



# Integrated real-time PAT through SIMATIC SIPAT

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**SIEMENS**



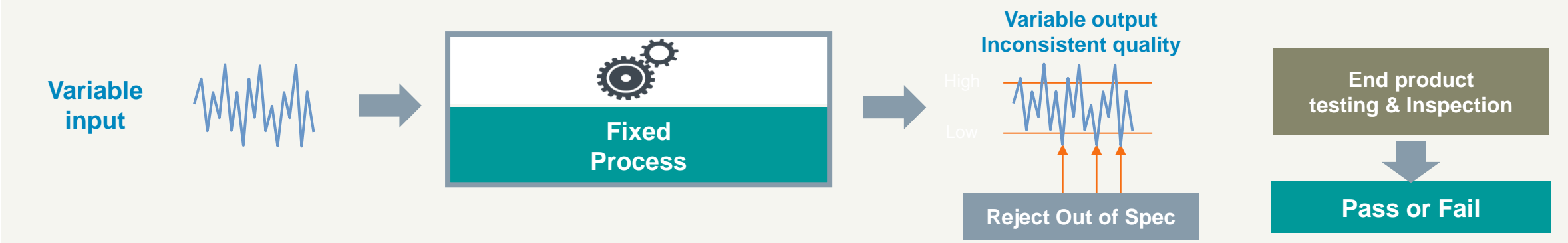
**PAT**  
**for eggs ?**



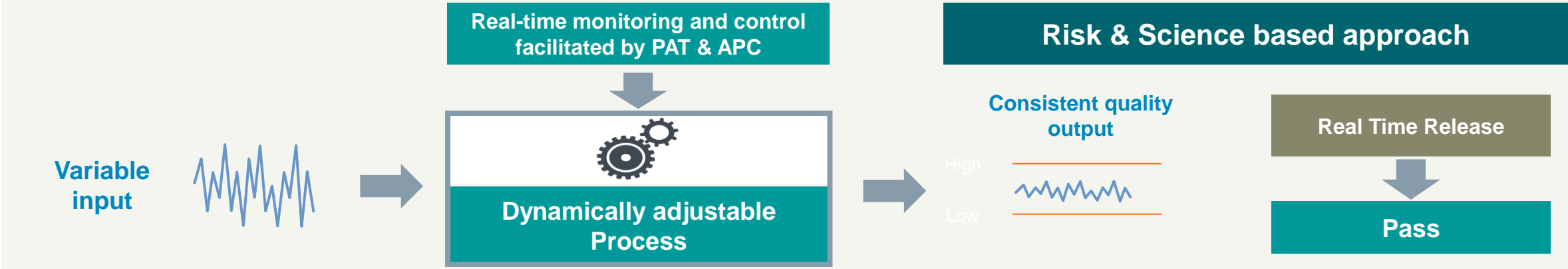
# Process control evolution

## Quality by Design (QbD)

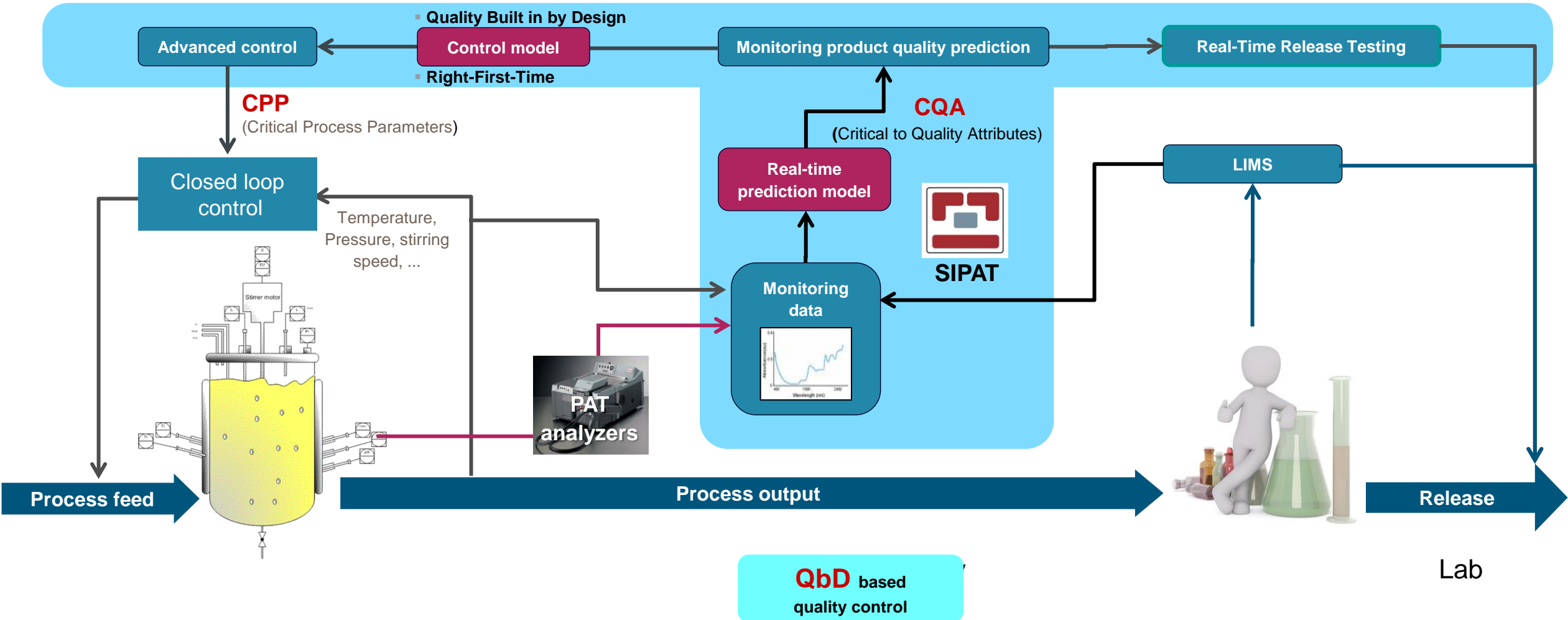
### Quality by Inspection – Current state



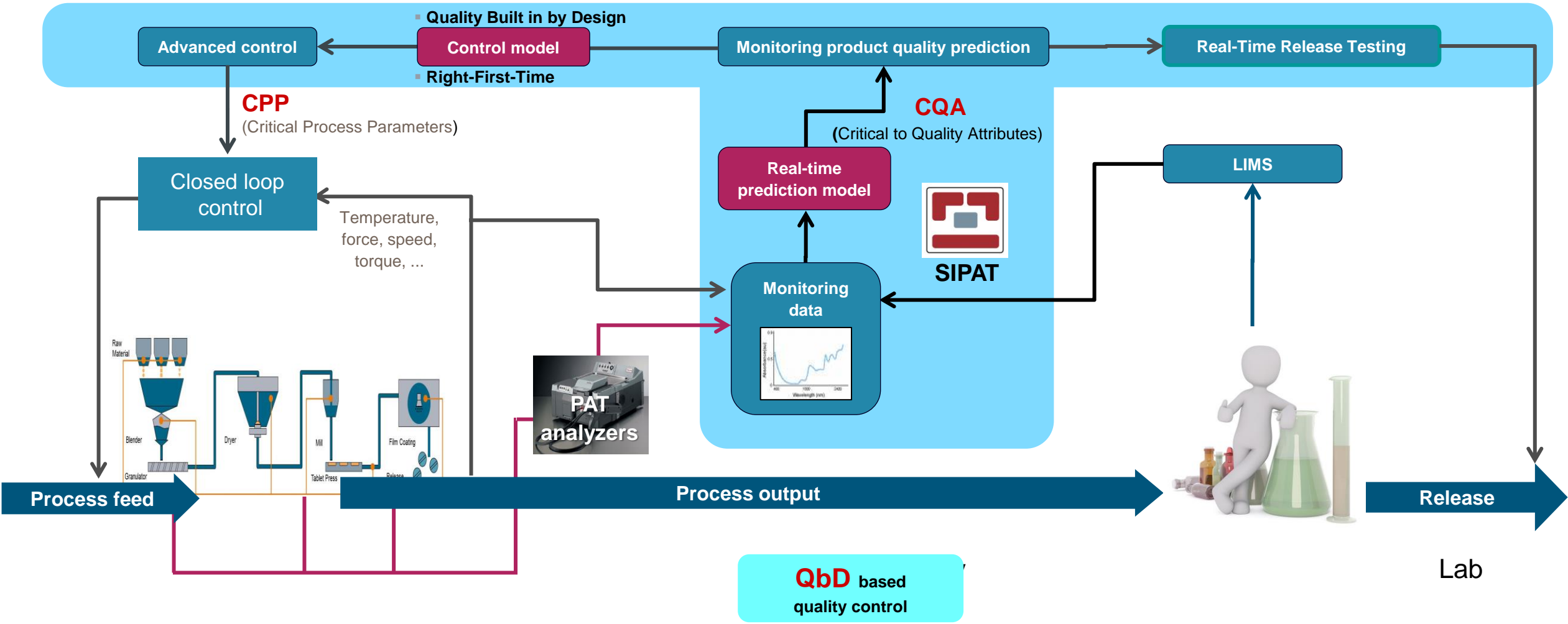
### Quality by Design – Desired future state



