# *Two case studies using spectroscopy and chemometrics as PAT for Injectable Finished Products in Pharmaceutical Manufacturing*

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**Analytical Scientist, Novo Nordisk A/S**

**DSK – 8th of November 2024**

# Agenda

Motivation

What is PAT?

Case Study 1: Cleaning Verification and Validation

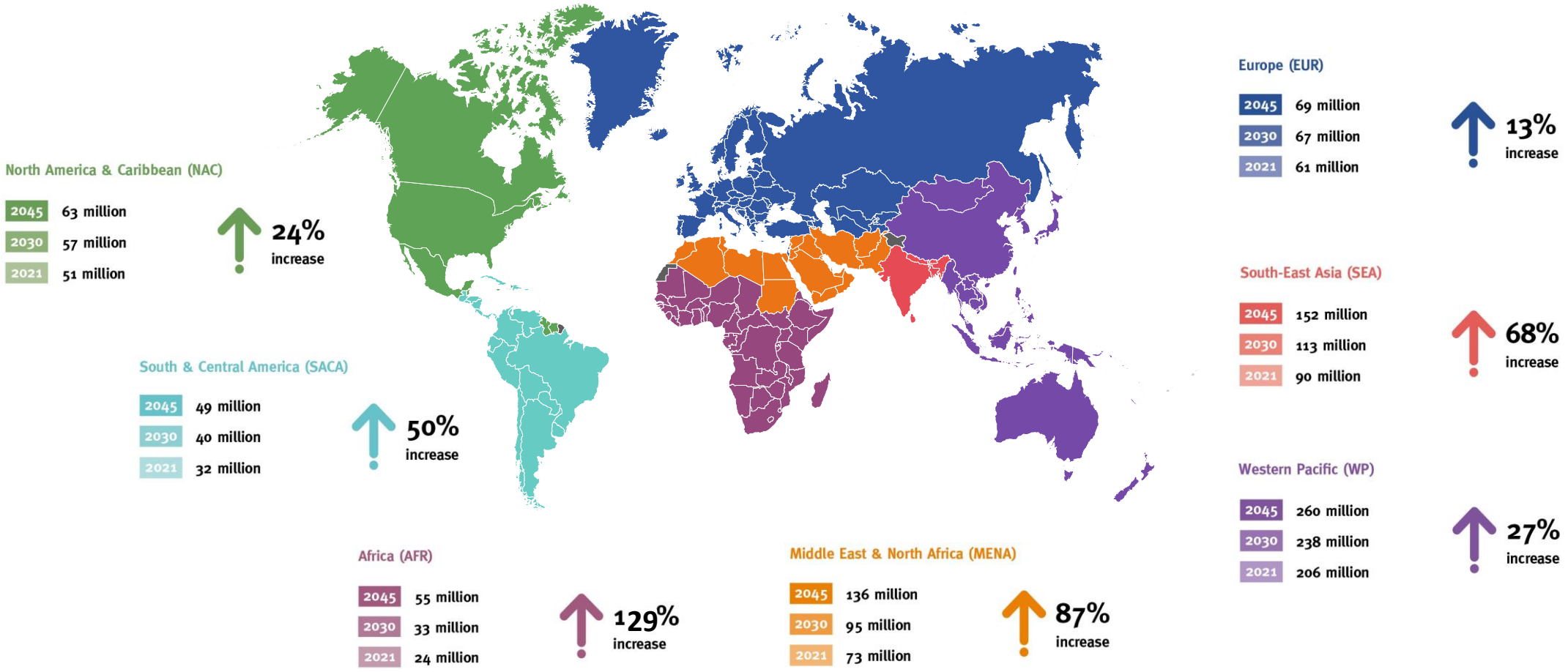
Results from Case Study 1

Case Study 2: Formulation of Crystalline Drug Product

Results from Case Study 2

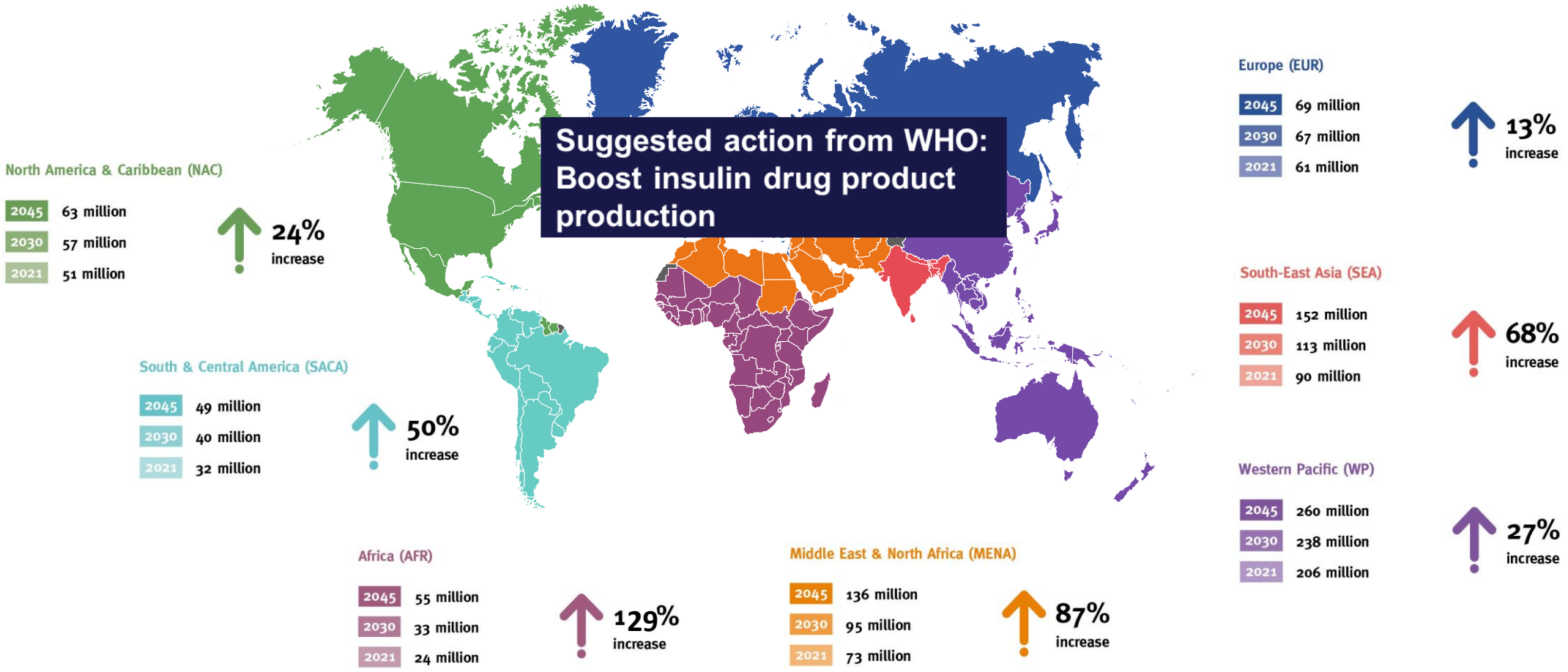
Conclusion

# Diabetes Prevalence in the World




Source: IDF Diabetes Atlas

# Diabetes Prevalence in the World

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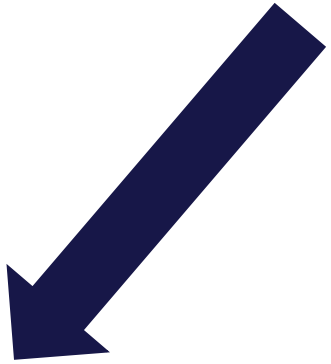
# Why Process Analytical Technologies (PAT)?

