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Simplifying Progress

How CDMOs Can Adopt a Modular PAT Strategy

Tiffany McLeod, Henry Weichert, Stefan Rannar

Agenda

Introduction to the PAT Landscape at CDMOs

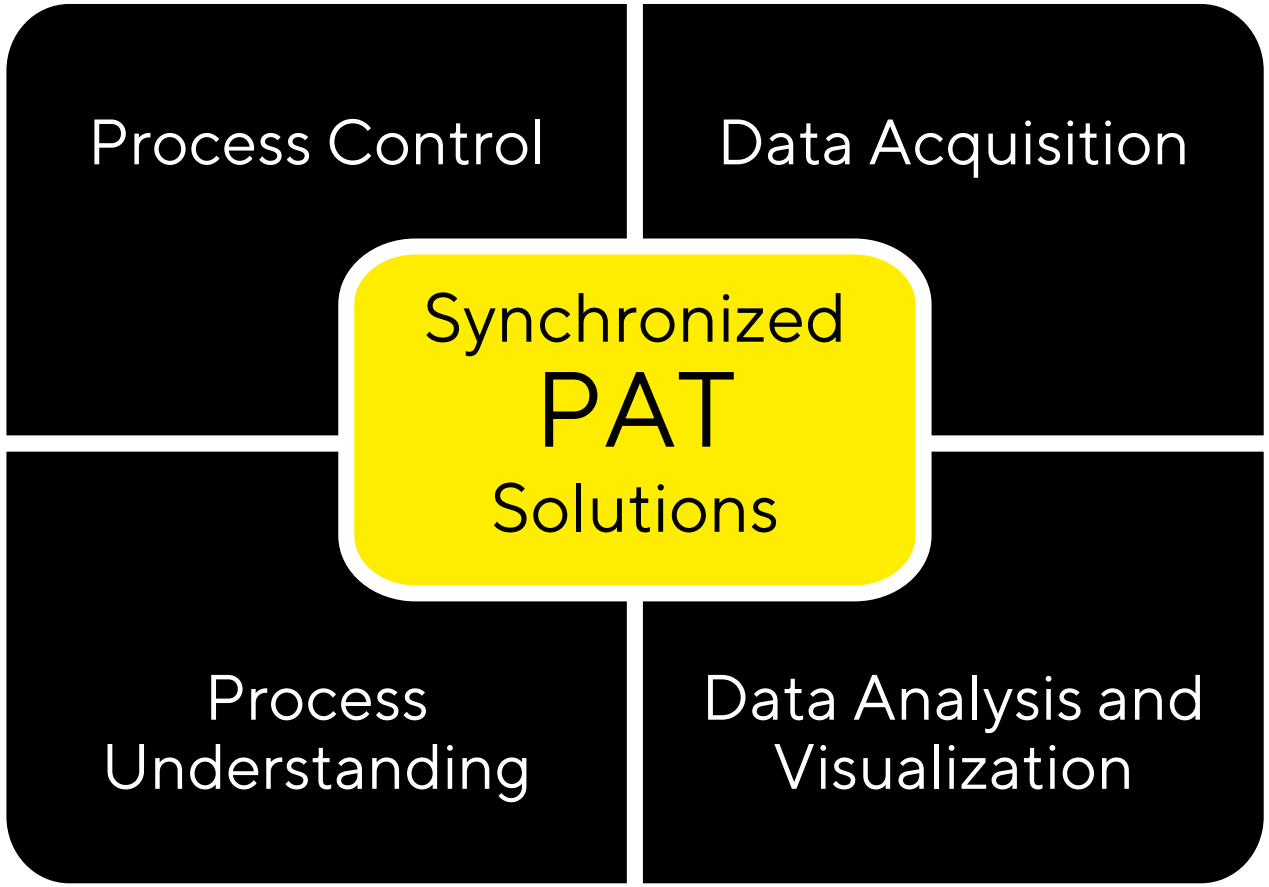
Special Requirements for PAT Implementation at CDMOs

