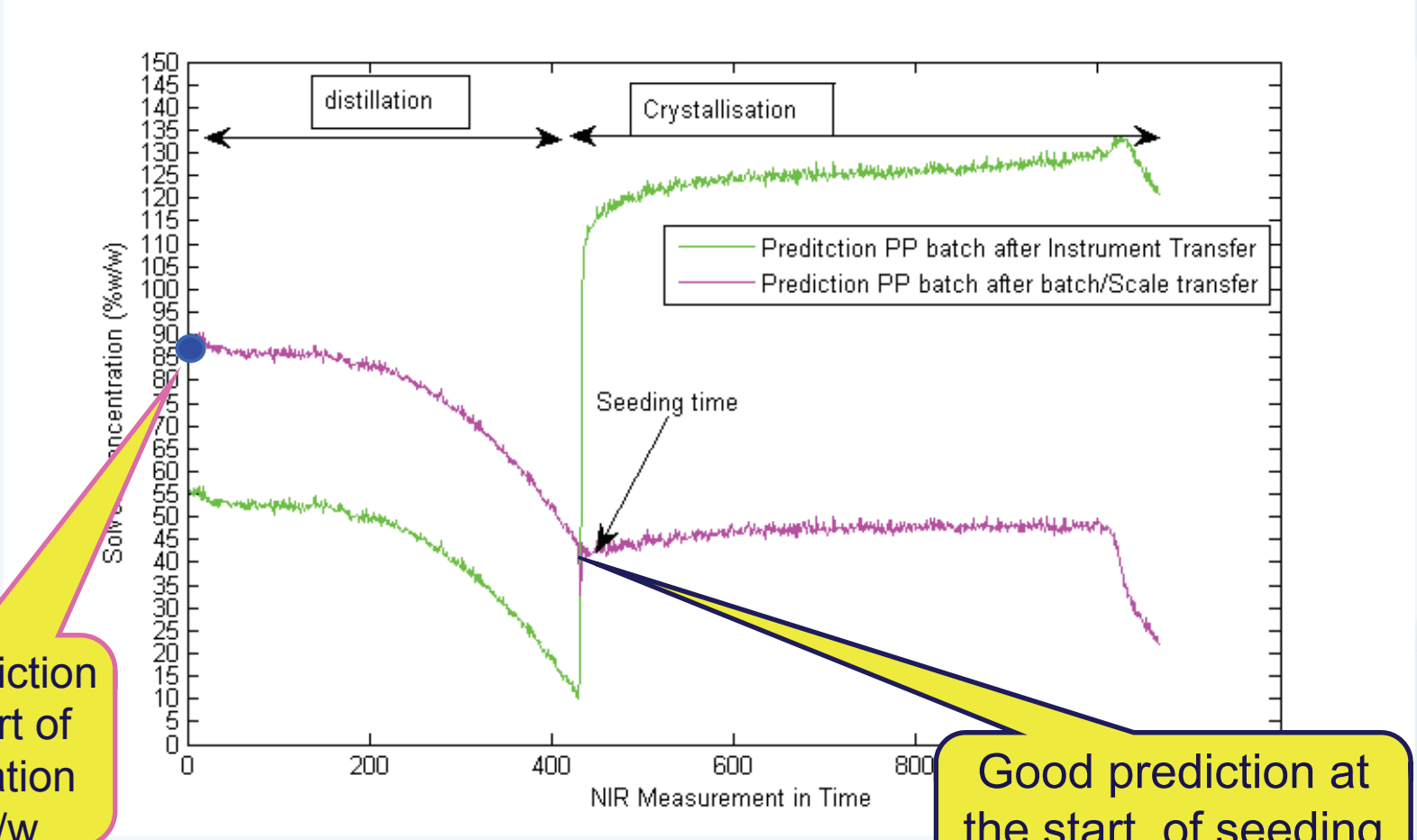


IN RED : Original Model predictions on the batch scale