**How to increase production?**



Build more
manufacturing facilities

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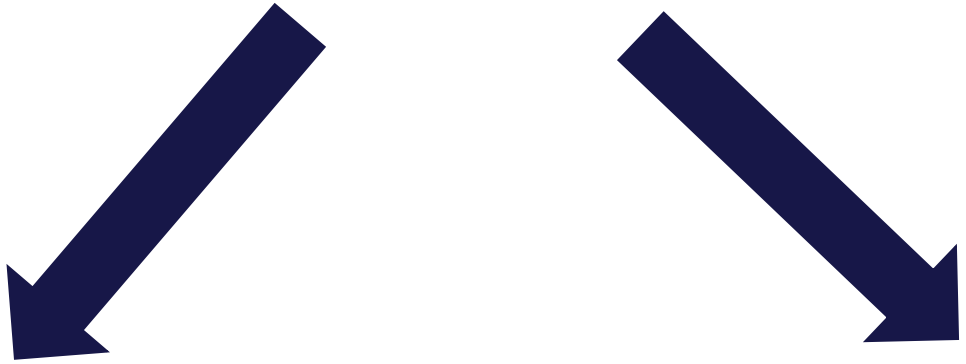

Build more
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Make production more
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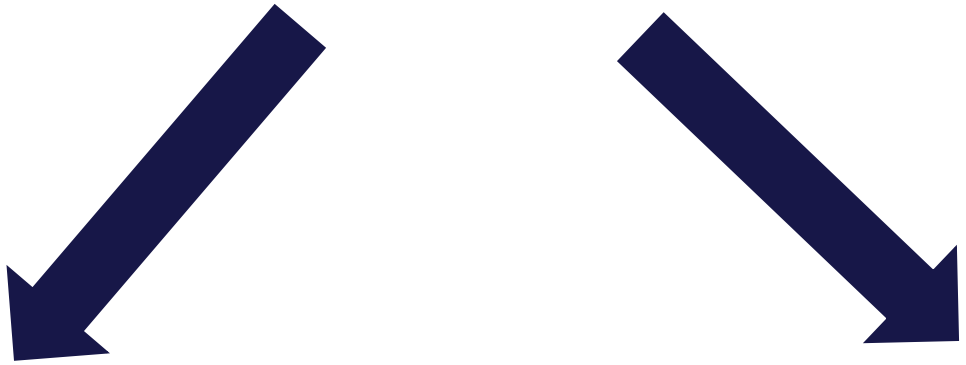

Build more
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Make production more
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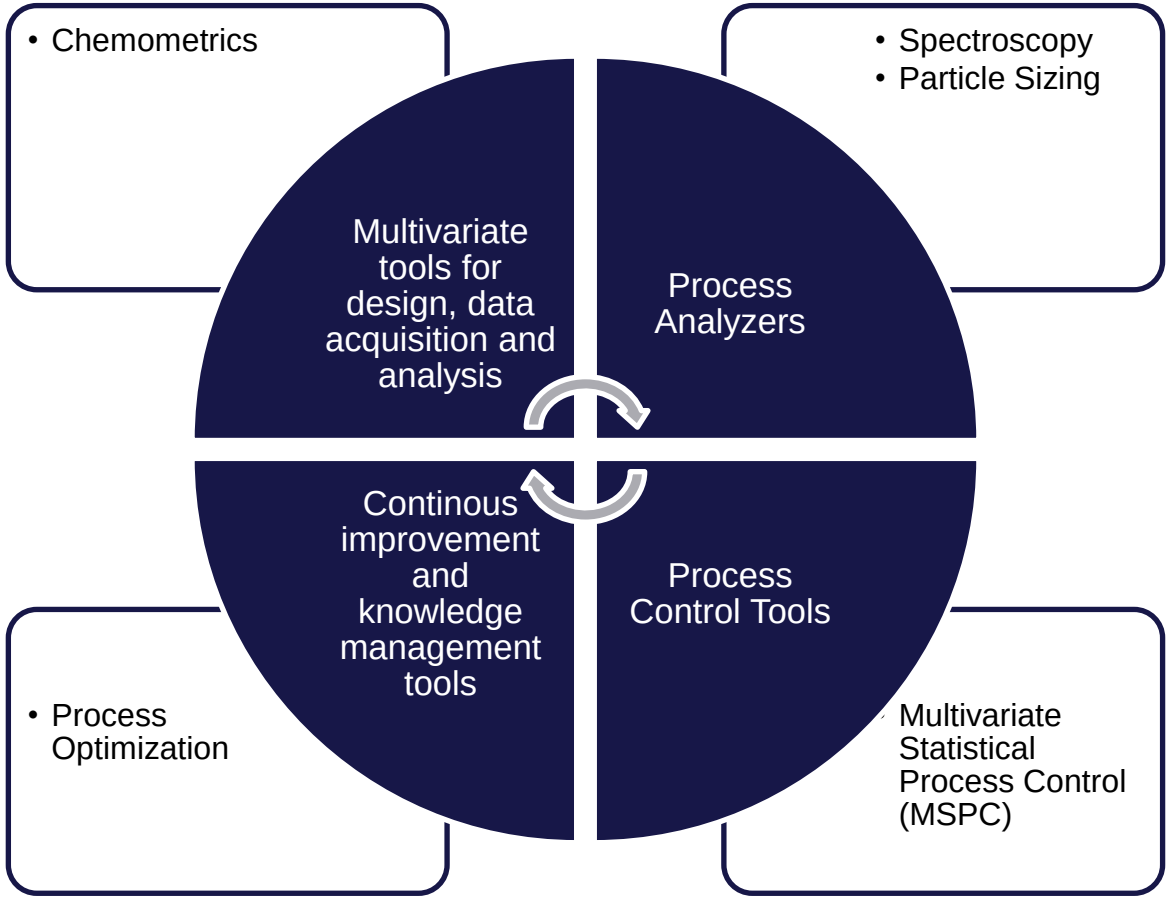
**Process Analytical
Technologies**

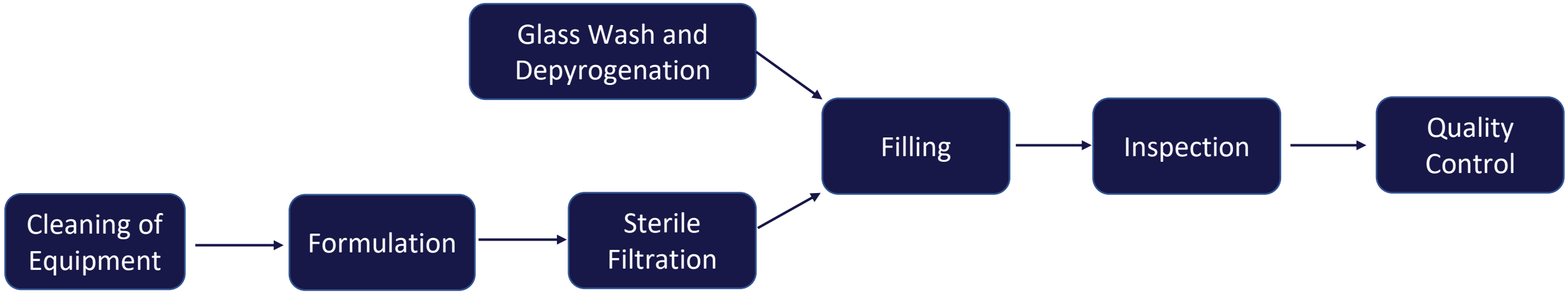
# What is PAT?

FDA definition from 2004:
” system for designing, **analyzing**, and **controlling** manufacturing through **timely measurements** (..) of **critical quality** and performance attributes (…), with the **goal of ensuring final product quality**”

# What is PAT?


• Chemometrics
• Spectroscopy
• Particle Sizing
Multivariate tools for design, data acquisition and analysis
Process Analyzers
Continous improvement and knowledge management tools
Process Control Tools
• Process Optimization
Multivariate Statistical Process Control (MSPC)