Sartorius BioPAT® Landscape

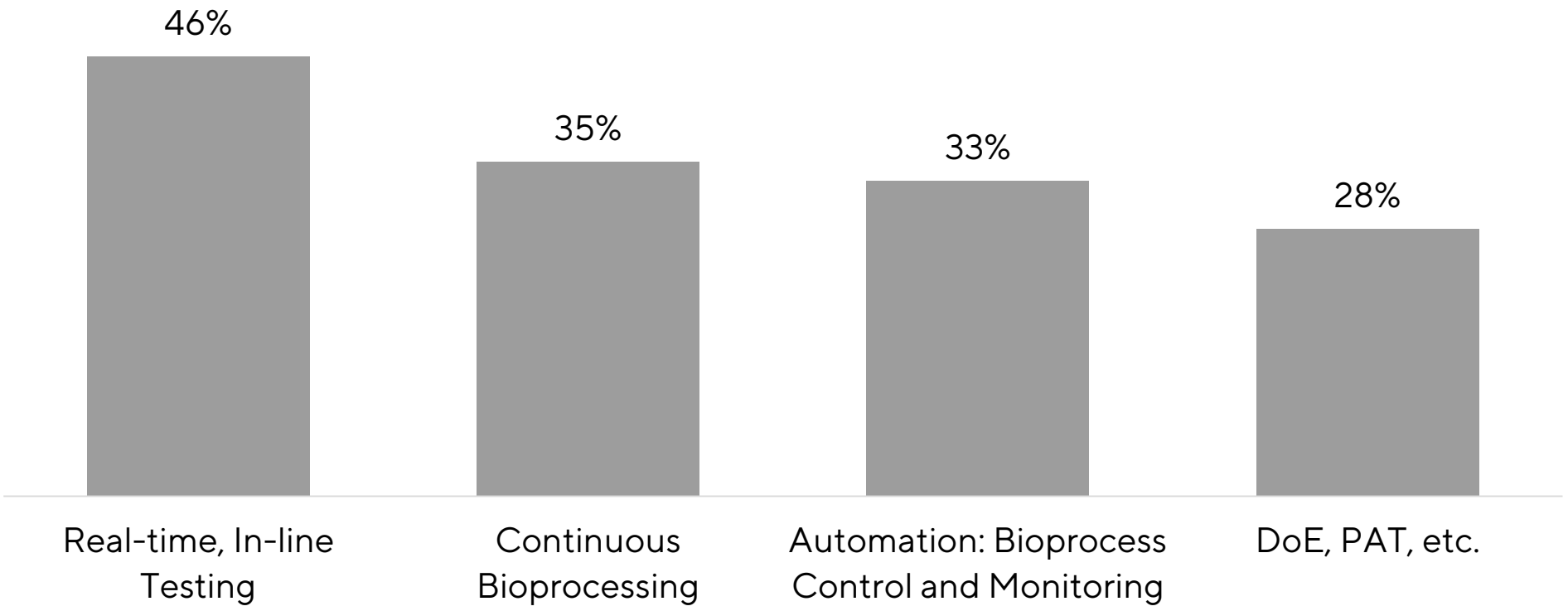
SIMCA® Model Building with BioPAT ® Spectro for Modular Raman Implementation

The Role of PAT at CDMOs

1. Enhancing the “D” in CDMO with Advanced Process Development
2. Shift from quality testing to online monitoring, predictions, and control
3. Elevate Manufacturing Safety and Reliability