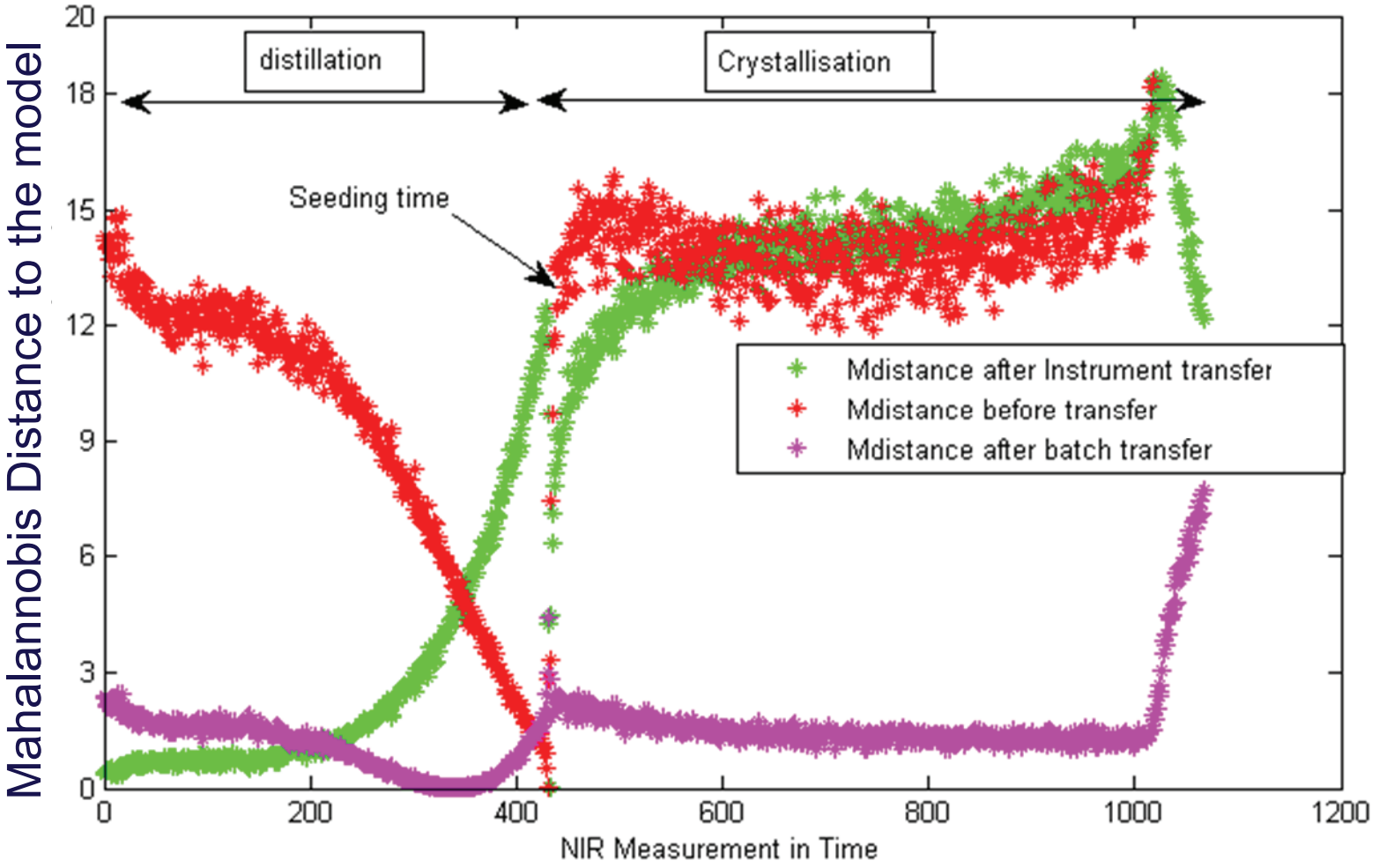
IN Green : Model predictions after instrument transfer only