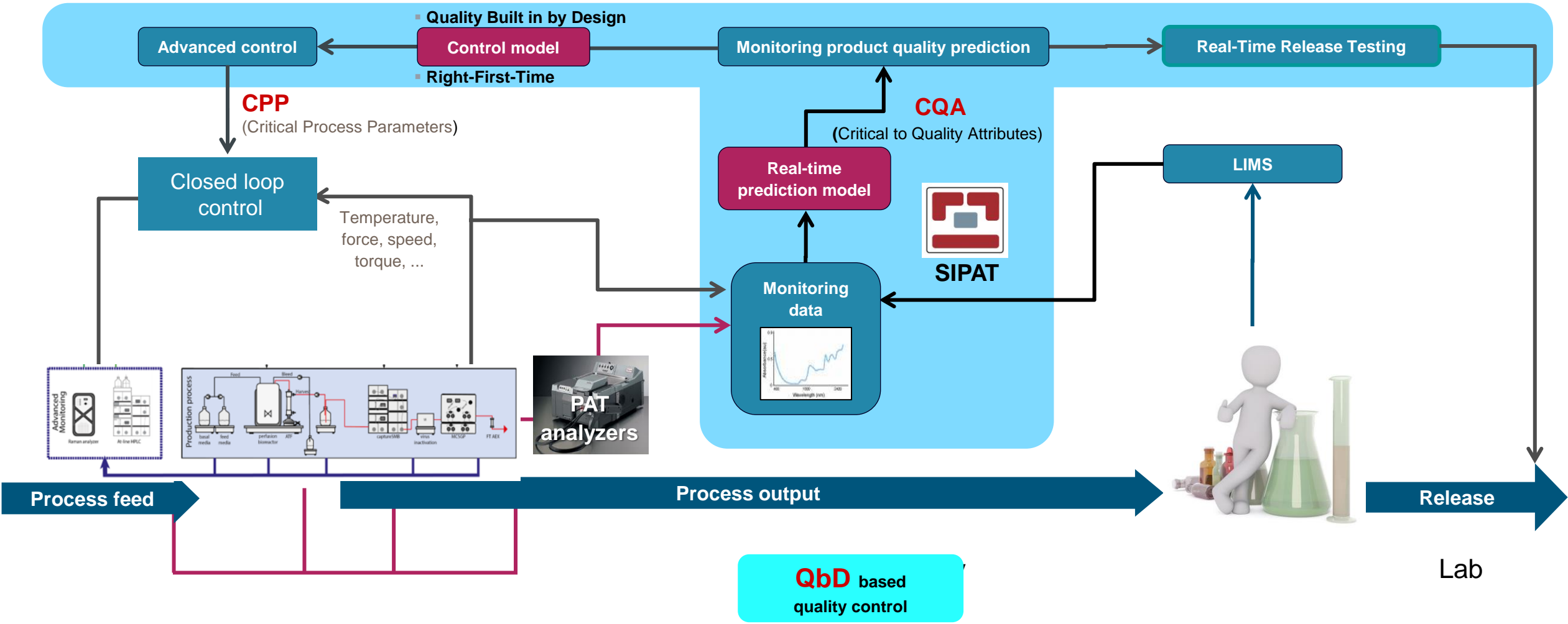
# The principle of PAT & Quality by Design (QbD)



# The principle of PAT & Quality by Design (QbD)



# The principle of PAT & Quality by Design (QbD)





The screenshot displays the SIMATIC SIPAT software interface, which is used for configuring and monitoring industrial processes. The interface is divided into several sections:

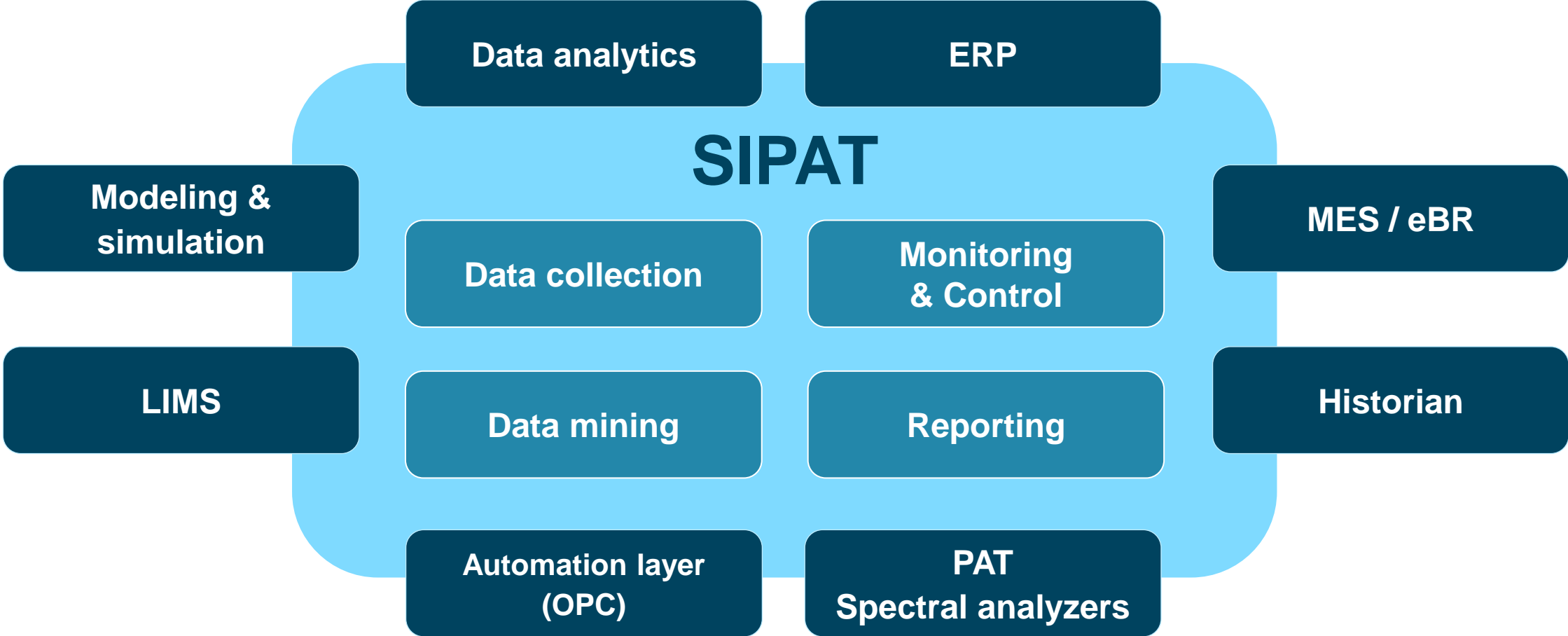
- Methods:** A list of methods is shown, with the selected method being "01-1-0500-MTB-11 (001.00) On X6403SIPATQAW7 (runs on SIPATQAW7X6413) (001.01)".
- Method is started:** A status bar indicates that the method is running.
- Collectors:** A list of active collectors is shown, including "01-1-0500-CHC", "01-1-0500-XM", and "01-1-0500-SHD".
- Data Plots:** Several graphs are displayed, showing data trends over time. The plots include:
  - 01-1-0500-CHC: A line graph showing data points over time.
  - 01-1-0500-CHD: A line graph showing data points over time.
  - 01-1-0500-CHG: A scatter plot showing data points over time.
  - 01-1-0500-CHH: A line graph showing data points over time.
- Manual Data:** A table of manual data is shown, with columns for "Time\_K", "T1-PCA", "T2-PCA", "T3-PCA", "T4-PCA", and "T1-PLS".
- Configuration:** A detailed configuration window is open, showing various parameters and settings for the method. It includes sections for "Reference" and "Validity", and a "CO2 level" section with a "Validity Range" set to "60" and "75".

