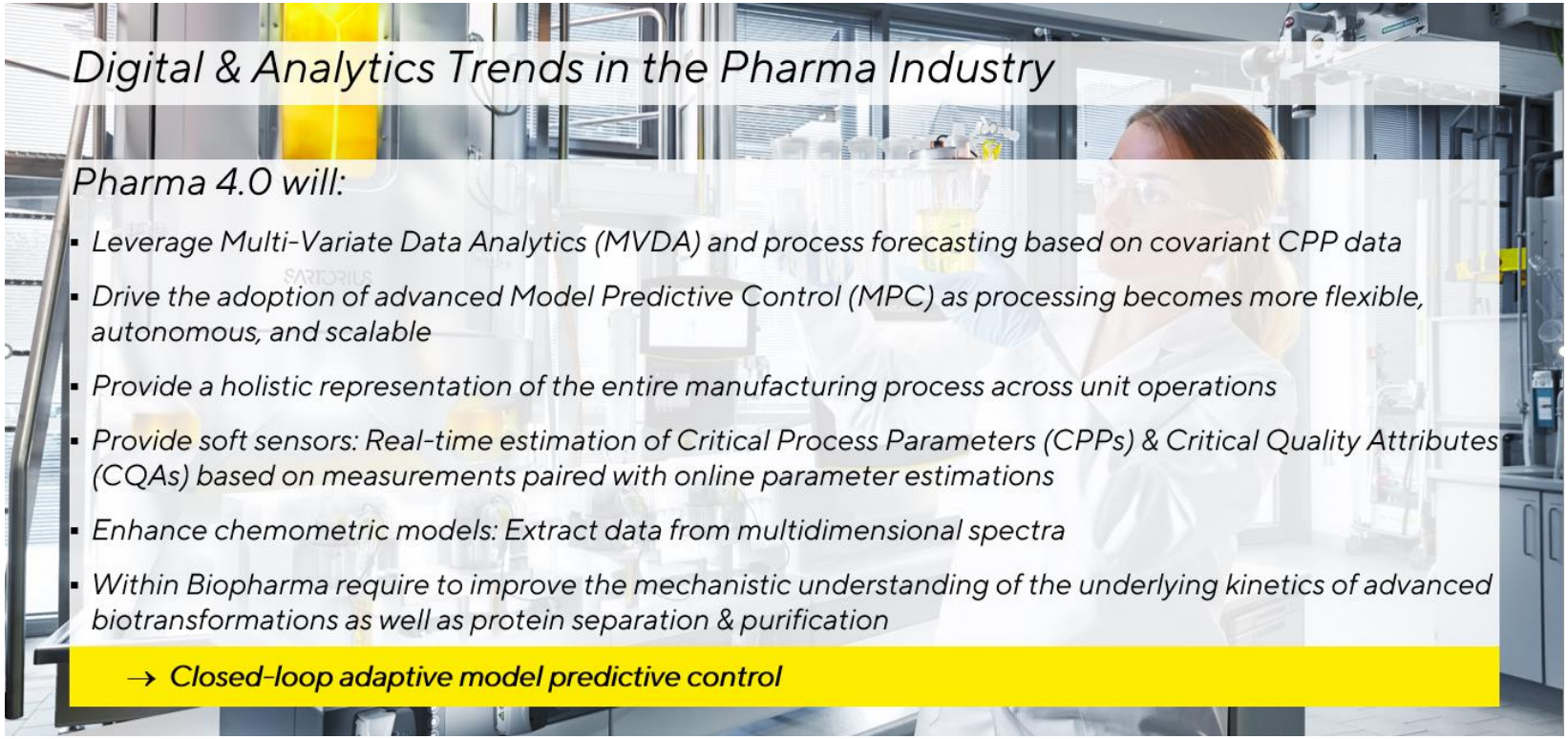
Sensors and Automation in Single-Use Systems

Sartorius, Göttingen, May 11th, 2023

PDA
Parenteral Drug Association

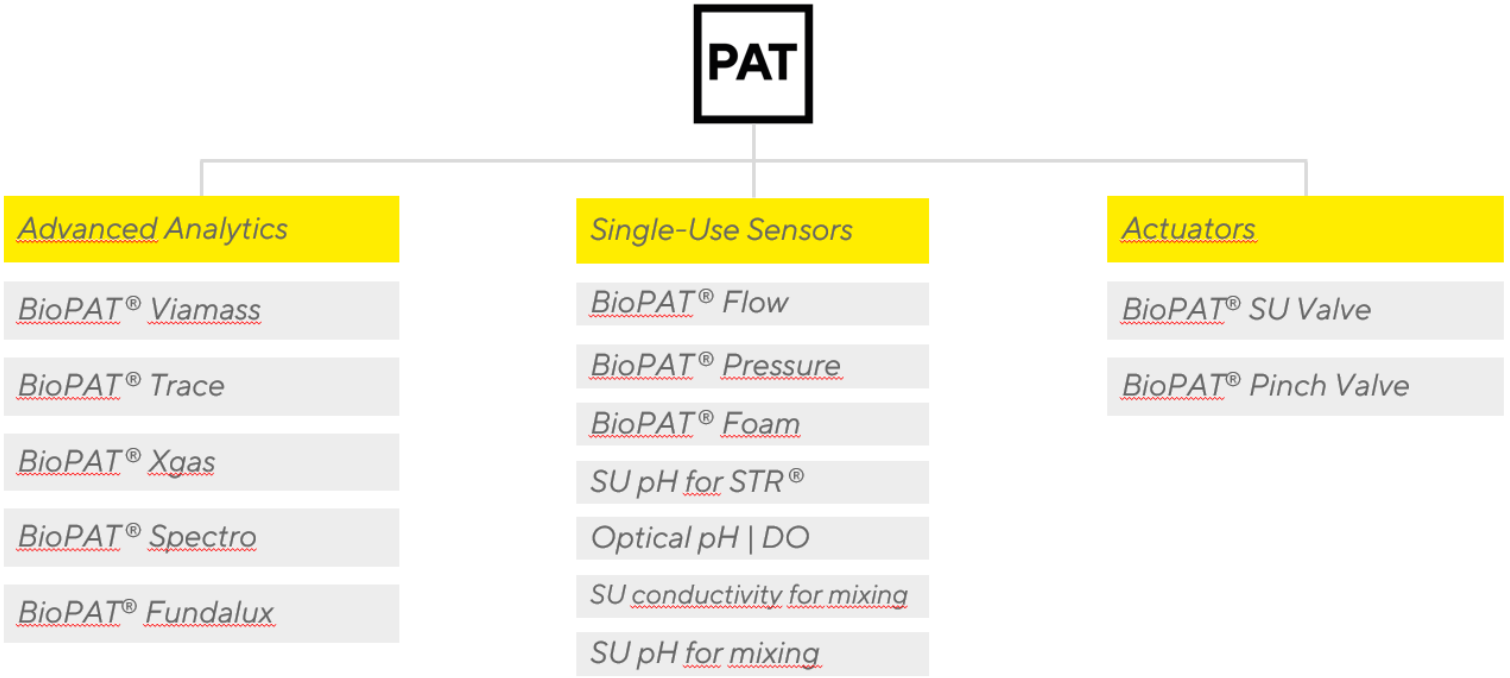
CONNECTING PEOPLE SCIENCE AND REGULATION®