Use DOP to Update the model against new variations on the batch scale PP1

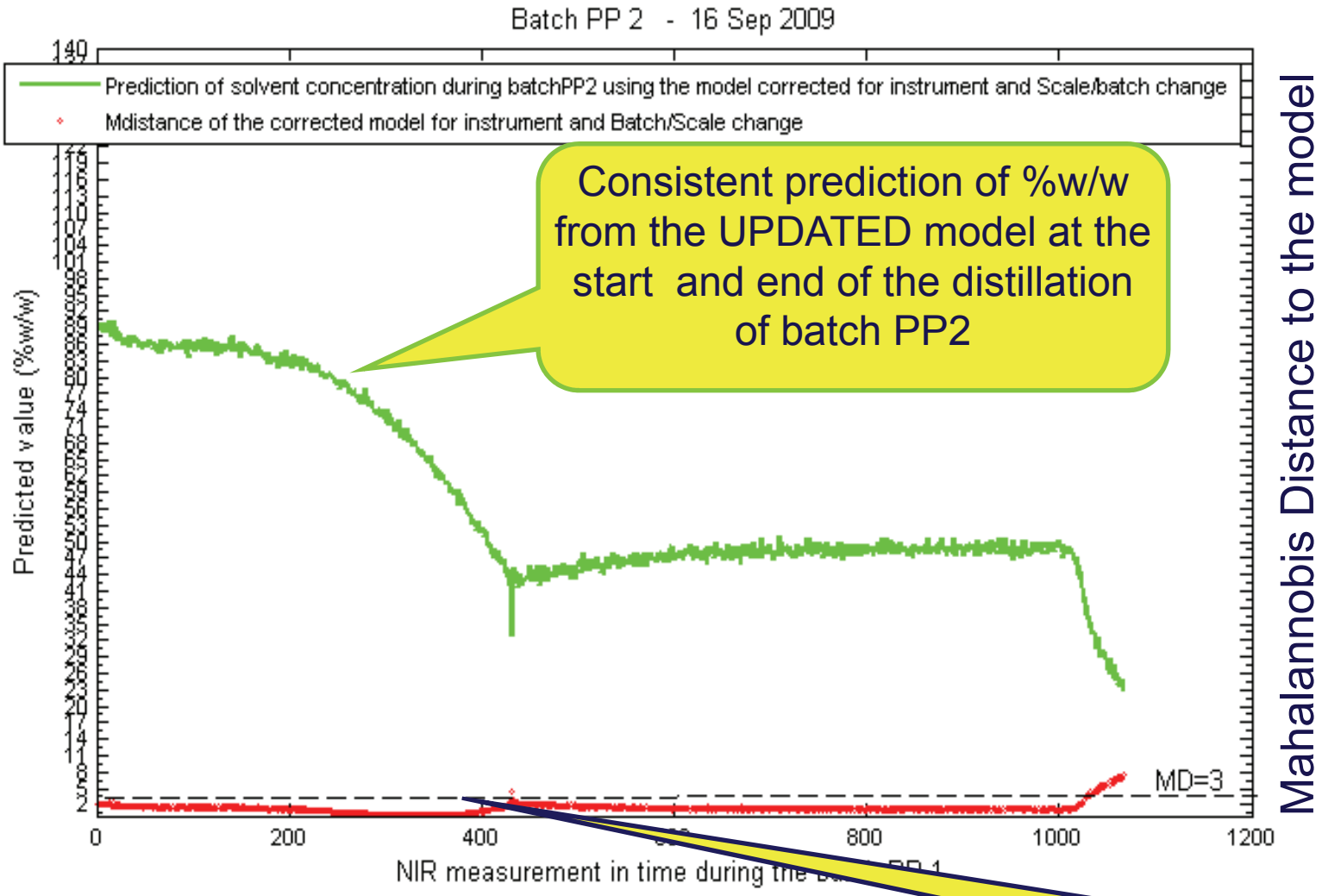
- Use the first sample of the distillation batch estimated volumetrically as 86%w/w to UPDATE the calibration model.