# SIMATIC SIPAT

## Look & feel

# SIMATIC SIPAT

Our offering for integrated PAT Data Management



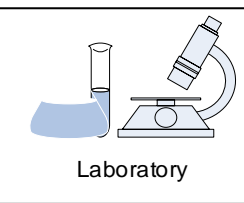


# SIMATIC SIPAT

## Real time capabilities



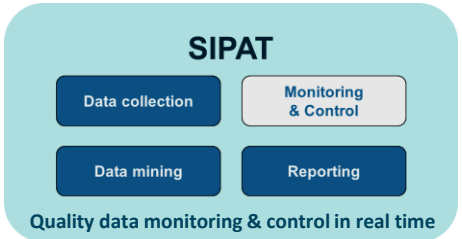
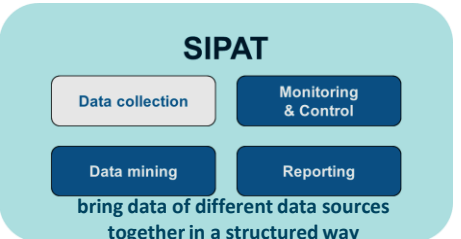
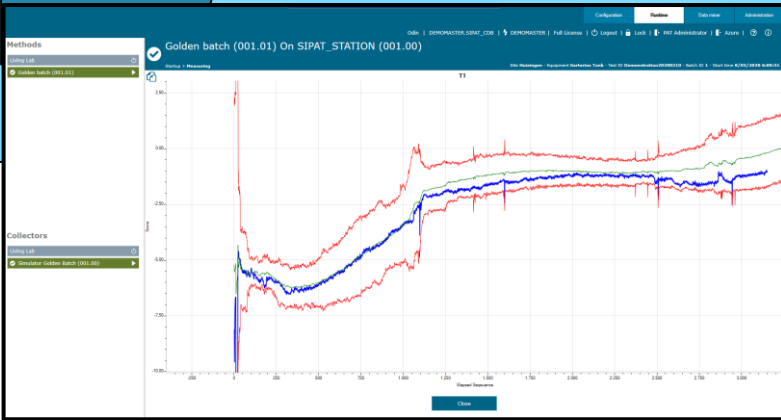
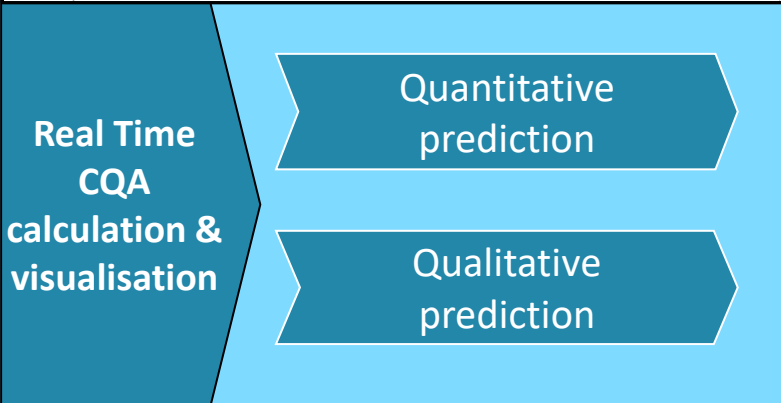
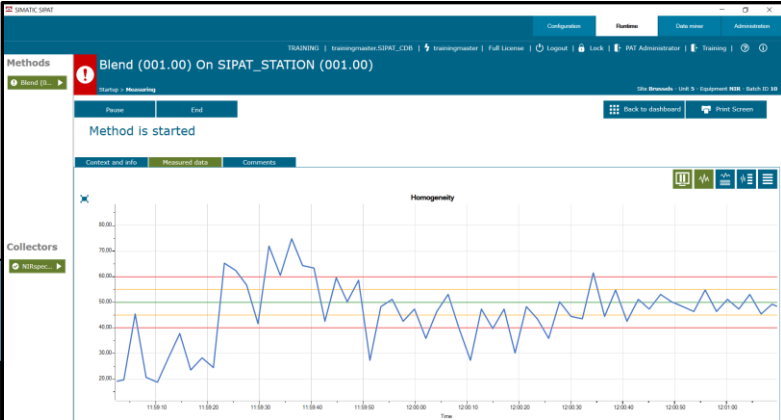
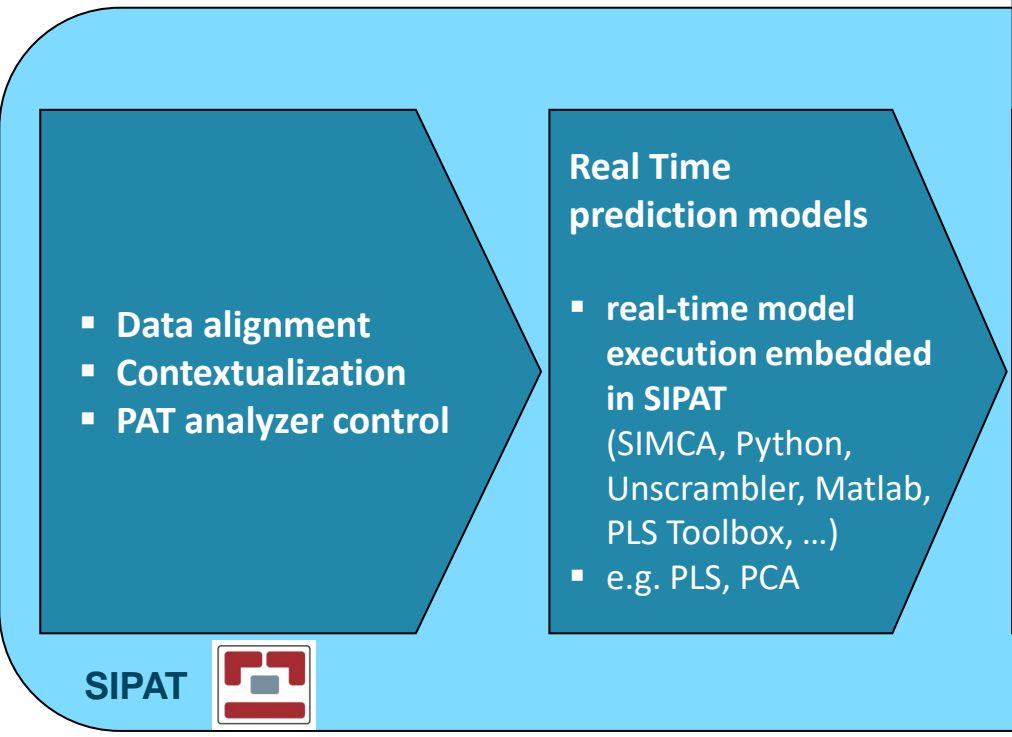
**PAT analyzer data**



**LIMS data  
(e.g. raw material data)**



**Process data**



# SIMATIC SIPAT - collectors

## Bidirectional communication with process analyzers for 21CFR11

Standard analyzer connection –  
data collection & instrument control - available for:

- Kaiser RxN-series - Raman
- Sentronic SentroPAT - NIR
- Bruker Matrix-F - NIR
- Bruker MPA - NIR
- Zeiss MCS 500 series – UV-VIS photodiode array
- Zeiss MCS 600 series – UV-VIS / FT-IR
- Mettler Toledo ReactIR - FT-IR
- Mettler Toledo FBRM - PSD
- Thermo Scientific Antaris family - NIR
- Malvern Insitac/Mastersizer via Link II - PSD
- ABB FT-IR 2000 – FT-NIR
- Expo/Prozess Industries ePAT 601 - NIR
- Ocean Optics QEPro – UV
- Tornado Hyperflux - Raman
- Viavi MicroNIR - NIR

Project based analyzer connection –  
done with :

- Bruker Tandem tablet tester
- GEA LightHouseProbe
- Waters Patrol - UPLC
- Indatech - Raman/UV
- InProcess LSP NanoFlowSizer - PSD
- Thermo Scientific U3000 – UPLC
- GE AKTA Unicorn
- Horiba Aqualog
- Parsum probe
  
- (Siemens Maxum GC)

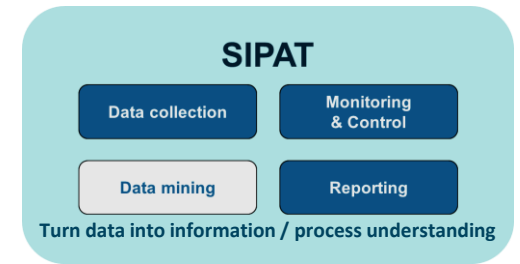
Exact supported instrument software versions depend on the SIPAT version in place.