# Aseptic Injectable Drug Product Manufacturing



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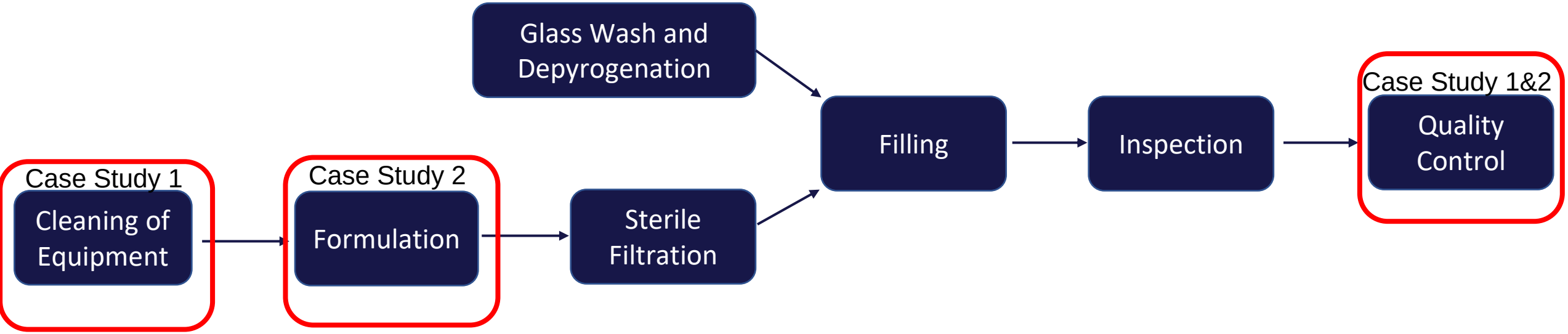
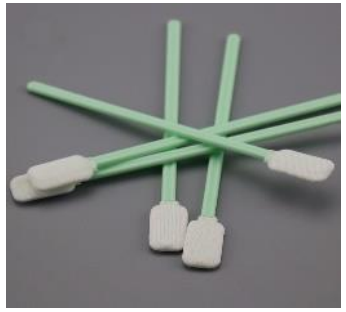
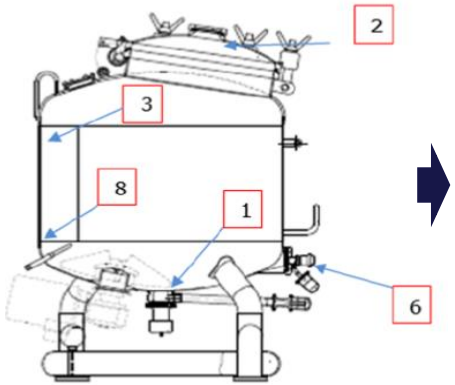


# Case Study 1: Cleaning Validation and Verification






Manual Sampling



**Up to 14 days lead time**
**→ wait or produce at risk**

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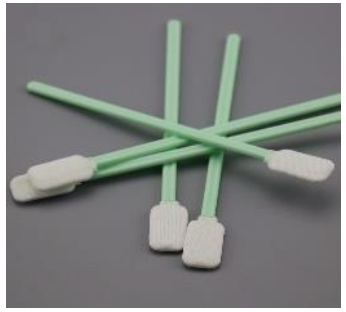

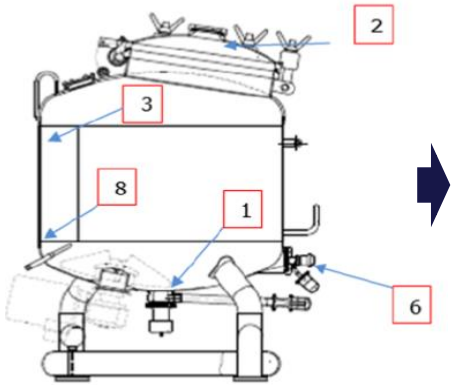




**Manual Sampling**

**Up to 14 days lead time**
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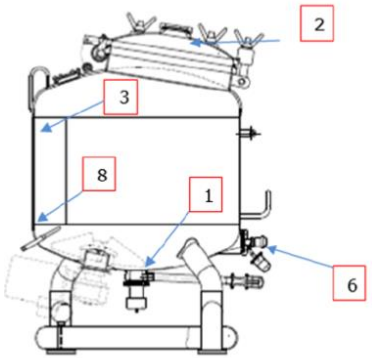
I. Jul-Jørgensen, C. A. Hundahl, E. Skibsted & K. V. Gernaey. ”Sampling Error of TOC swab in Pharmaceutical Cleaning Verification”. In *Journal of Pharmaceutical and Biomedical Analysis* 215 (2022), 114763

I. Jul-Jørgensen, K. V. Gernaey, C. A. Hundahl. ”Handheld FTIR outperforms total organic carbon swab in pharmaceutical cleaning validation”. In *Analyst* 148 (2023), 3835

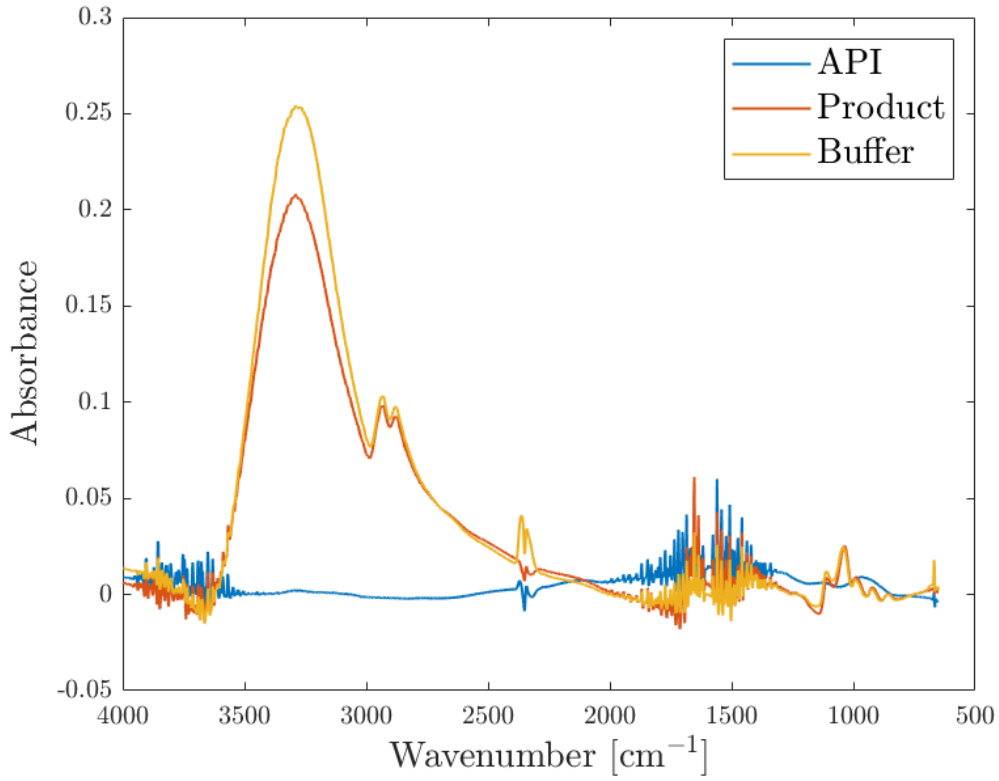
# Case Study 1: Cleaning Validation and Verification





**Instant results**

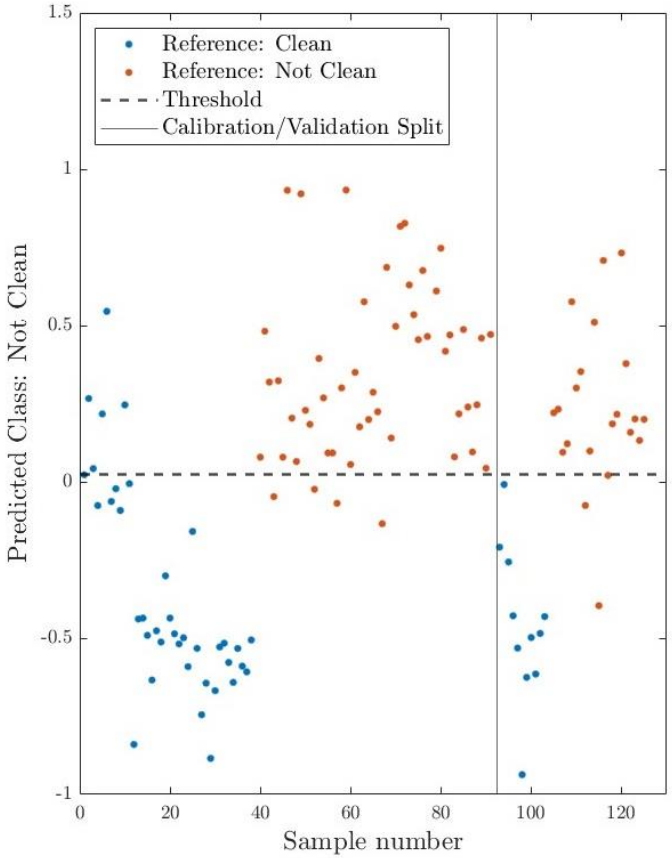
# Model Choices




**Model Choices**

- Low active pharmaceutical ingredient (API)/excipient ratio → predict TOC
- Pass/Fail→ classification model