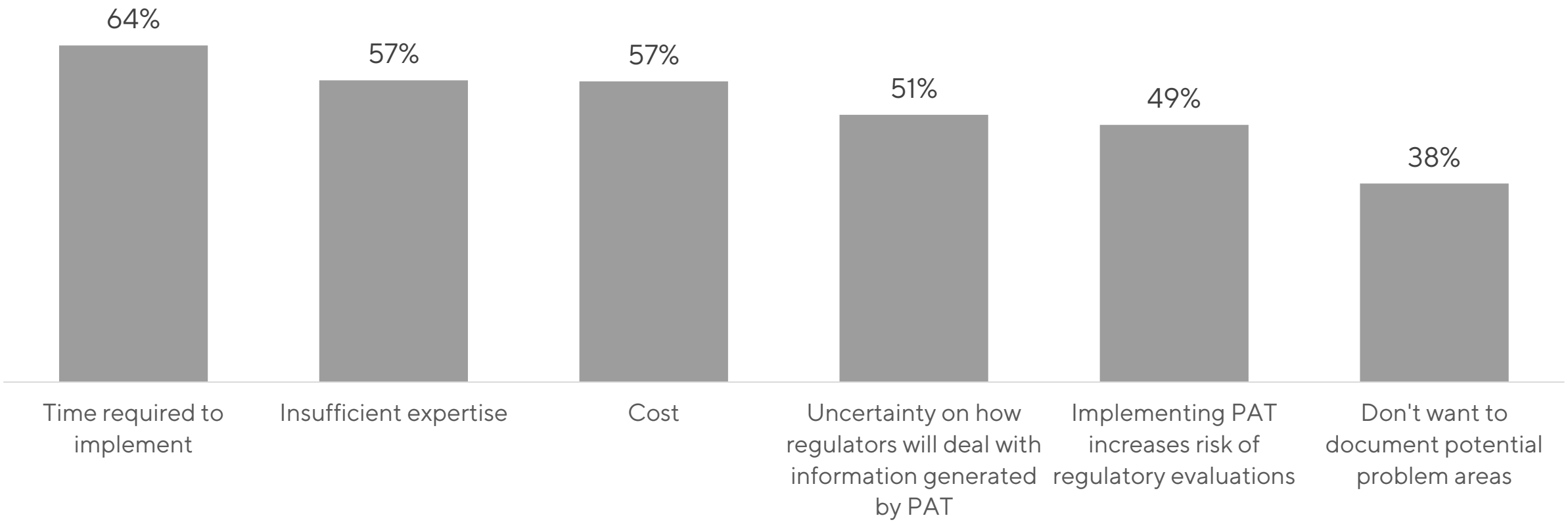
Top new product development areas needed at CDMOs



PAT and other types of advanced process models for process control are pivotal to support the industry trend toward continuous manufacturing

17th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, BioPlan Associates, Inc., April 2020

Hurdles Hindering Implementation of PAT



The industry's primary perceived difficulties in implementing PAT involve allocating the time and staff to perform this task. But there may be other factors in play as well: Lack of understanding, familiarity and associated fear may also be holding back industry-wide adoption of PAT.

17th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, BioPlan Associates, Inc., April 2020

Why PAT Adoption is Expected to Increase

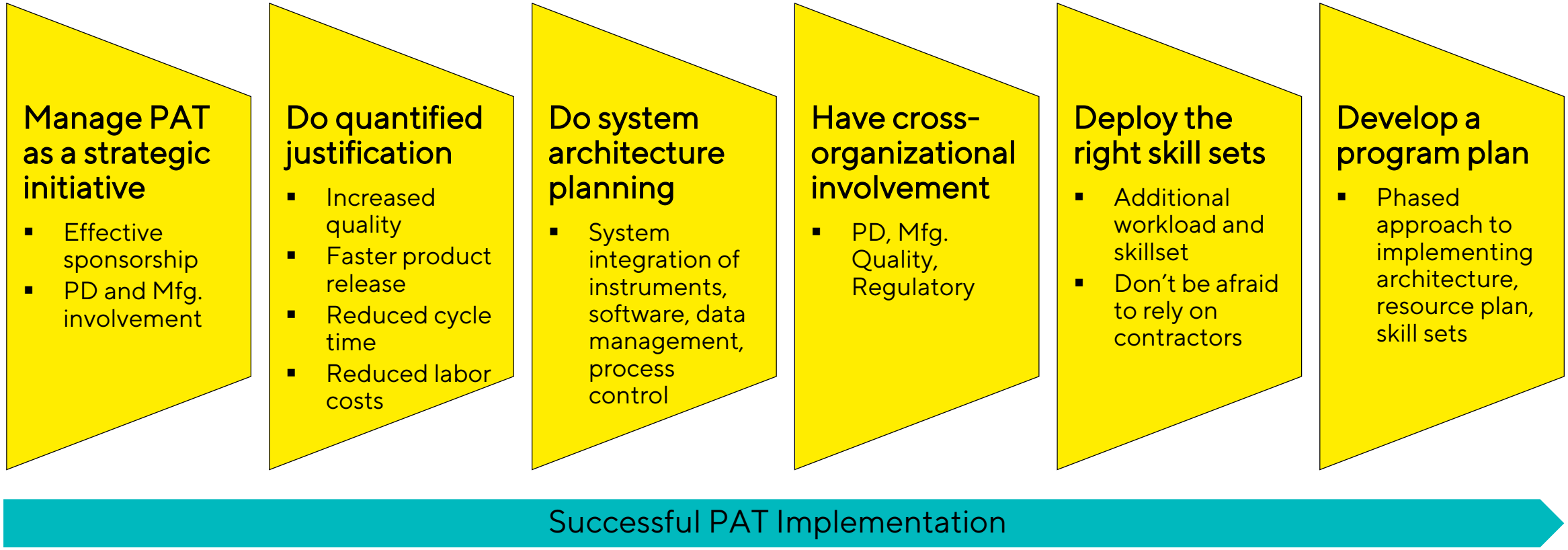
Considerations for Implementing the PAT Strategy at your CDMO