New standard bidirectional interfaces for instruments between brackets under investigation.

This list is showing instruments that can be controlled by SIPAT off the shelf, collection of (spectral) data generally always possible on project basis.

# SIMATIC SIPAT

## Offline capabilities



### Data Miner

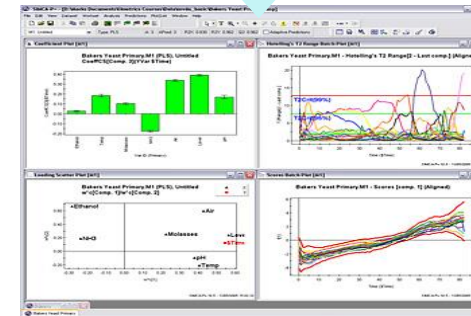
- Use collected **structured datasets** into useful process information
- Reality check** on existing statistical models - create / optimize model
- Seamless **bidirectional interaction** with multiple modeling tools:

### Turning data into knowledge

- Improved **process understanding**
- Continuous improvement cycles**  
→ Essence of QbD philosophy


DATE ↓	Batch ID ↓	Equipment ↓	Intensity ↓	Temperature ↓	Shear Rate ↓	PSD ... ↓	Quality ↓	DModX ↓	Organic ... ↓	Aqueous... ↓
05/11/2019 13:09:16...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1863,9	0	1,23	051119	041119
05/11/2019 13:14:55...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1163,5	1	1,08	051119	041119
05/11/2019 13:26:37...	19ASB049	NanoflowSizer	Spectrum	296,3	161	1186,0	0	1,33	051119	041119
05/11/2019 13:26:52...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	771,9	1	1,15	051119	041119
05/11/2019 13:27:04...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1523,8	1	1,23	051119	041119
05/11/2019 13:27:16...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1381,6	1	1,19	051119	041119
05/11/2019 13:27:28...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1646,3	0	1,12	051119	041119
05/11/2019 13:27:40...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1321,8	1	1,25	051119	041119
05/11/2019 13:27:52...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1278,5	1	1,39	051119	041119
05/11/2019 13:28:05...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1248,0	1	1,27	051119	041119
05/11/2019 13:28:17...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1326,2	1	1,45	051119	041119
05/11/2019 13:28:41...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1178,1	1	1,51	051119	041119
05/11/2019 13:28:53...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1445,6	0	1,12	051119	041119
05/11/2019 13:29:18...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1185,0	1	1,21	051119	041119
05/11/2019 13:29:30...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1541,7	0	1,45	051119	041119
05/11/2019 13:29:54...	19ASB049	NanoflowSizer	Spectrum	296,3	1794	1503,1	1	1,11	051119	041119

Create / optimize models



# SIMATIC SIPAT

## Offline capabilities

	<b>JANUVIA SIPAT BATCH Release Report</b>	
	Batch ID: 3401330	Product Name: JANUVIA

SIPAT

Data collection

Monitoring & Control

Data mining

Reporting

Example of Real Time Release report

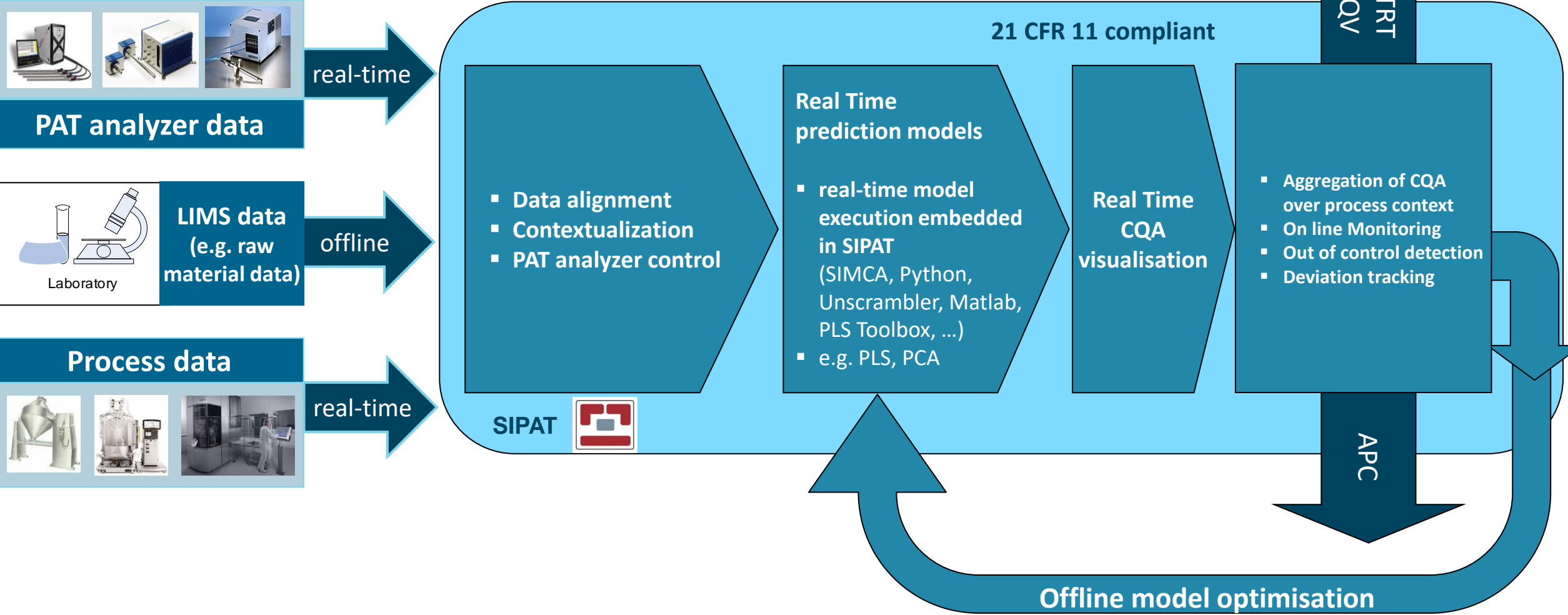
BATCH SUMMARY			
		Site:	MSD Cramlington
		Product Strength:	50mg
		Batch ID:	3401330
NIR Assay Method ID and Result:	NIR Identity Method ID and Result:	Disintegration Method ID and Result:	Weights and Results Method ID and Result:
MK-0431 50mg Tab CA NIR-01 v 001.00	RM MK-0431 Tablet NR-01 v 001.00	MK-0431 Tab Disintegration v 001.00	MK-0431 Weights and Results v 001.00
PASS	PASS	PASS	PASS