# Prediction of Samples



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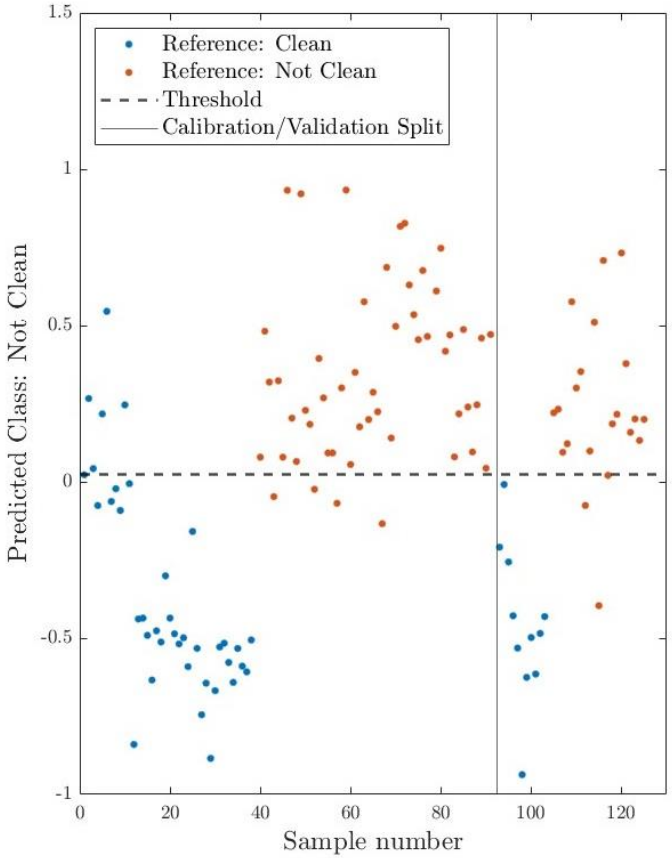
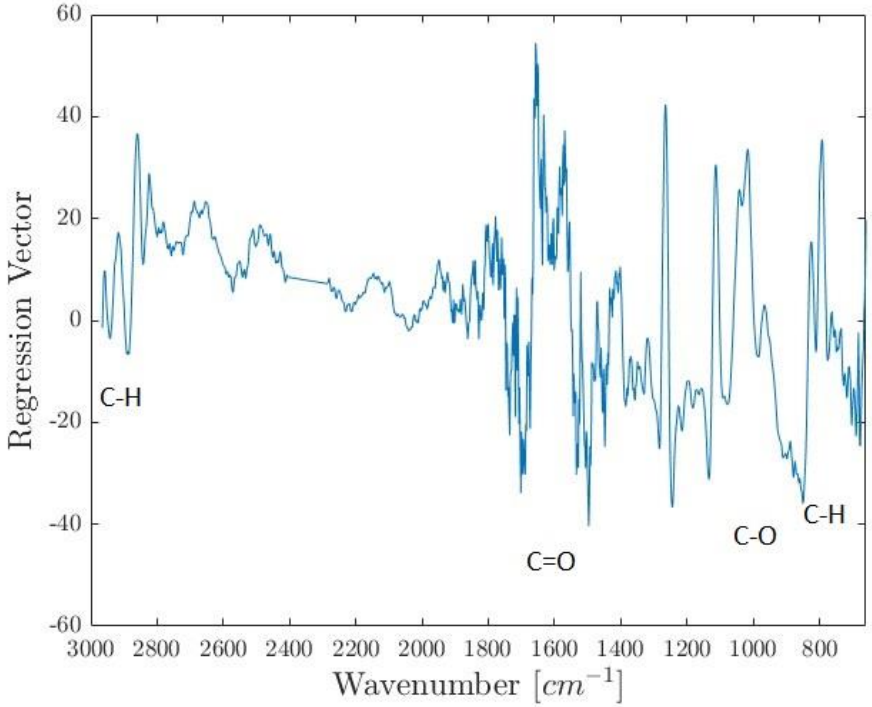


# Performance of Model

| | Calibration | Cross-Validation | External Validation |
|---|---|---|---|
| Sensitivity | 0.98 | 0.96 | 0.94 |
| Specificity | 0.84 | 0.82 | 0.83 |

$$sensitivity = \frac{true\ positives}{true\ positives + false\ negatives}$$

$$specificity = \frac{true\ negatives}{true\ negatives + false\ positives}$$

# Comparison of FTIR vs. TOC swab

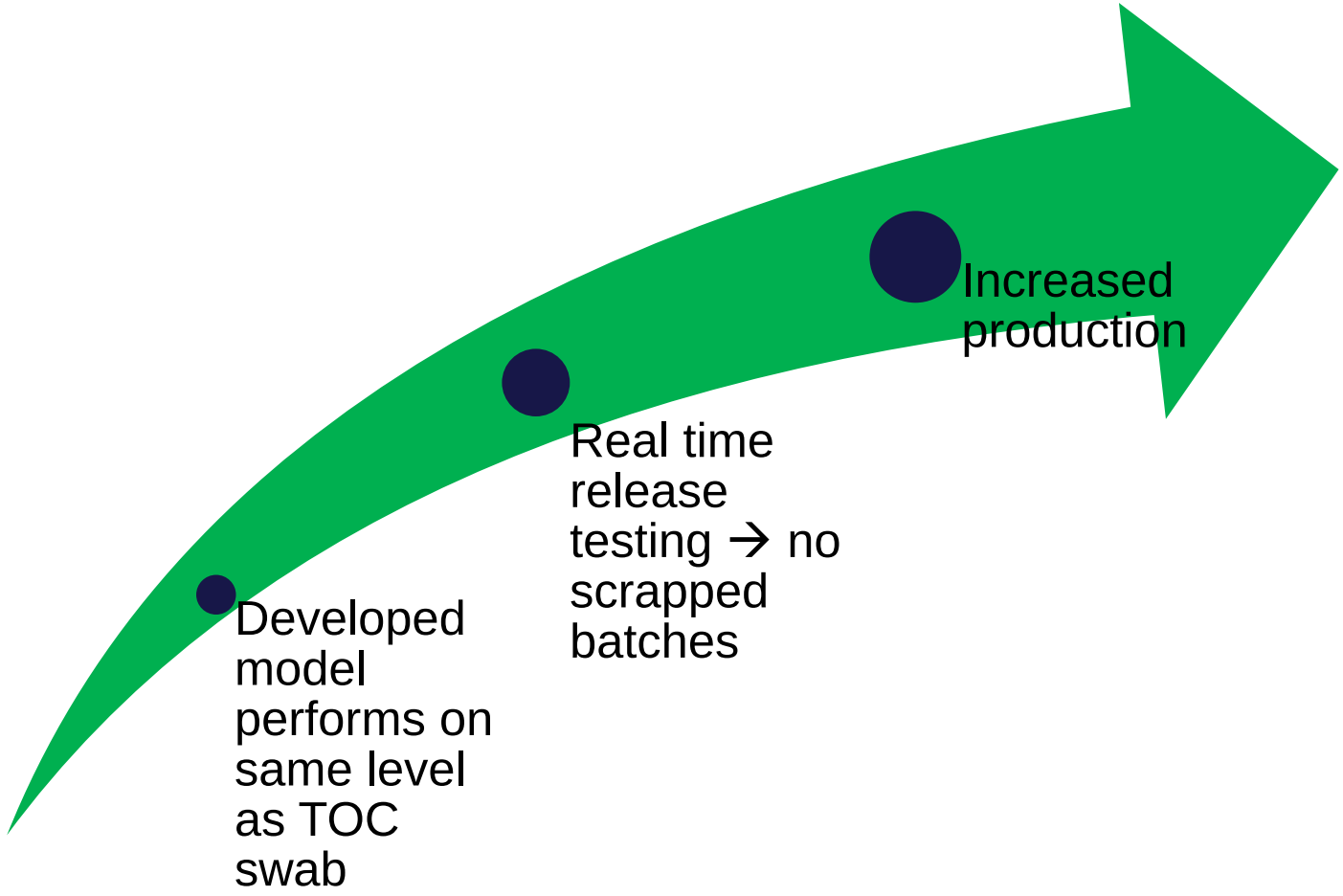
| | FTIR + PLS-DA | TOC swab – Gaussian Error |
|---|---|---|
| Sensitivity | 0.98 | 0.92 |
| Specificity | 0.84 | 0.94 |

Specificity lower for FTIR, but consequence less problematic due to it being RTRT

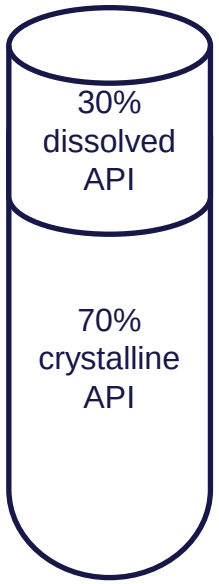
$$sensitivity = \frac{true\ positives}{true\ positives + false\ negatives}$$