#1 Versatile

#2 Modular

#3 Scalable

Best Practices for PAT Roll-out



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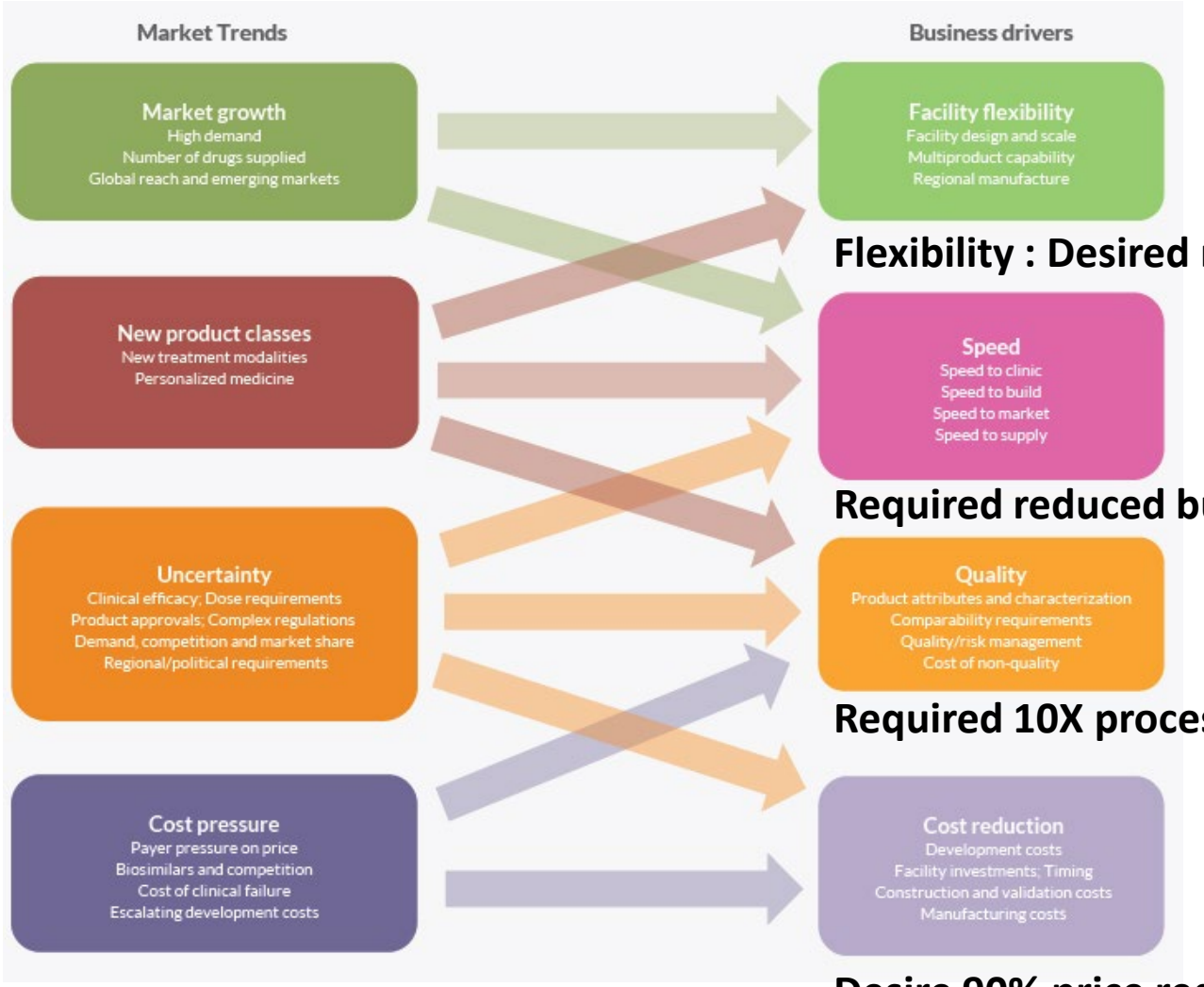
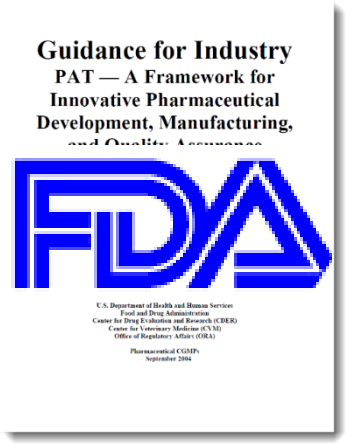
BioPhorum BIOMANUFACTURING TECHNOLOGY ROADMAP