Introduction



Sensors in Single-Use Applications

Overview



SU sensors in GMP _ upstream

	Pre-use Calibration | Certificate	Certificate Traceability	Adjustment | Calibration Before Usage	Readjustment During Process	Functional Check of Reusable Transmitters	Functional Check of SU Component	Post-use Calibration
Optical pH 	lot-wise pre-calibration, 13 sensors of each lot (size:1000) are tested --> calibration parameters for the lot are determined	calibration pH buffers of reference electrode at supplier are NIST certified	1-point adjustment (at current pH) VS external reference	1-point adjustment (at current pH) VS external reference	Signal simulators	plausibility check if amplitude and phase value (raw values of sensor) are within expected range	before/during harvest: take sample and compare to offline reference
Optical DO 	lot-wise pre-calibration, 13 sensors of each lot (size:1000) are tested --> calibration parameters for the lot are determined	certified gas mixes are used for calibration at supplier	1-point adjustment at 100% air oxygen saturation	theoretically 1-point adjustment possible VS external reference, but procedure prone to high errors	Signal simulators	plausibility check if amplitude and phase value (raw values of sensor) are within expected range	before/during harvest: take sample and compare to offline reference but procedure prone to high errors
SU pH STR 	each electrode is precalibrated, values printed on label and certificate available via http://mt.com/pro-certificates	calibration pH buffers at supplier are NIST certified	1-point adjustment (at current pH) VS external reference	1-point adjustment (at current pH) VS external reference	With pH probe and certified calibration buffers or via pH simulator (no Sartorius product)	check internal temperature probe, pH value can be checked after initialization time in process	before/during harvest: take sample and compare to offline reference
BioPAT® Viamass (SU application) 	Transmitter: factory calibration of electronics incl. adaption of electronics to SU application based on stastical evaluation of SU components (cell constant)	factory calibration traceable to national or international standards - calibration certificate provided	Zeroing function		Two signal simulators (0 pF/cm, 0 mS/cm, and 100 pF/cm, 40 mS/cm) for calibration check only	plausibility check if capacity and conductivity values are within expected range	take sample at end of process and check at certified offline analyzer /// electronic can be tested again via signal simulators

SU sensors in GMP _ downstream

	Pre-use Calibration | Certificate	Certificate Traceability	Adjustment | Calibration Before Usage	Readjustment During Process	Functional Check of Reusable Transmitters	Functional Check of SU Component	Post-use Calibration
BioPAT® Flow 	Transmitter: precalibrated (calibration tables stored on Flow Clamp-On), calibration report from supplier provided with Clamp-On	measurement equipment from supplier is traceable	Zeroing function (offset correction)	readjustment possible at 0 flow	At connection of Clamp-On transmitter to amplifier unit calibration tables are transferred. If they are displayed the connection is successfully established. /// additionally: Clamp-on sensor can be checked on SU Flow Pipe in an external calibration loop	Coupling can be checked after filling with media. (must be >= 50%)	Clamp-on sensor can be checked on SU Flow Pipe in an external calibration loop
BioPAT®Pressure 	Transmitter: is calibrated at supplier (test report provided) SU component: statistically qualified	test report according to supplier procedure, test equipment at supplier is regular monitored inspection equipment	Zeroing function (offset correction)	readjustment possible at 0 barg	Transmitter can be checked on SU Pressure Pipe via connected pressure controller at process line or in external test setup (also using a SU Pressure Pipe)	Offset after attachement of SU component onto transmitter can be checked (must be within 100 mbar - 1150 mbar) /// additionally: SU Pressure Pipe can be tested via connected pressure controller at process line (system must be closed, e.g. via valves)	Transmitter can be checked on SU Pressure Pipe via connected pressure controller at process line

SU sensors in GMP _ mixing

	Pre-use Calibration | Certificate	Certificate Traceability	Adjustment | Calibration Before Usage	Readjustment During Process	Functional Check of Reusable Transmitters	Functional Check of SU Component	Post-use Calibration
pH Mixing 	electrode specification is checked at supplier and SU electrode can be identified via serial number		2-point calibration can be performed directly before usage	1-point adjustment (at current pH) VS external reference /// The electrode can be retracted during process and a 2-point calibration can be performed. Then the electrode can be pushed back into the bag. This readjustment can only be performed once.	pH simulator (no Sartorius product)	check mV value in storage buffer: typical value for KCl storage buffer (pH 6.5 @20°C) /// check temperature value	2-point calibration possible (retraction of electrode)
Conductivity 	precalibrated (cell constant determined at sensor supplier, provided on label on SU component)	usage of certified buffers at supplier	insert cell constant into automation software	not necessary (cell constant does not change as sensor dimensions do not change)	Conductivity simulator (no Sartorius product)	check temperature probe /// plausibility check of conductivity value in process possible	take sample at end of process and check at certified offline analyzer /// transmitter can be tested again via signal simulator

Usage of sensors in intensified production _ as an example

What are intensified processes?