Comparison of Mahalanobis distance to the model before and after DOP correction



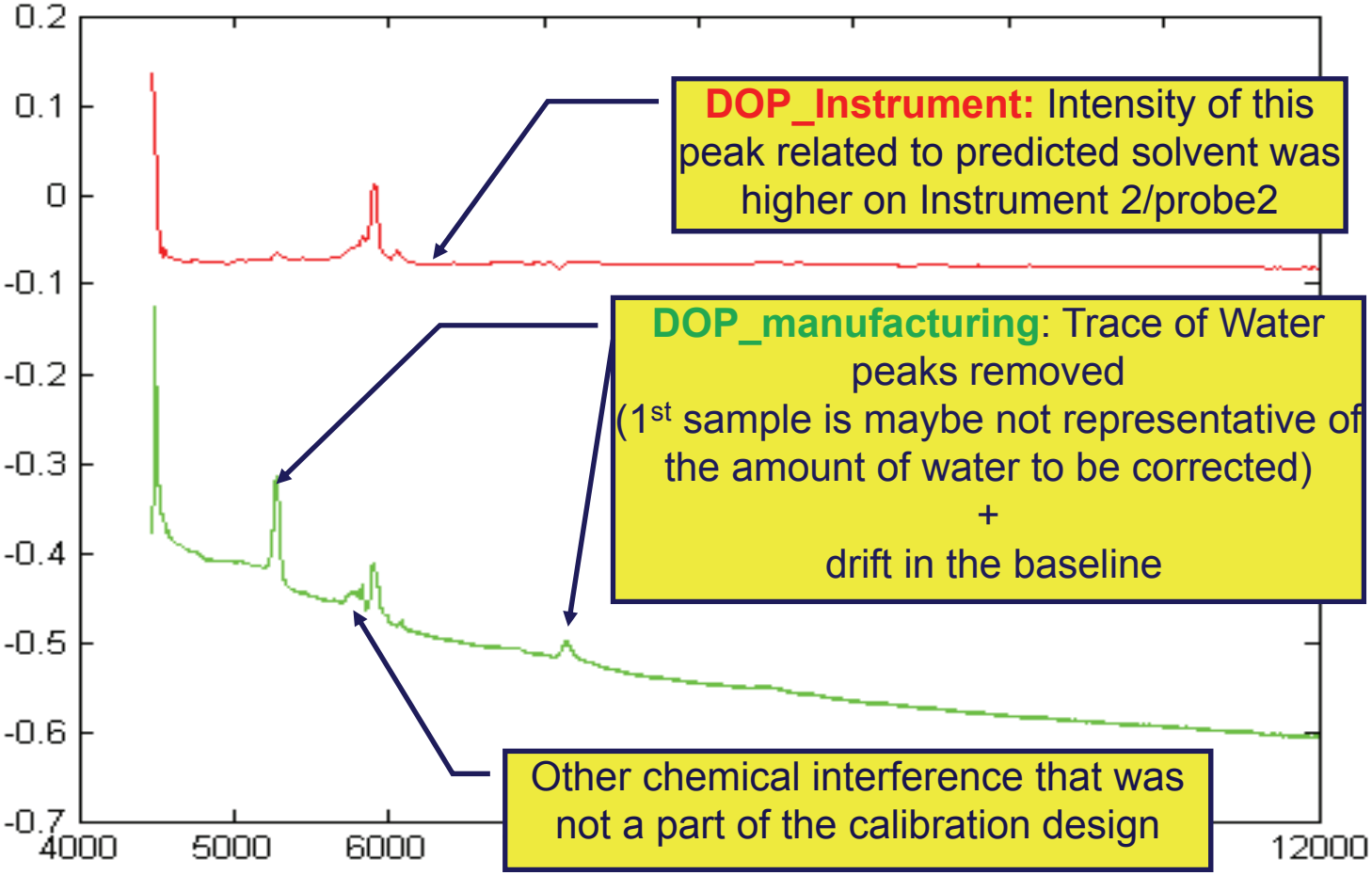
Test the updated model on data from new batch PP2