Prepared By: \_\_\_\_\_ Date: \_\_\_\_\_



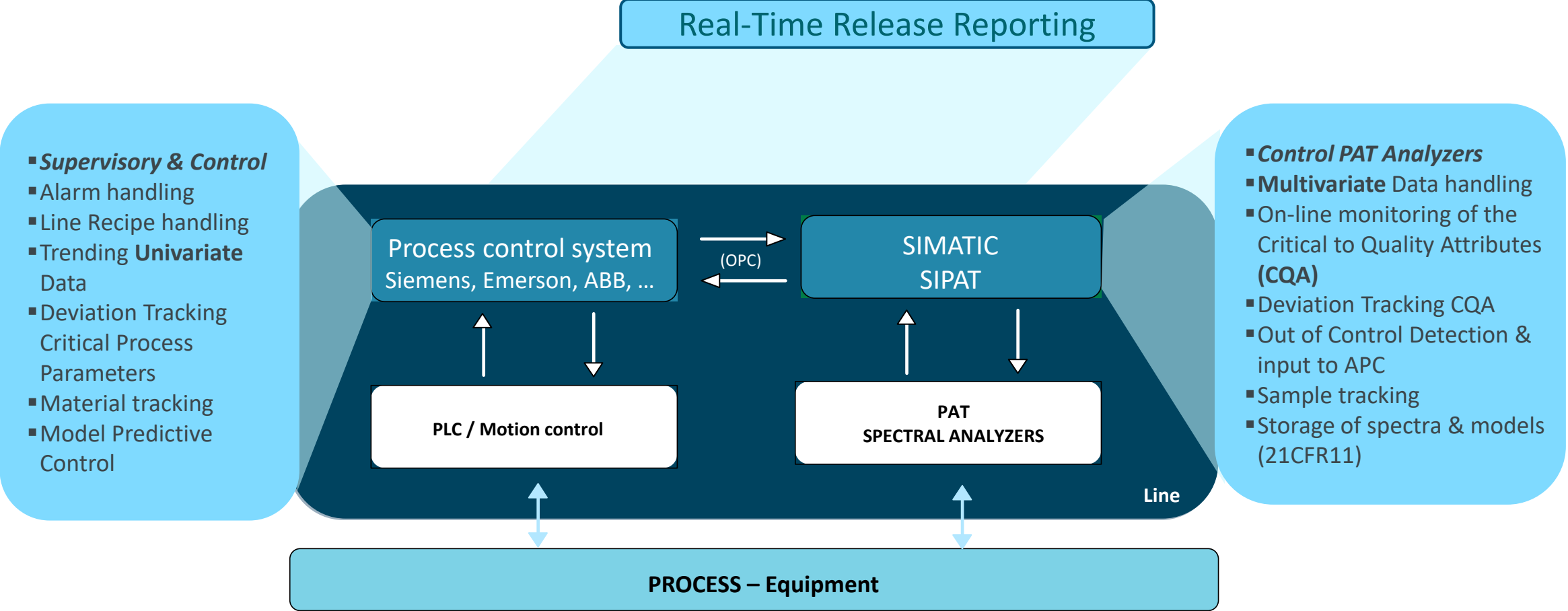
# SIMATIC SIPAT

## Functional summary



# SIMATIC SIPAT

## High level system architecture



# SIMATIC SIPAT, the perfect tool for PAT data management

## SIEMENS, the perfect partner for PAT projects

### SIPAT Benefits

- Central PAT data management
- Real-time quality prediction & monitoring
- Enabling Real time release
- Shorten Time to Market
- Supporting QbD-based process development in a structured way
- Reduce Scrap/Rework
- Reduce development & production time
- Key-enabler for continuous manufacturing
- Enabling Advanced Process Control (APC)
- Part of Digital Twin initiatives

### SIPAT

- Development started in 2006
- Market introduction: mid 2007
- To date: SIPAT 5.1.2. (September 2022)
- Development based on customer needs and market needs

### Corporate SIPAT customers

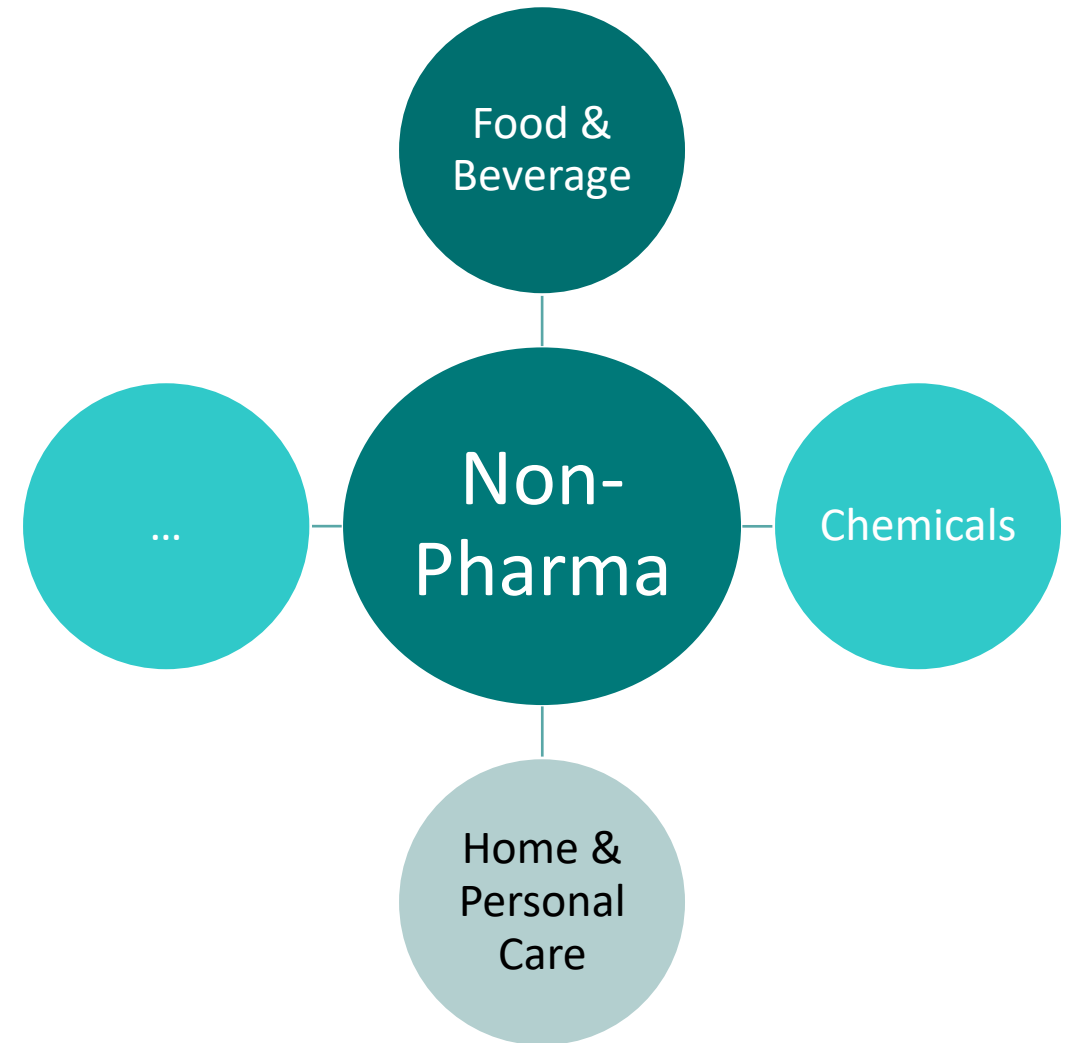
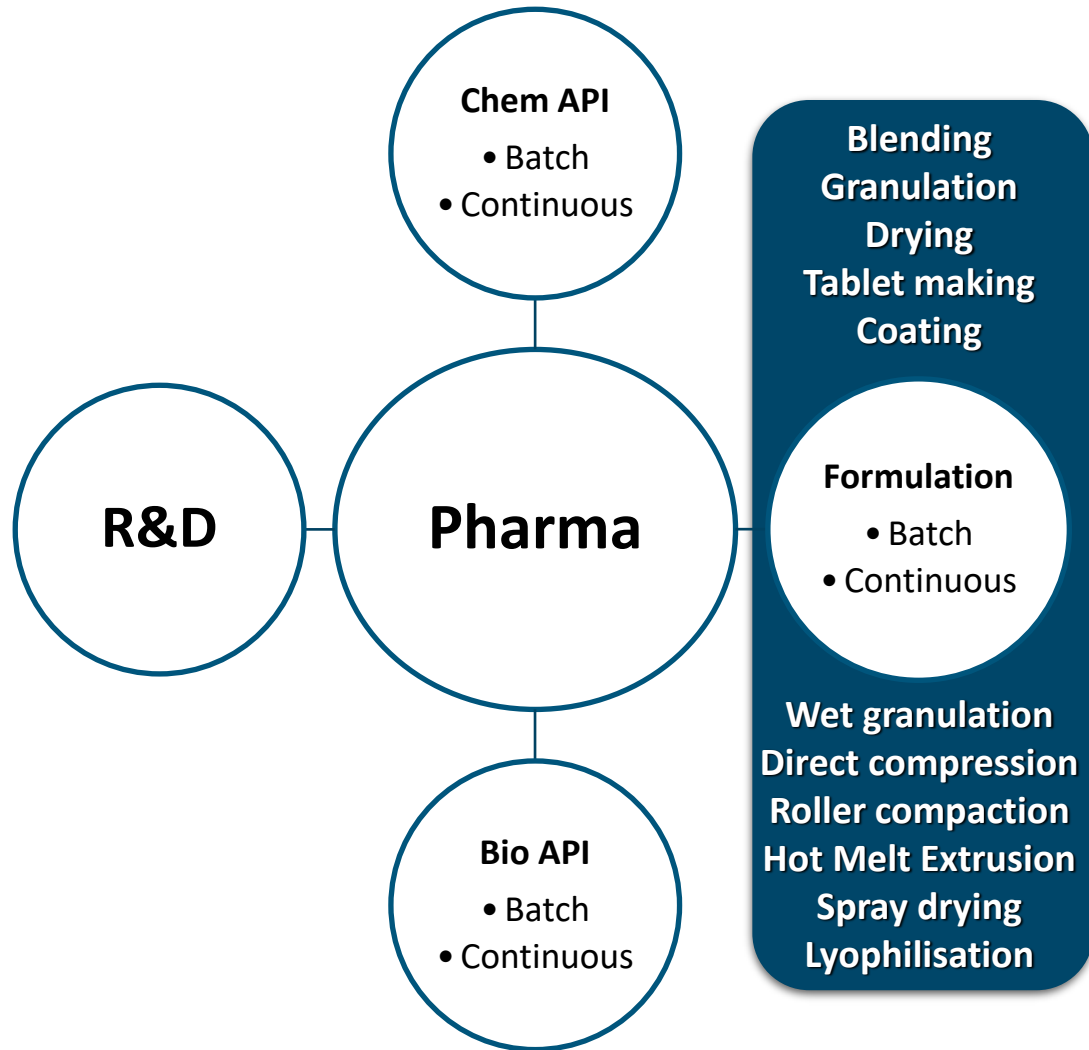