Process intensification summarizes all processes that are designed to optimize the productivity of unit operations. They all involve perfusion.

Continuous Bioprocess

- *bleed control*
- *cells are kept in the exponential growth phase at a constant viable cell density (VCD)*
- *the product is constantly removed and further processed from the harvest container*
- *feed and harvest control*
- *process can run for long times*

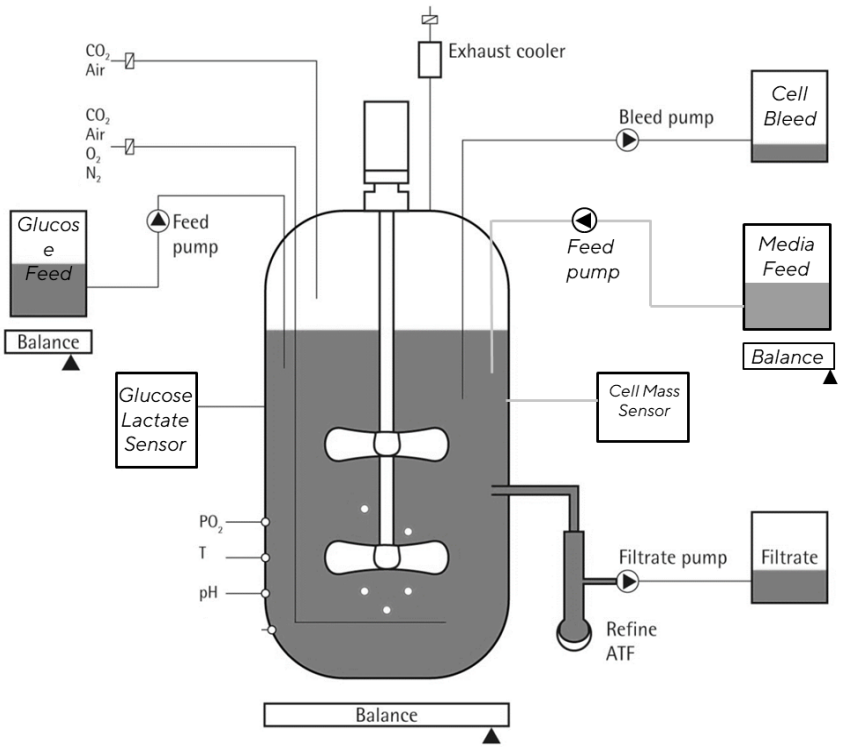
Concentrated Fed-Batch

- *the product is retained in the bioreactor*
- *no bleed control*
- *feed and permeate (filtrate) control*
- *media is constantly exchanged*
- *process runs for a normal time*
- *the VCD and the product titer is higher than in conventional Fed-Batch*

N-1 Perfusion

- *N-1 refers to last seed train bioreactor before the production bioreactor*
- *the product of the N-1 are the cells*
- *goal: Minimize the steps of the seed train and to reach very high viable cell densities*
- *allows seeding the production bioreactor at a higher starting cell density, which shortens the production bioreactor run time*

Intensified processes can be automated by analytical technologies



Requirements

- *cell retention device*
- *realtime, robust sensor technologies in-situ*
- *automated control loops for feed and bleed*

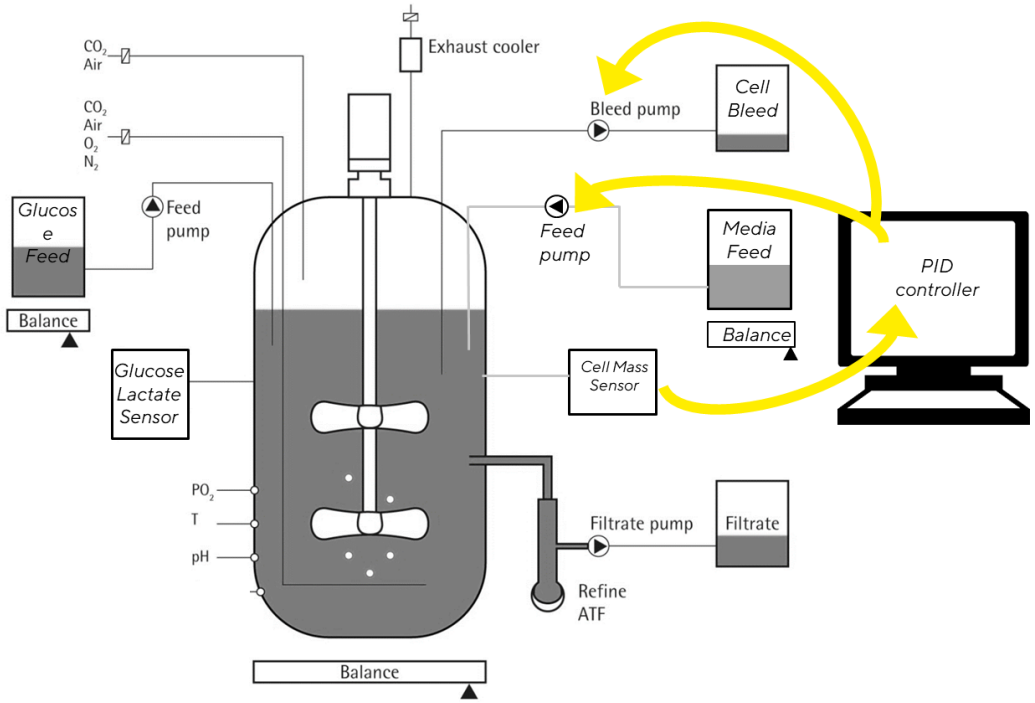
Advantages of perfusion

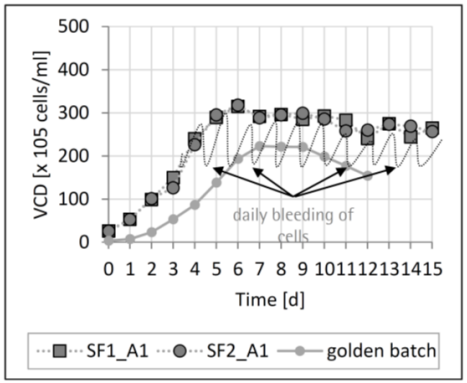
- *extended process time*
- *up to 5-fold enhanced productivity per bioreactor*
- *maximizes product/cell yield*
- *reduced CoG*