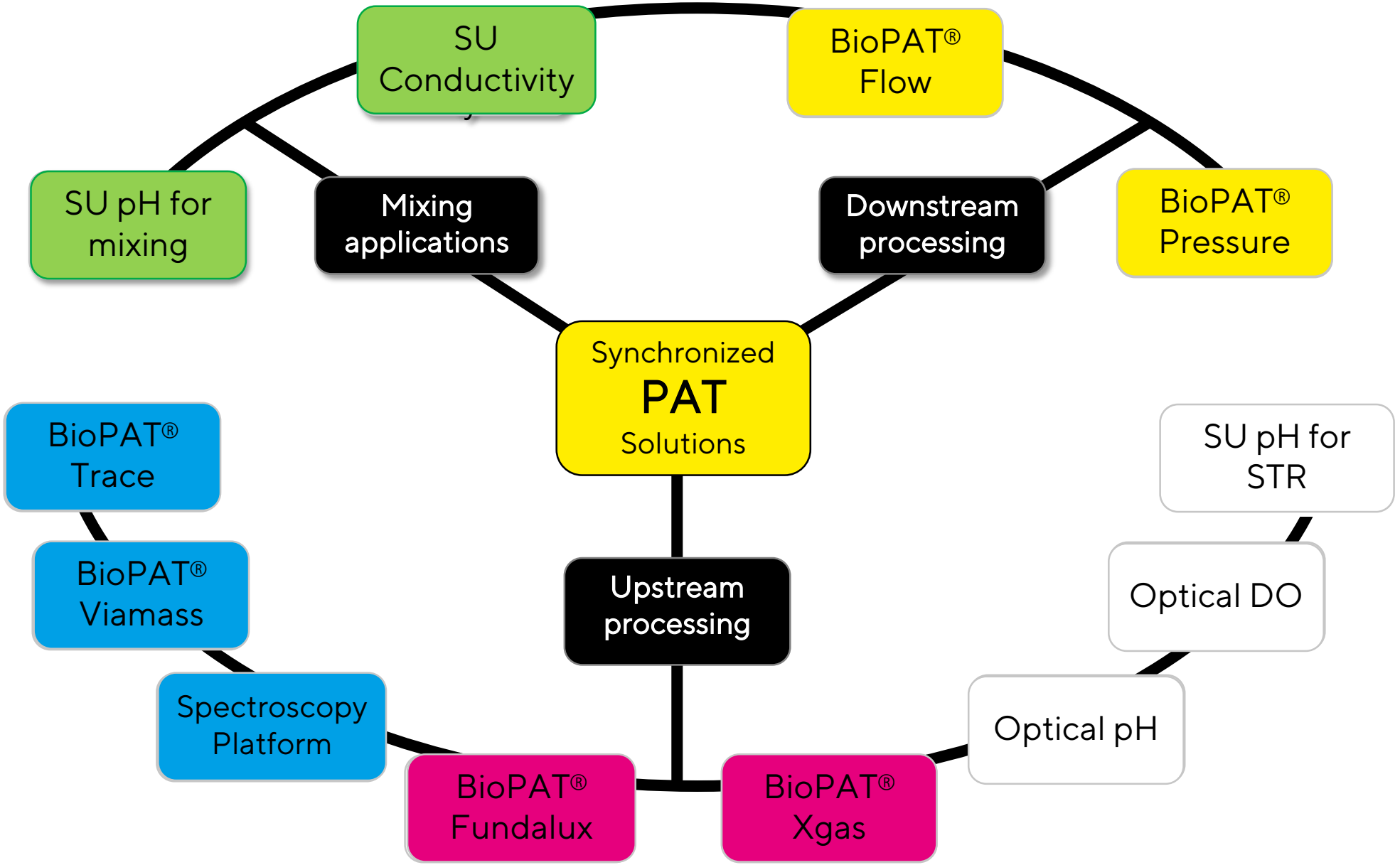
Flexibility : Desired reduced changeover time by 90%