### Some of our SIPAT customers



# SIMATIC SIPAT designed for pharma

applicable in different branches





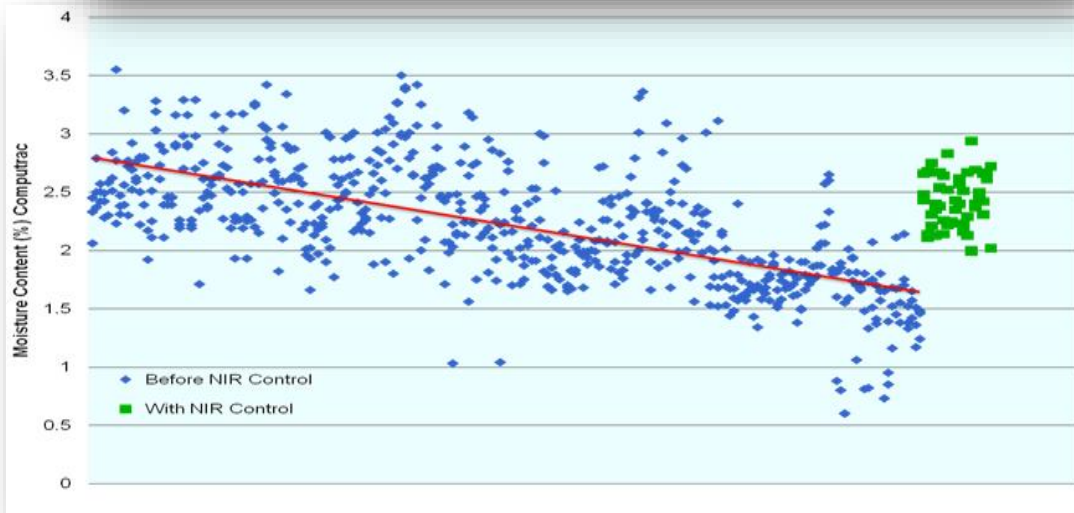
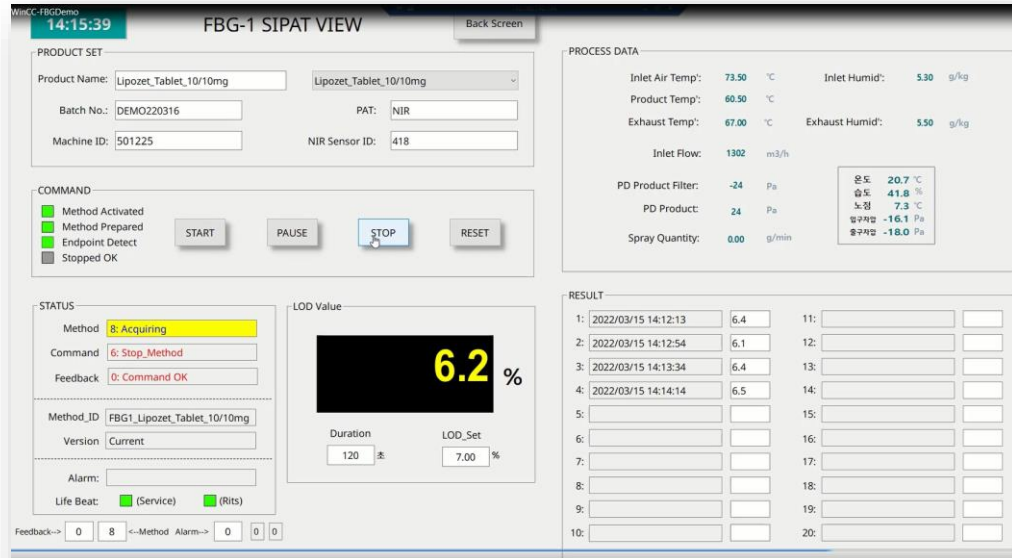


SIPAT –

Some use cases

# Use case

## End point determination on drying / blending processes



### Scope

- Moisture content monitoring of drying granules in real-time to determine the end of the process (NIR)
- Blend uniformity determination in e.g. feed frame of a tablet press (NIR)
- Moisture content in liquids (e.g. alcohols) (NIR)
- Residual humidity in coated tablets (MW)

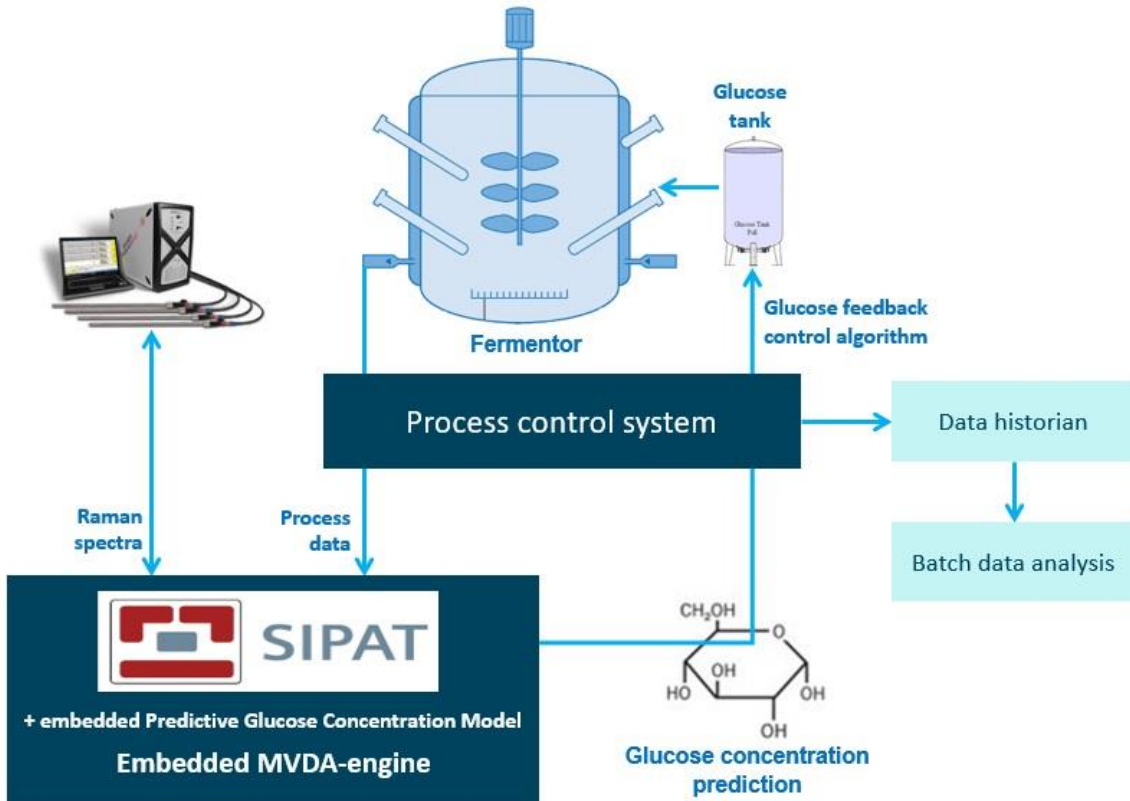
### Benefits

- Yield increase
- Minimize waste product
- Minimize energy consumption



# Use case

## Glucose monitoring on fermentation unit



### Scope

- Real-time prediction of **glucose concentration** through Raman / NIR integration
- Real-time monitoring of **metabolics**
- Real-time **glucose feeding calculation** to increase cell growth