Advantages of automation

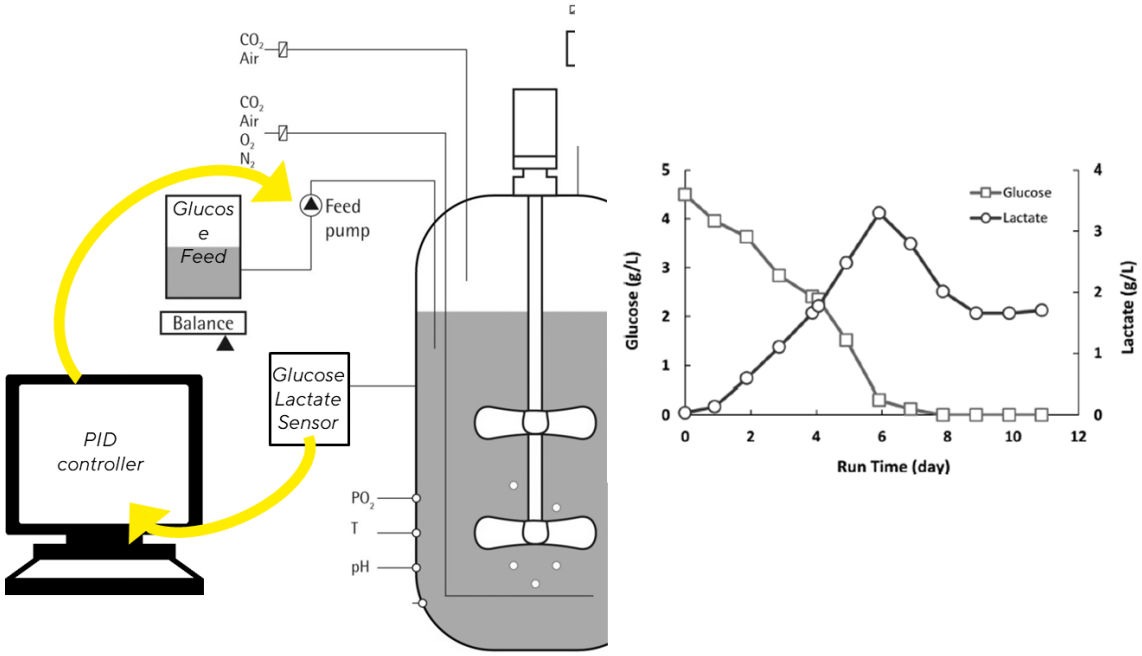
- *100% batch monitoring*
- *reduced risk of contamination*
- *free up operators*
- *increased quality and productivity*

An inline biomass sensor controls the cell bleed

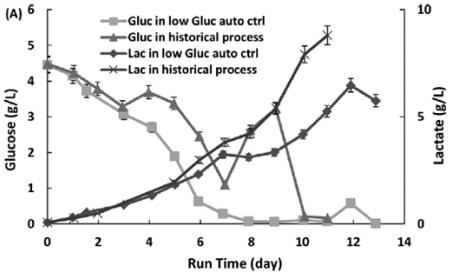




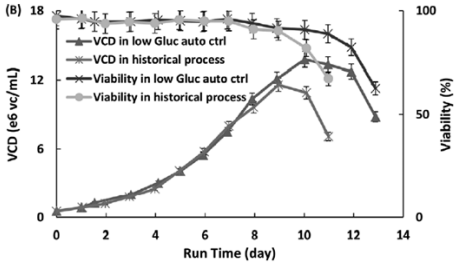
A glucose/lactate sensor can control a low glucose concentration



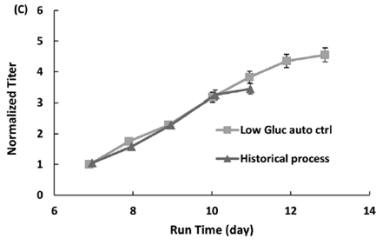
Low glucose has significant positive impact on product titer and quality



- *low glucose control (<0.5g/l) maintains low lactate levels*



- *low lactate levels lead to higher peak cell density and longer cell viability*
- *The culture time could be extended by 2 days*



- *low glucose control results in titer increase (32% overall titer increase)*

Benefits of glucose control below 1g/l:

- *longer cultivations*
- *higher viable cell densities*
- *increased product titers*
- *homogenious glycation*

Requirements for low glucose control:

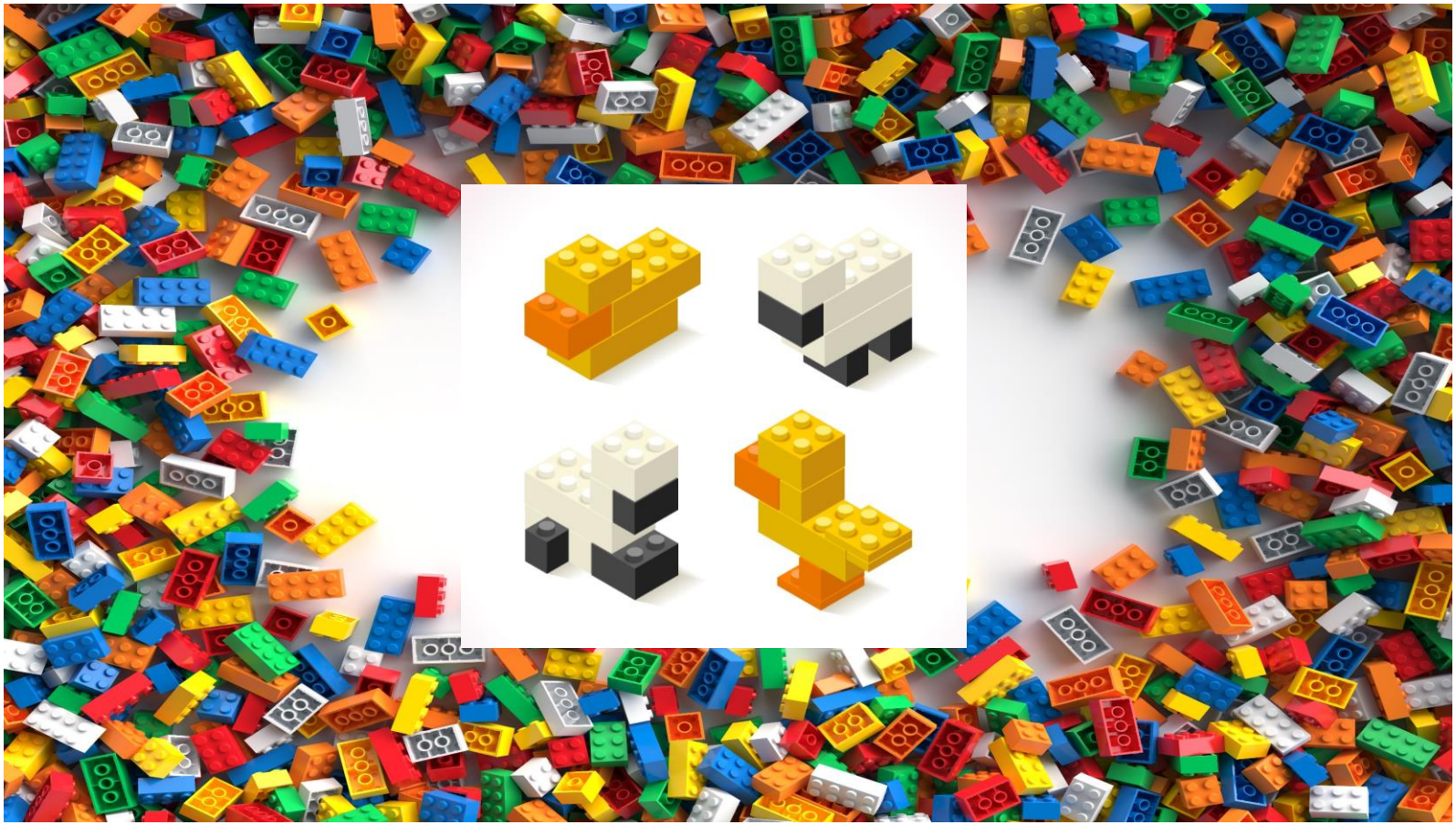
- *measurement of both glucose and lactate*
- *high sampling frequency: min. 30min*
- *no sample removal required*
- *easy PID control implementation*

*Source: Advanced process monitoring and feedback control to enhance cell culture process production and robustness. Zhang et al., **Biogen**, Biotec and BioEng, 2015*