Required reduced build up time by 70% and lead times by 80%



Required 10X process robustness

Desire 90% price reduction in manufacturing cost and Capex


SU Conductivity
BioPAT® Flow
SU pH for mixing
Mixing applications
Downstream processing
BioPAT® Pressure
Synchronized PAT Solutions
BioPAT® Trace
SU pH for STR
BioPAT® Viamass
Optical DO
Upstream processing
Spectroscopy Platform
Optical pH
BioPAT® Fundalux
BioPAT® Xgas

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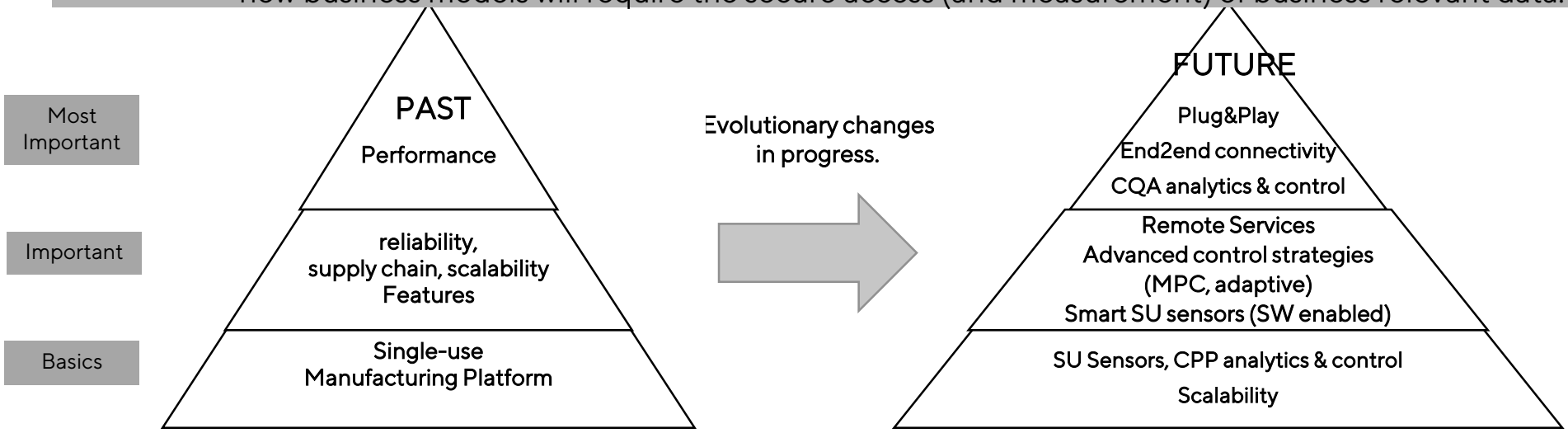
PAT, Automation & Software Market Trends

Major Trends – Intensified | Data-Driven & CQA Control | Plug&Play

1. Intensified processes - seed train, continuous downstream processing
2. Data driven process development, QbD and PAT– CQAs monitoring and control
3. End-to-end connectivity with Plug&Play, Modular and standard interfaces