### Benefits

- Product yield optimization
- Storage of spectral data in SIPAT conform 21CFR11

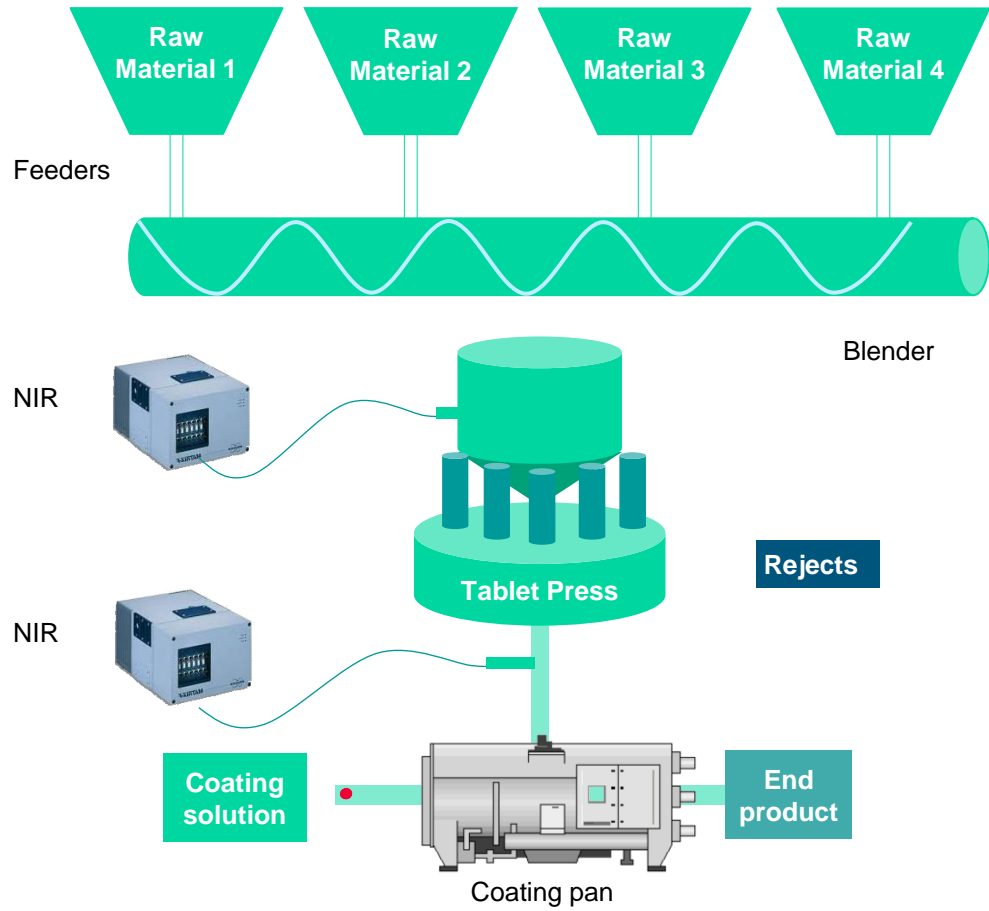


GEDEON RICHTER

SIEMENS

# Use case

## Continuous tablet manufacturing



### Scope

- Blend Uniformity in feed frame of the press via NIR
- Moisture content (wet granulation) after dryer via NIR
- Content Uniformity after the press via NIR
- Coating thickness after coater via Raman
- API concentration in feeders via NIR or Raman
- Particle size after milling via PSD
- Diverter control based on quality predictions through PAT

### Benefits

- Continuous quality verification
- Real-time release testing
- Improved yield



# Use case

## (Continuous flow) chemistry



### Scope

- Residual impurity concentration monitoring in real-time at the end of the line/process (HPLC)
- Real-time monitoring of particle size (UV)
- Real-time API content monitoring on the purification step (HPLC)

### Benefits

- Minimize waste product
- Increase Right-first-time

teva

GSK

Cambrex



University of  
Zagreb

AstraZeneca

CMAC  
FUTURE MANUFACTURING  
RESEARCH HUB

Agency for  
Science, Technology  
and Research  
SINGAPORE

SIEMENS

## Use case

# Continuous biomanufacturing combining upstream and downstream



### Scope

- **Glucose concentration** monitoring in real-time on the fermentor step (Raman / NIR)
- Real-time monitoring of **protein concentration** (UV)
- Real-time **API content** monitoring on the purification step (HPLC)
- Elution curves as basis for **protein concentration** (UPLC)

### Benefits

- Minimize waste product
- Increase Right-first-time



**GSK**

**ETH** zürich

**SIEMENS**

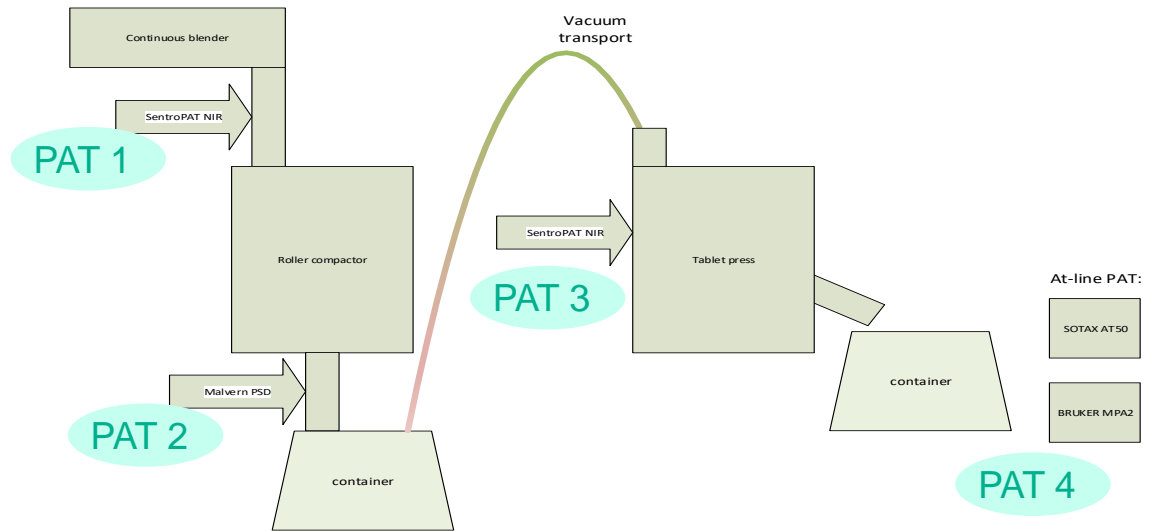


SIPAT –

Some use cases in Scandinavia...

# SIMATIC SIPAT - Use case formulation

## SIPAT on a continuous dry granulation tableting process



### Project scope

- Continuous dry granulation tablet compression line
  - Composed of unit operations of different providers
  - Sandbox pilot in process development

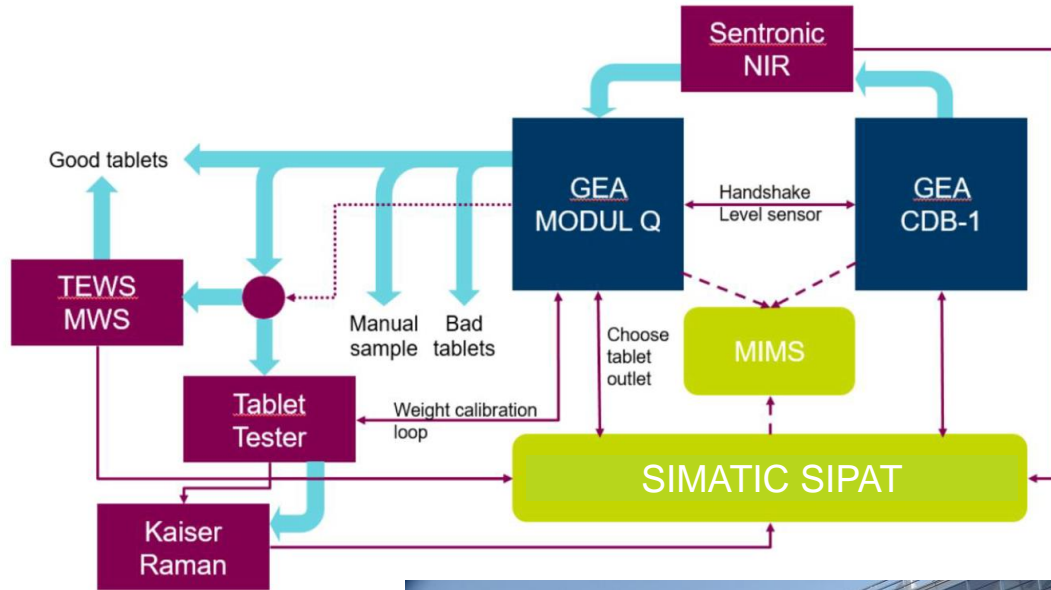
### PAT scope

- Particle Size
  - Malvern Insitec after roller compactor
- Blend uniformity
  - 2x Sentronic SentroPAT NIR, one after conti blender and one in the tablet press feed frame
- Content uniformity
  - Bruker MPA-II with Sotax AT-50 tablet tester after tablet press