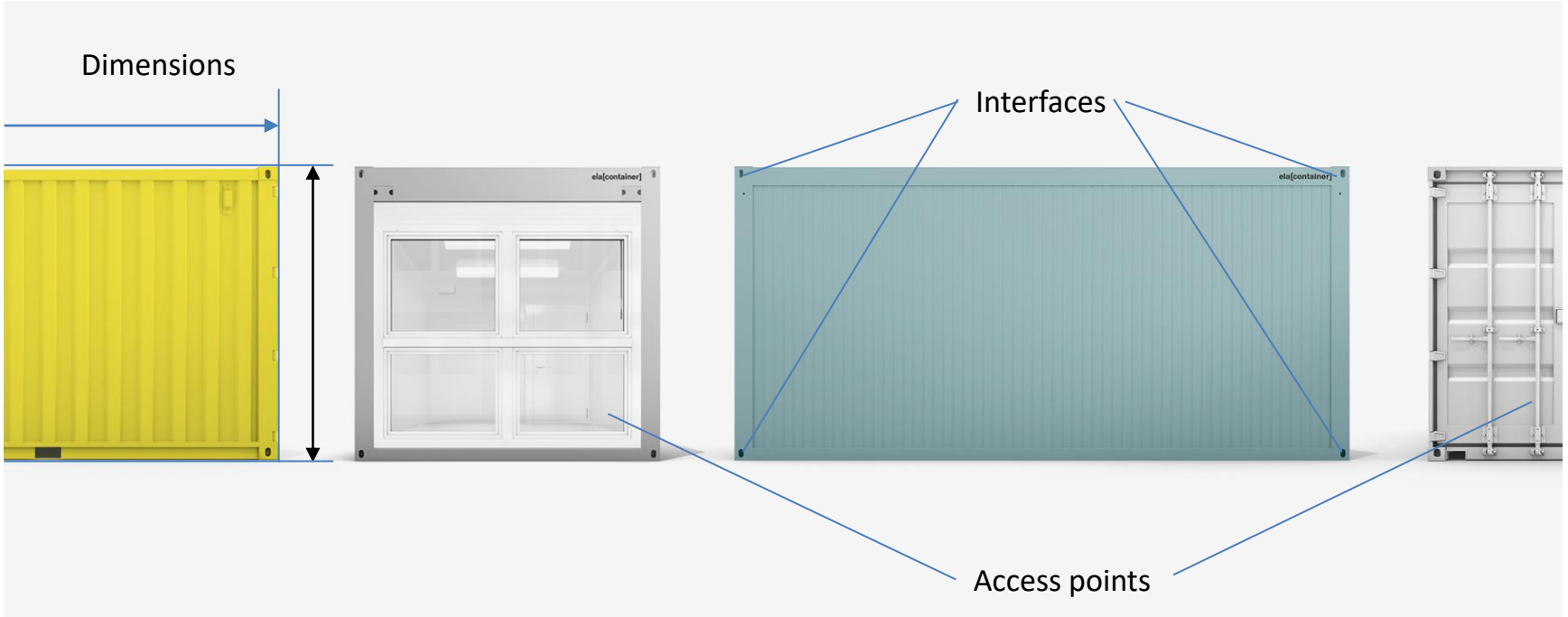
Automation for Single-Use Applications

How modularization can help future manufacturing concepts

Modularization needs Standardization



Example Container



Benefits of Modularization

Increase in Efficiency

- container boosted worldwide logistic chains
- interoperability between:

  ships, trucks, airplanes

Benefits of Modularization (cont.)

Increase in Flexibility

- SmartHome modules

- fast and easy setup
- flexibility of networks (initial and in lifecycle)
- change functionality of module by parametrization
- easy integration of new appliances

- interoperability between vendors partly given

Bosch SmartHome program

Modularization in single-use technologies

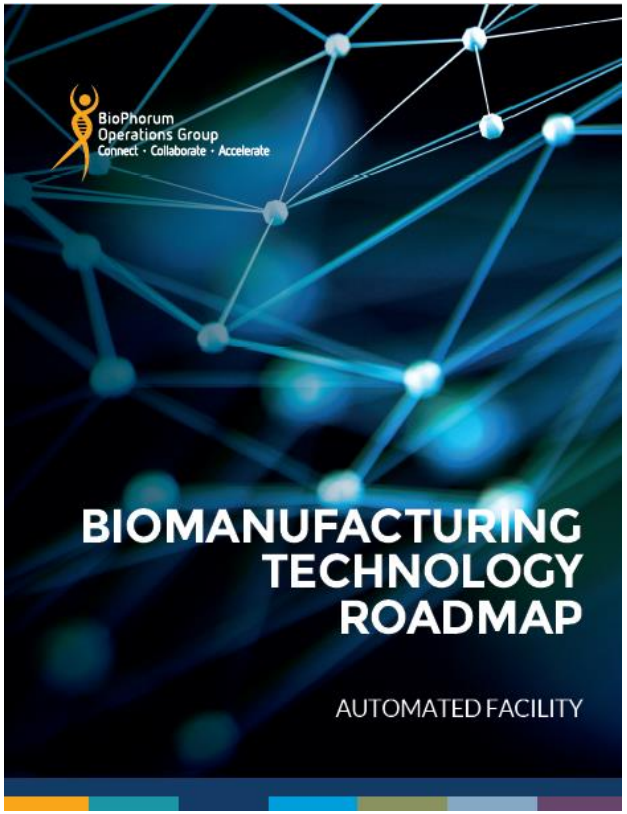
Past

- High initial cost
- Considerable cleaning effort
- Risk of cross-contamination
- **Mostly dedicated plants with dedicated, ‚monolithic' automation**

Present

+ CAPEX reduction over entire lifecycle
+ Lower water and energy consumption
+ **Higher flexibility**
+ **Base for flexible manufacturing (ballroom)**
+ **Modularization needed (Hardware & Automation)**

Automated Facilities need standardized integration to reduce build times of facilities



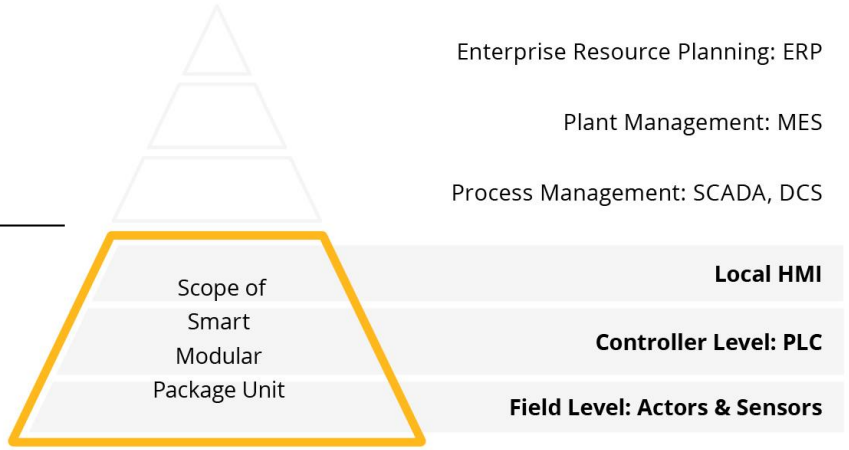
"…
full integration allows
quicker and cheaper build times …"

BPOG Technology Roadmap
Automated Facility

Smart Modular Package Units

- ... focus on local automation of a process step
- ... integrates well into upper SCADA or DCS world
- ... has a range of interfaces
- ... integrates sensors and actuators
- ... form basic controls
- ... offers executable sequences & recipes