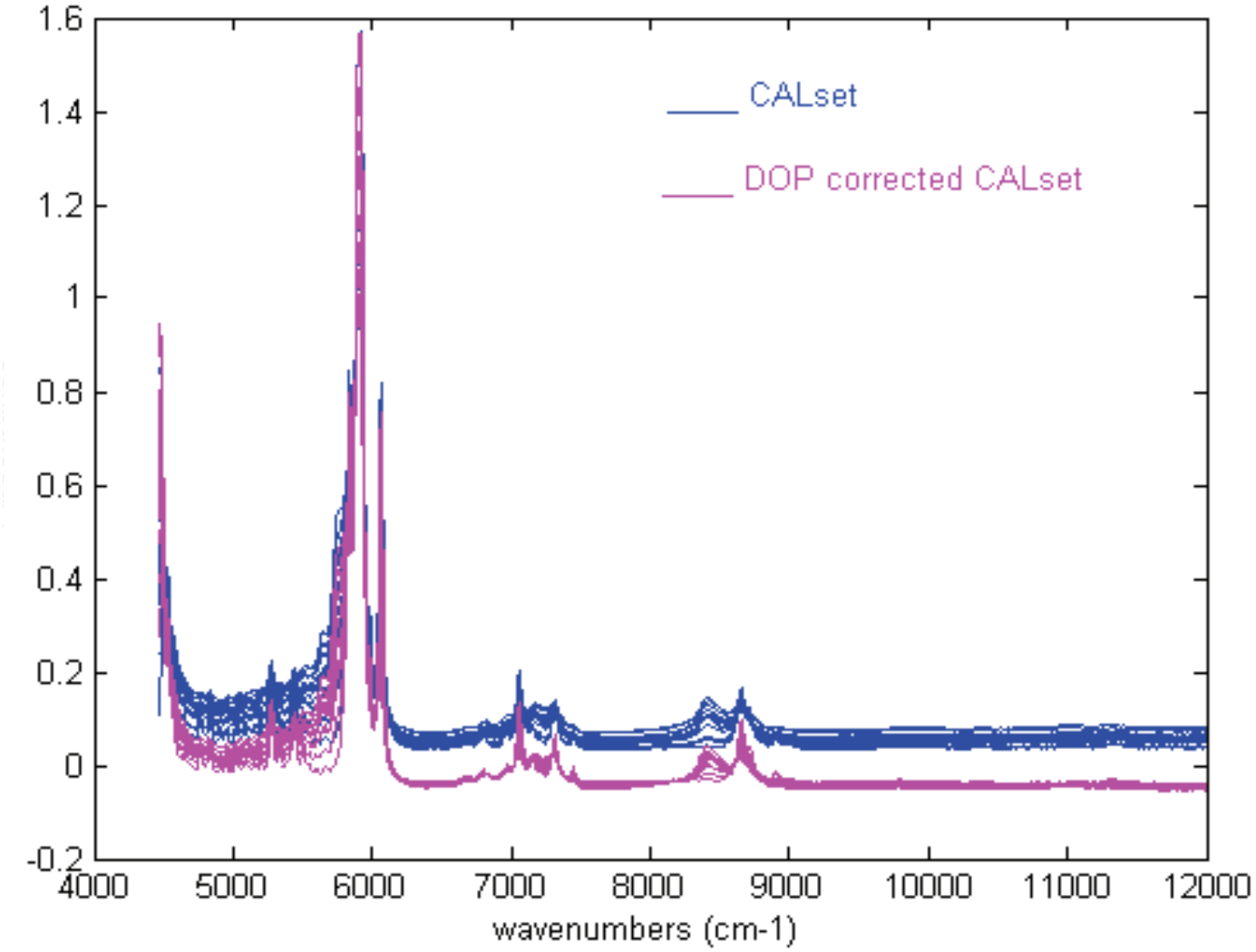
Diagnostic of the corrected part of the spectra during the model update to understand the source of model failure

In **red** is the FIRST correction using the validation test sample (1st sample)

In **green** is the SECOND correction using the PP Batch (1st sample)



Calibration set after DOP correction



Conclusion

- Transfer and Update of Regression Model or Performance Maintenance is a **key part using PAT in the Control Strategy** for Pharmaceutical Applications

- In this presentation the DOP method has **successfully proven its use with PLS Model transfer** between NIR spectroscopy Instruments and batch variability, production line.
  - Use only ***few offline samples*** to transfer the model successfully
  - ***Low cost*** for model transfer
  - ***Reduce*** transfer ***time*** and ***resources***
  - Make the NIR On-line applications ***more cost effective***

- ***However, validity of the predicted values and its uncertainty needs to be evaluated, quantified and monitored in real-time to give enough confidence to make quality decision based on these values.***

Acknowledgments

- Flamel Technologies – Pessac- FRANCE for providing the Data and the support.

- Ondalys Company for providing the results of the study (FBD example – Comparison of the 3 existing model transfer method)

- Robert Davenport, GlaxoSmithkline, Dartford, UK (distillation example)