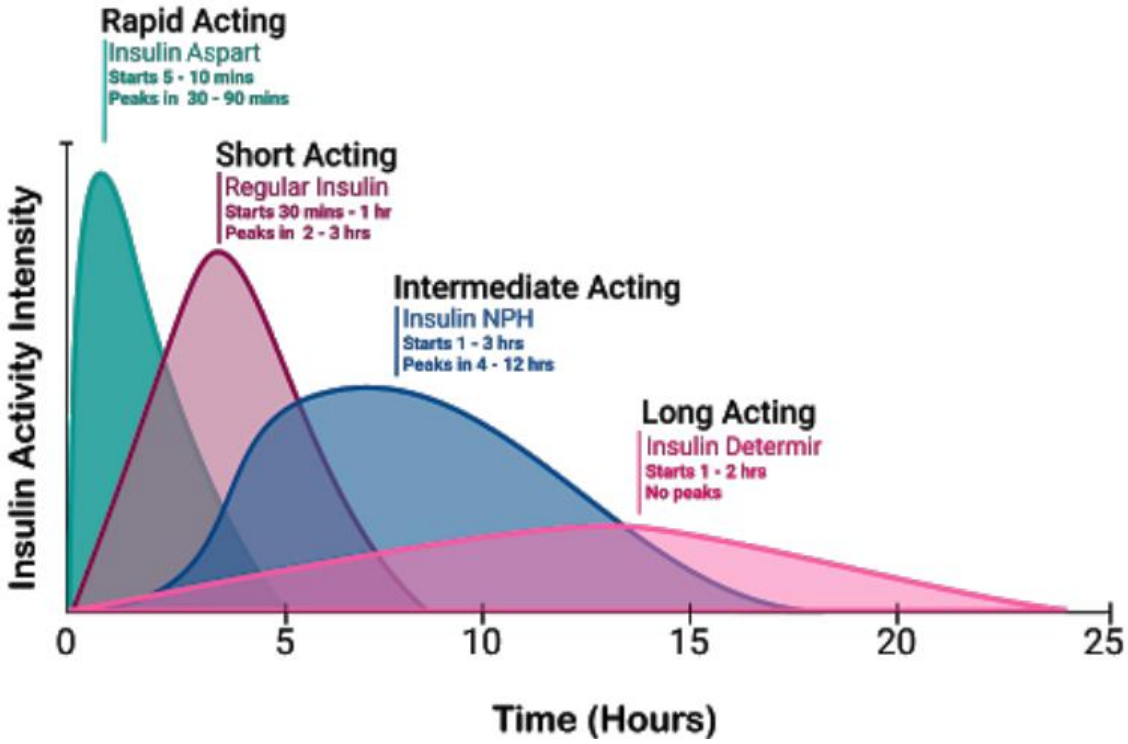
$$specificity = \frac{true\ negatives}{true\ negatives + false\ positives}$$

# Conclusion and opportunities



# Case Study 2: Formulation of Crystalline Drug Product




Source: Diabetes Educational Tool (ucsd.edu)

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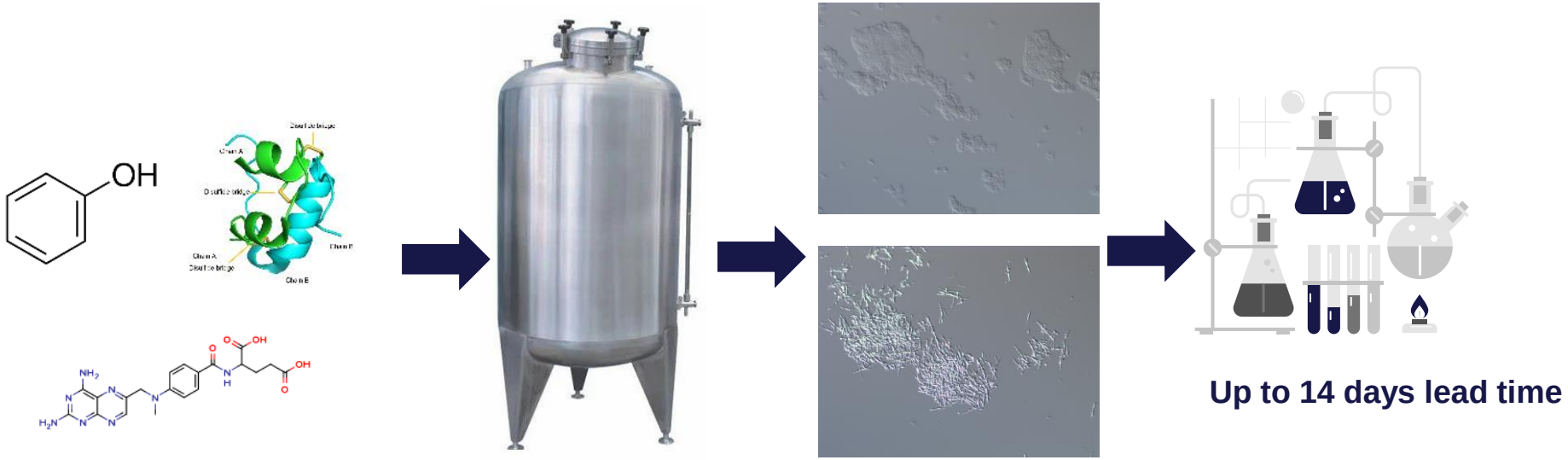



I. Jul-Jørgensen, P. Facco, K.V. Gernaey, M. Barolo & C. A. Hundahl. ”Data Fusion of Raman Spectra in MSPC for Fault Detection and Diagnosis in Pharmaceutical Manufacturing”. In *Computers and Chemical Engineering*

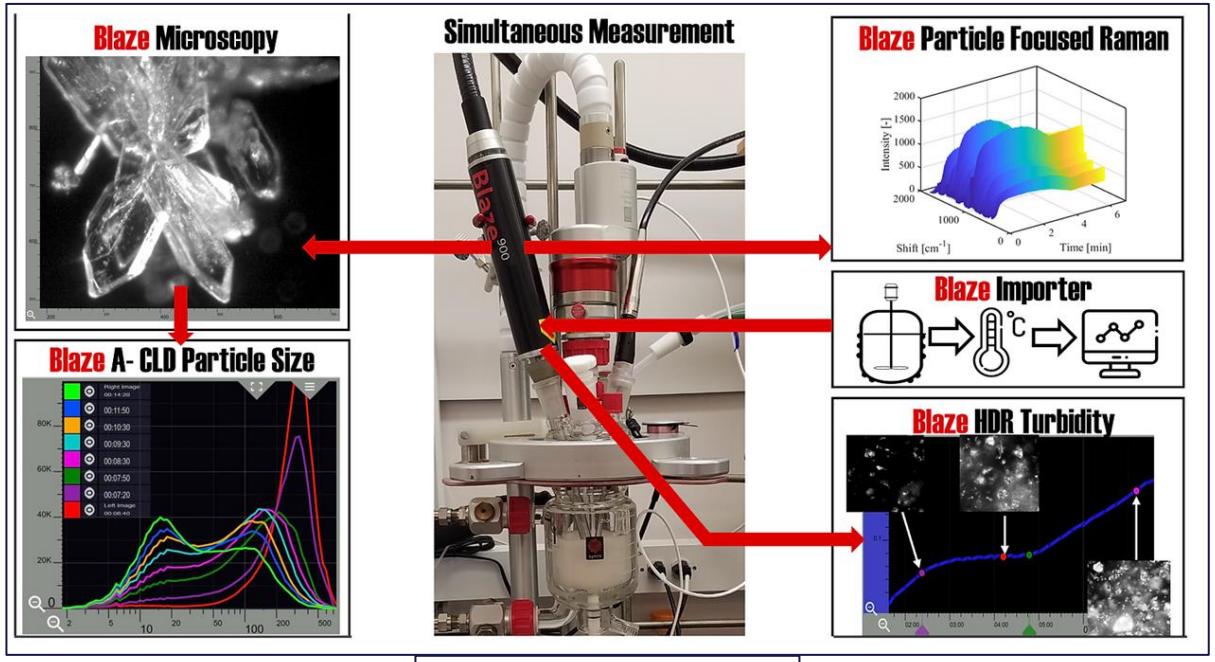
I. Jul-Jørgensen, R. Oliver, K.V. Gernaey & C. A. Hundahl. ”Modernizing Non-Classical Protein Crystallization through Pharma 4.0: Advanced Monitoring and Modelling Utilizing Process Analytical Technology”. In *Chemical Engineering Research and Design*