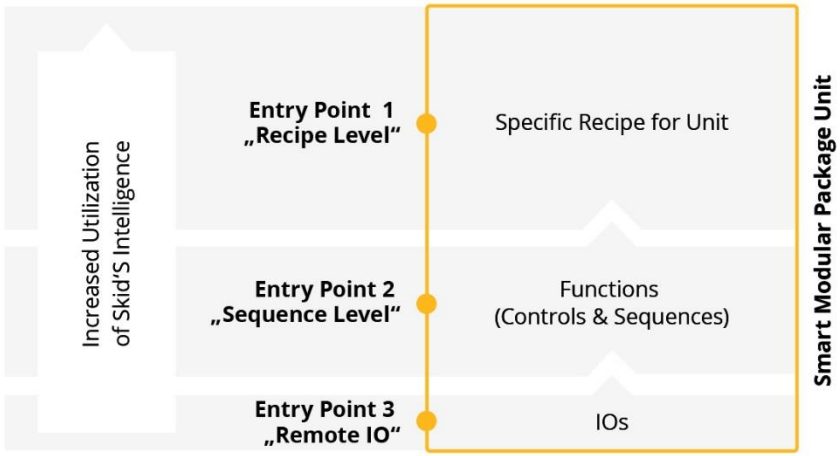
Copyright Sartorius Stedim Biotech



SIEMENS
EMERSON
Rockwell Automation

Integration of package unit into SCADA / DCS - Options

Based on customer requirements different integration options can be used:




```
select recipe buffer_prep_buffer_A
set volume_produce 425 L
set pH 6.5
execute recipe
```

```
set low_pH 3.4
set high_pH 7.0
set inactivation_time 20 min
start pH_inactivation
```

```
write pump_rpm = 200
read sensor_pH_value
```

simplified SCADA/DCS commands

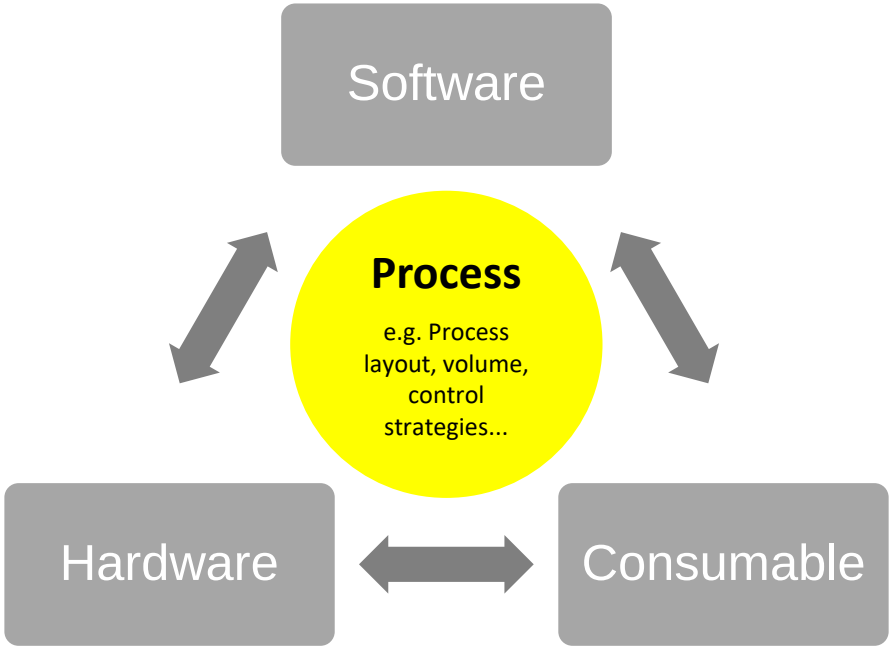
Modular Integration lead to 50-75% time reduction

Activity	Remote IO	Modular Integration
Functional Specification	●	●
Software Design Specification	●	
Hardware Design Specification	●	
Module Design and Configuration Specifications (CM/EM/EPH)	●	
Construction, Coding and Configuration	●	●
Module Design and Configuration Testing (CM/EM/EPH)	●	
Software Integration Testing	●	●
Hardware Acceptance Testing	●	●
Factory Acceptance Testing	●	●
Site Acceptance Testing	●	●

based on entry level 2 – Sequence Level

Flexibility

Software, Hardware & Consumables have to follow process requirements



Case FlexAct® | Crossflow filtration: example parametrization

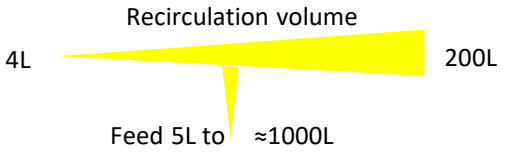
Design space flexibility (over 30k variations)

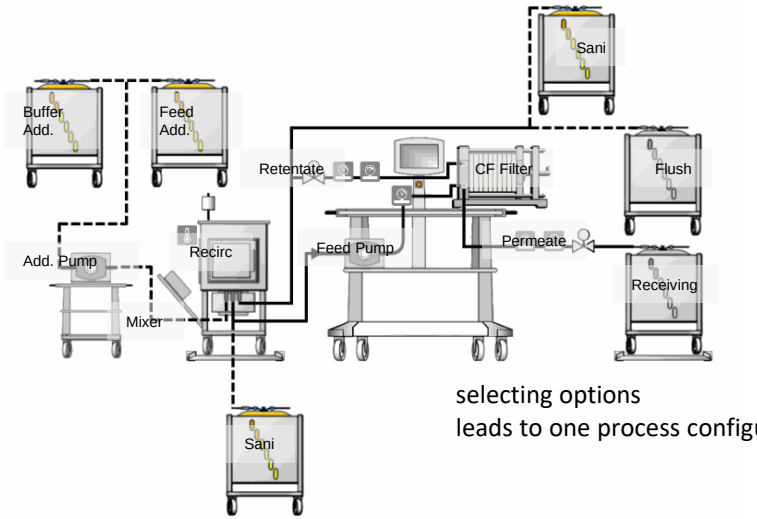
Example options:

Sartorius filter option:
Membrane material, molecular weight cut off or 3rd party filters

Process control
Temperature control, pH and conductivity monitoring

Permeate tubing diameter
½", 3/8" and ¼"