# SIMATIC SIPAT - Use case formulation

## SIPAT on a continuous direct compression process



### Project scope

- Continuous direct tablet compression line
  - Based on GEA ConsiGma CDB-1 conti blending unit in combination with GEA Modul-Q tablet press
  - Pilot setup for R&D purposes but GMP prepared for clinical trials

### PAT scope

- Blend uniformity
  - Sentronic SentroPAT multiprobe NIR, positioned in feed frame of tablet press and after blending unit
- Content uniformity
  - Kaiser Raman unit combined with Sotax AT-50 tablet tester after tablet press
- Moisture content in tablets
  - TEWS microwave sensor after tablet press



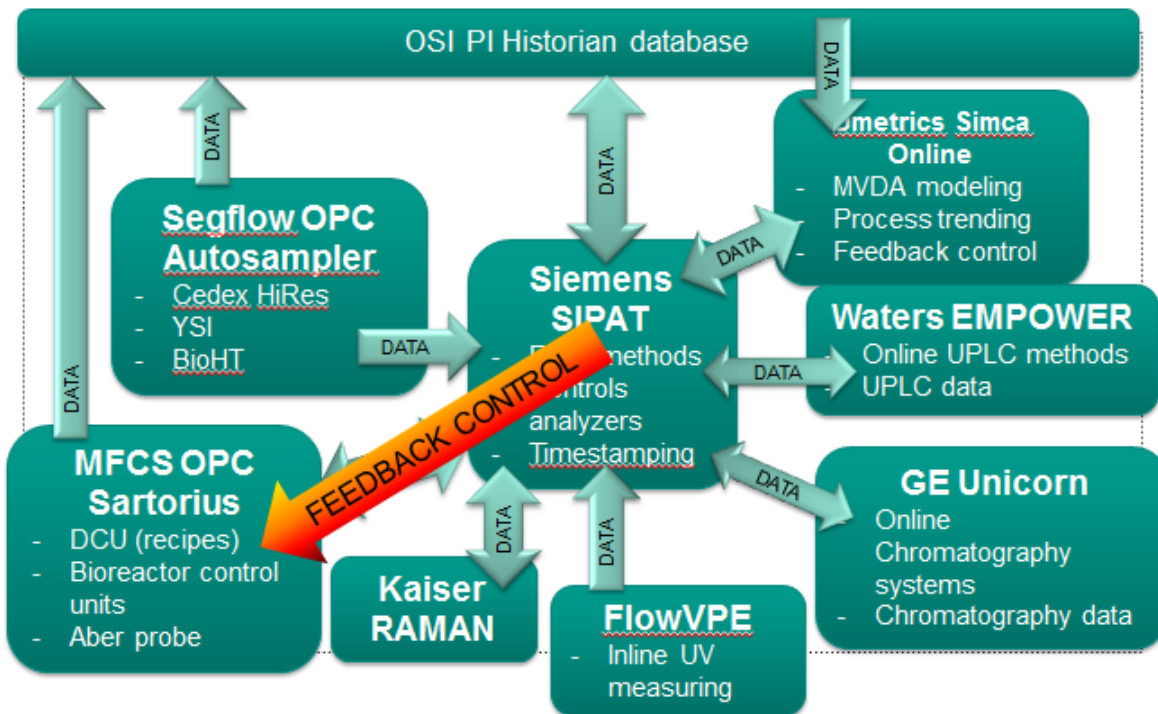
SIPAT –

Some use cases in Scandinavia...  
and beyond

# SIMATIC SIPAT - Use case large molecules API

SIPAT on a continuous bio-API process – upstream & downstream

## PAT IT: Draft layout for PAT Lab



## Project scope

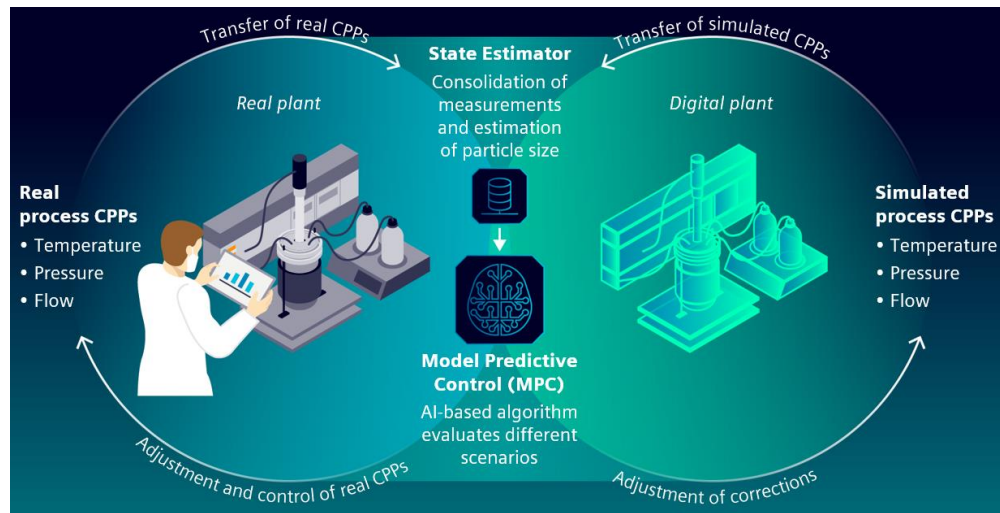
- Continuous bio-API line combining upstream & downstream process
  - Early stage and late stage process development
  - Pilot line for clinical trials
  - GMP based manufacturing line
  - Minimize waste product / increase Right-first-time

## PAT scope

- Kaiser Raman
  - Glucose concentration monitoring in real-time on the fermentor step
- Waters Patrol UPLC
  - Real-time API content monitoring on the purification step
  - Input used to control diverter of the GE AKTA
- Other PAT analyzers – see picture

# SIMATIC SIPAT - Use case large molecules API

## SIPAT as part of a digital process twin

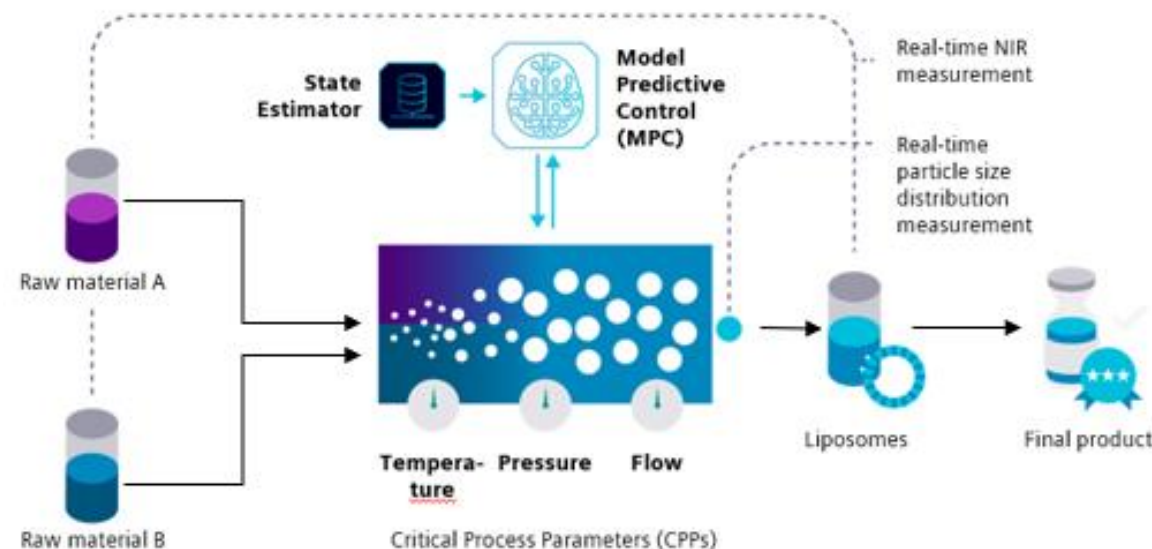


### Project scope

- Change classic batch process into miniaturized semi-continuous process
- Incorporate PAT for continuous digital quality management
- Simulation techniques to offline define the ideal liposome size for the real-time process
- An AI trained MPC model changes the process set points to keep the process within the desired specs

### PAT scope

- Indatech (NIR)
  - API concentration in the liposomes
- Soft sensor in Matlab embedded in SIPAT (PSD)
  - Particle size of the liposomes



# | Contact

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