# Objectives

Develop models based on Raman spectra, turbidity and CLD to in-line predict fraction of crystalline and dissolved API

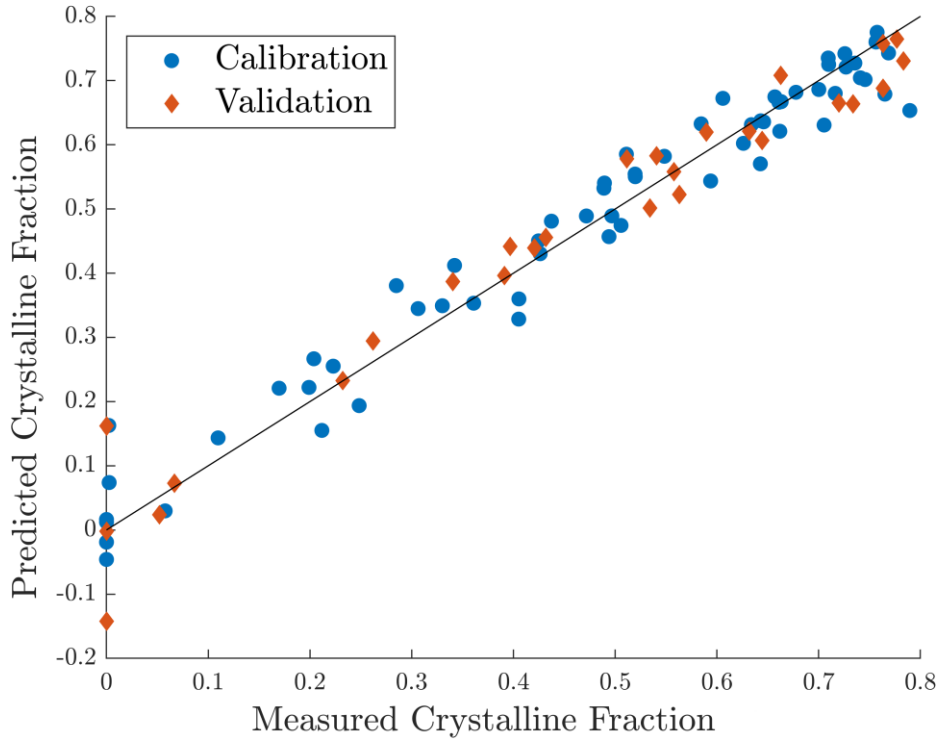
Monitor evolution of the mass fractions during crystallization

Model kinetics of the crystallization




Source: blazemetrics.com

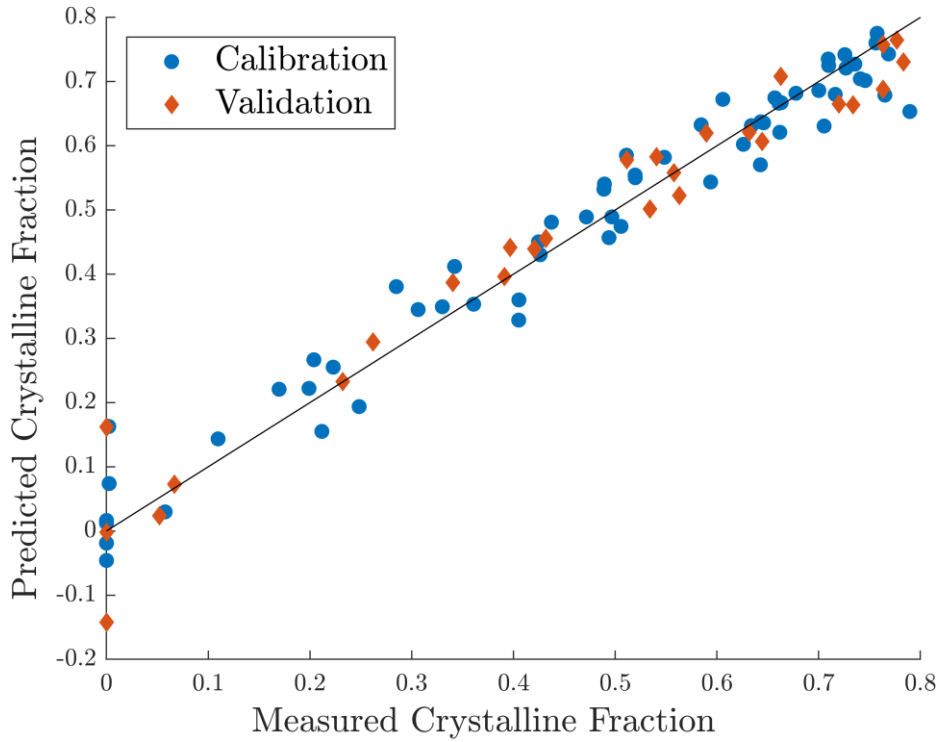
# Crystalline Fraction Model

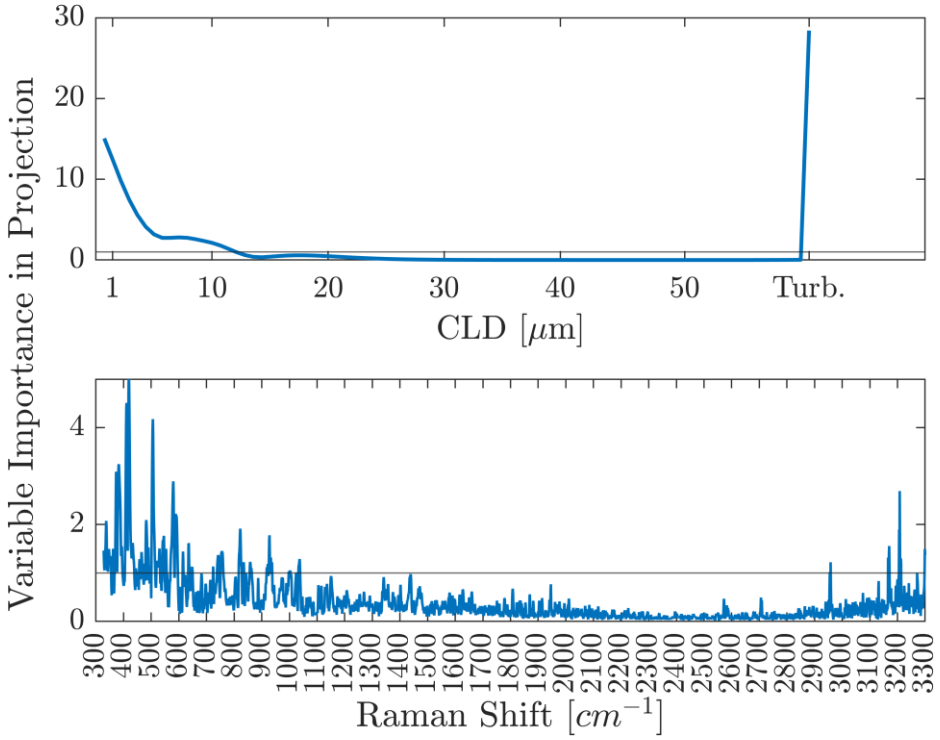



| Figure of Merit | Value |
|---|---|
| RMSEC | 0.01 |
| RMSECV | 0.05 |
| RMSEP | 0.05 |