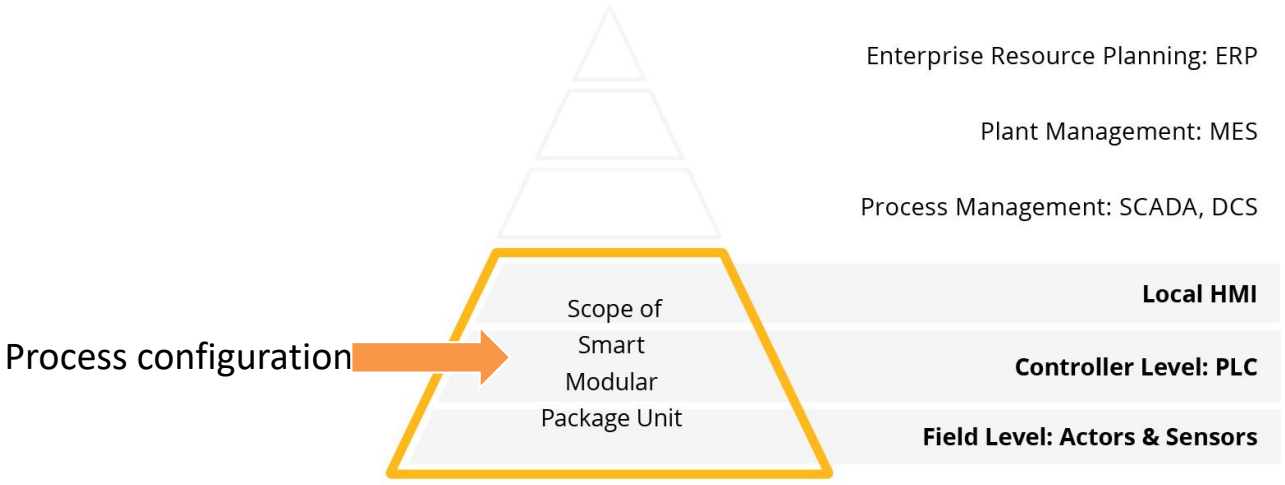


selecting options
leads to one process configuration

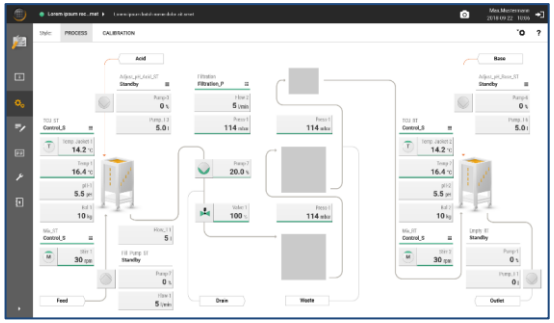
Automation flexibility

Based on the process configuration, the system will:

- ... change the unit operation e.g. buffer-preparation, crossflow filtration ...
- ... activate the right sensors & actuators including controls
- ... pre-parametrize sequences & recipes
- ... adapt the HMI



Automation and user interface follows selected hardware and consumables



Change your hardware and consumable set-up

Local Automation

Seed train products: Biostat® RM and STR® powered by Biobrain®

- Today a closer look at local automation
- Biopharma customer requirements

Some definitions

- What's in ?

Embedded
Integral part of our bioprocess instrument
Enable
Functions needed for the instrument in USP, DSP & FMT
Local
Represent the local automation

- What's out ?

Not a focus on the whole production line

- Automation of a full production line
- Process Recipe & batch report
- Full process data historian

Produce as early as possible

"Time-to-facility is business critical for many commercial manufacturing scenarios"

- Produce early with GMP compliance and integrate later
  - Biobrain® GMP stand-alone capability
  - No initial integration
  - Generate batch record, stored and archived

- Integrate faster with support
  - Up-to-date OPC UA interface standard in Biobrain®
    - Transfer all recorded process data, alarms & events and audit trails upwards
    - Execute ANSI-88 conform functions in Biobrain® by higher automation systems
  - Detailed documentations & interface consulting service are easing implementation

Advanced process control reduces risk of batch loss

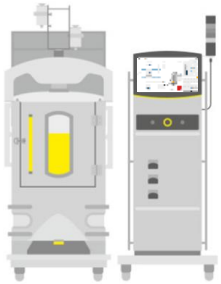
"False operator actions are a major root cause for rejected batches"

- Automate as much as possible to reduce operator interaction

BioPAT® MFCS4 module

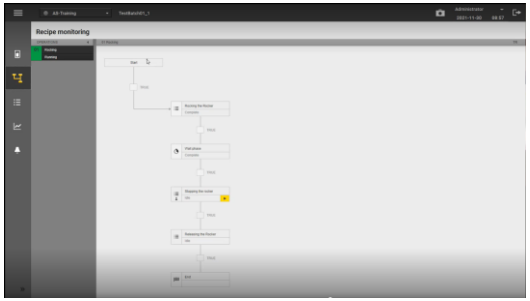
Generate the recipe

transfer



Biobrain ® instrument

Recipe locally executed



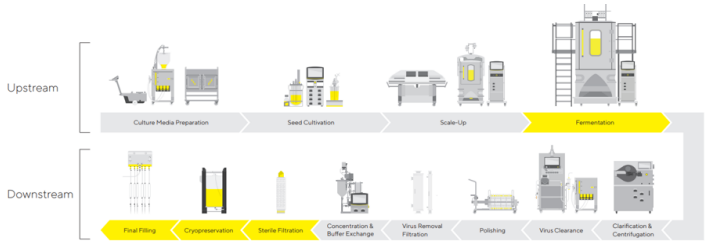
Biobrain ® screen

Following the execution

- Customized recipe service available

Key for flexible, modular manufacturing concepts

- Modularity does not stop with hardware
- Hardware, Consumable and Software to follow process requirements
- Flexibility is important to adapt for process changes
- Different integration scenarios support:
  - Produce as early as possible
  - Speed up in integration
  - Reduce errors



Thank You !

Andreas Prediger	Manager Single-Use Sensors	andreas.prediger@sartorius.com +49 160 9689 3337
Henry Weichert	Technology Consultant PAT	henry.weichert@sartorius.com +49 176 1894 1334
Burkhard Joksch	Technology Consultant Automation	burkhard.joksch@sartorius.com +49 176 1894 1356