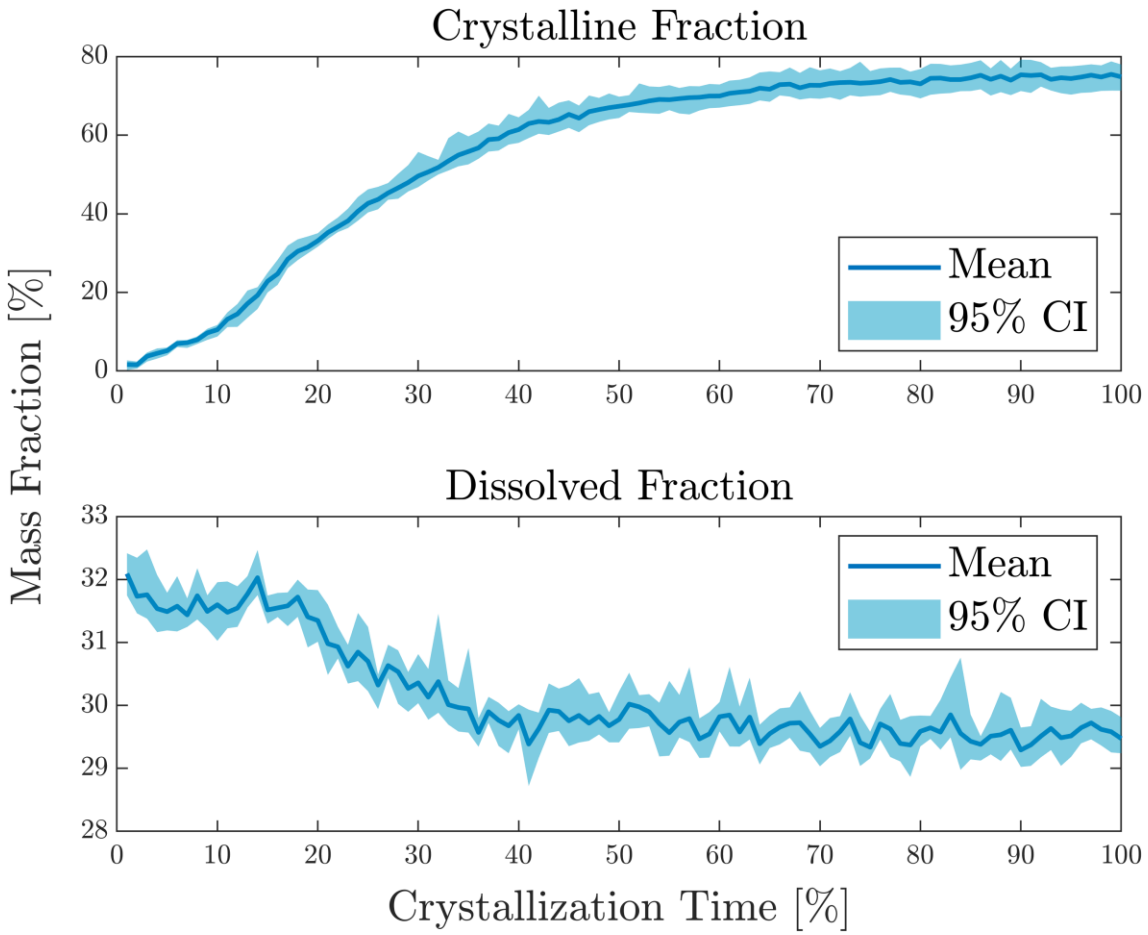
Small-angle X-ray scattering as reference

# Crystalline Fraction Model



# Mass Fraction Evolution



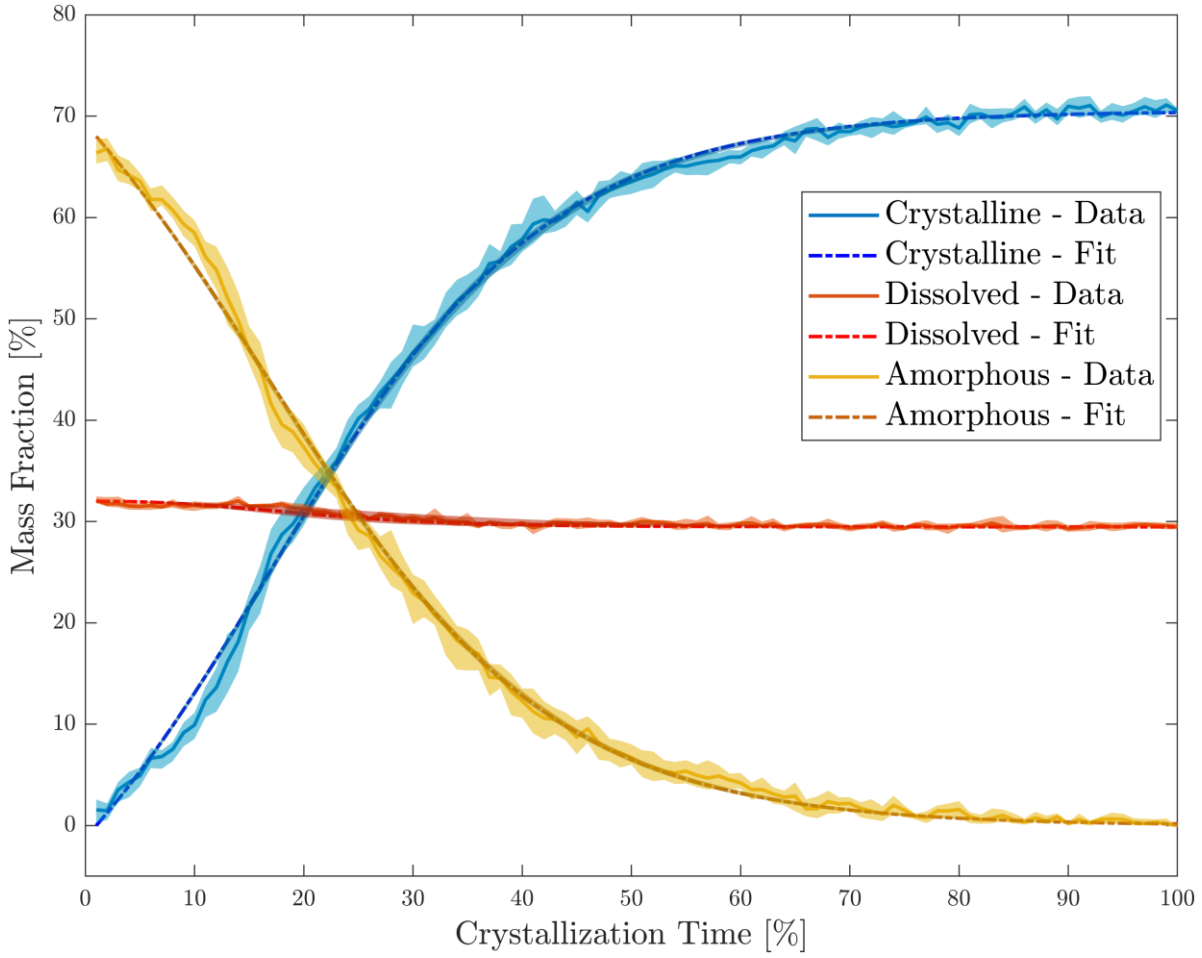

Crystallization Time can be reduced by 50%

# Mass Fraction Modelling

$$\frac{\partial L}{\partial t} = -k_A(L - L_{eq}) - k_{gL}(L - L_{eq})C$$

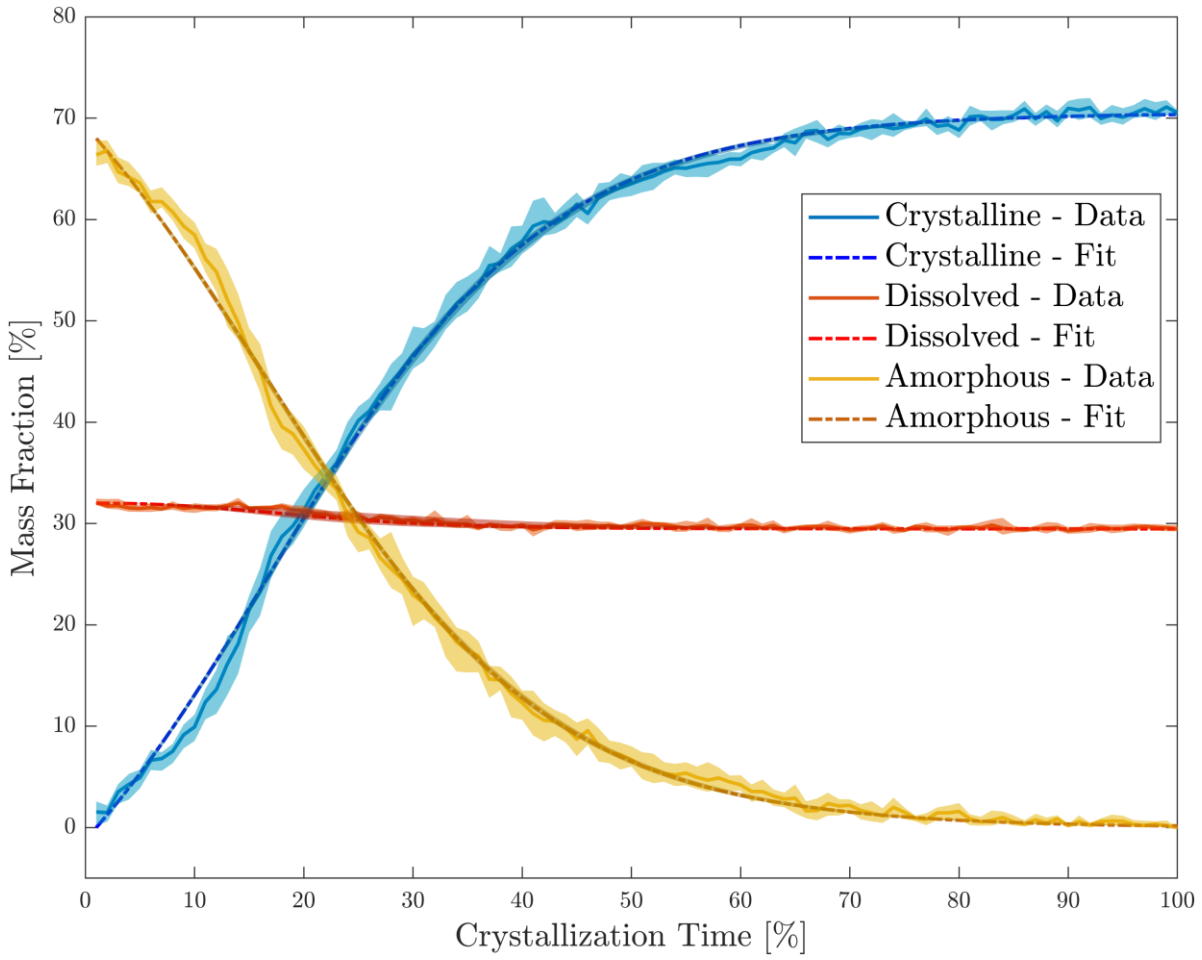
$$\frac{\partial A}{\partial t} = k_A(L - L_{eq}) - k_n A - k_{gA} AC$$

$$\frac{\partial C}{\partial t} = k_n A + k_{gA} AC + k_{gL}(L - L_{eq})C$$

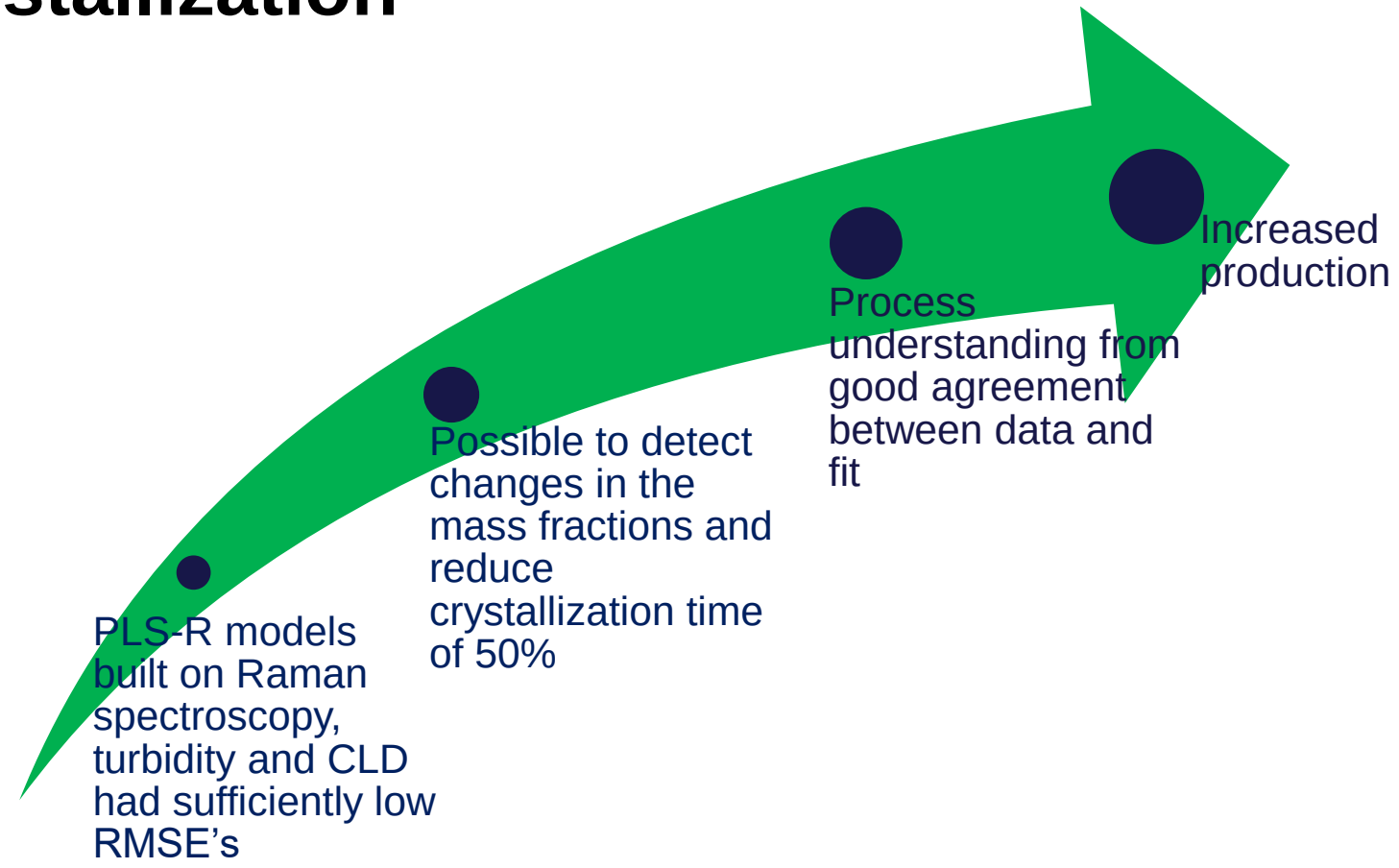


# Mass Fraction Modelling

| RMSE | Value |
|---|---|
| $RMSE_{crystalline}$ | $2.0\% \pm 0.7\%$ |
| $RMSE_{dissolved}$ | $0.6\% \pm 0.2\%$ |
| $RMSE_{amorphous}$ | $2.1\% \pm 0.8\%$ |
| $RMSE_{mean}$ | $1.6\% \pm 0.9\%$ |



# PAT for Monitoring and Modelling a Non-classical Crystallization

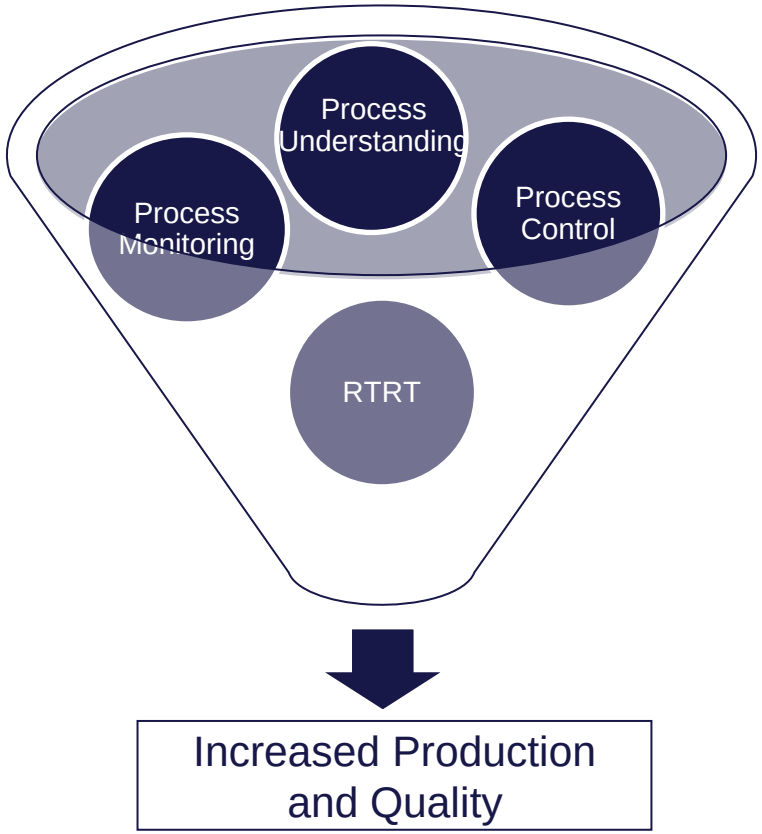


# Conclusions

Using PAT, incl. Chemometrics,

**Case Study 1**: Revitalized pharmaceutical cleaning validation and verification through RTRT

**Case Study 2**: Process monitoring and understanding enables reducing the process time by 50%



# Thank you!