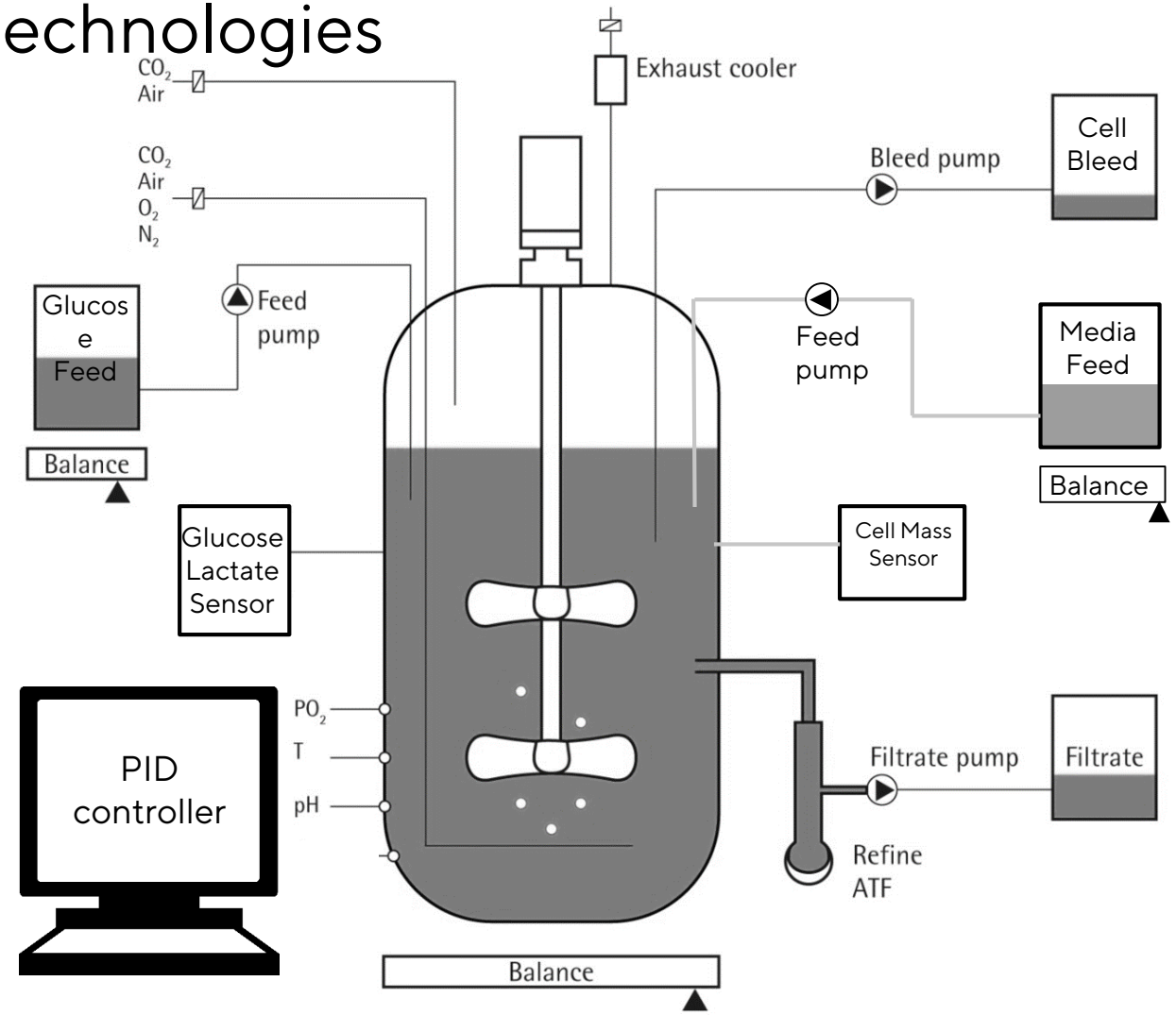
Basic Single-use sensors and CPP measurement becomes commodity, new complex processes require higher degree of sensing and control, namely for CQAs, and modular automation that connects seamlessly to other platforms. Deployment of new business models will require the secure access (and measurement) of business relevant data.



Customer needs are evolving!

Complex processes and advanced automation require advanced services and are key for future Winning Proposition

Intensified processes can be automated by advanced analytical technologies



Requirements

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

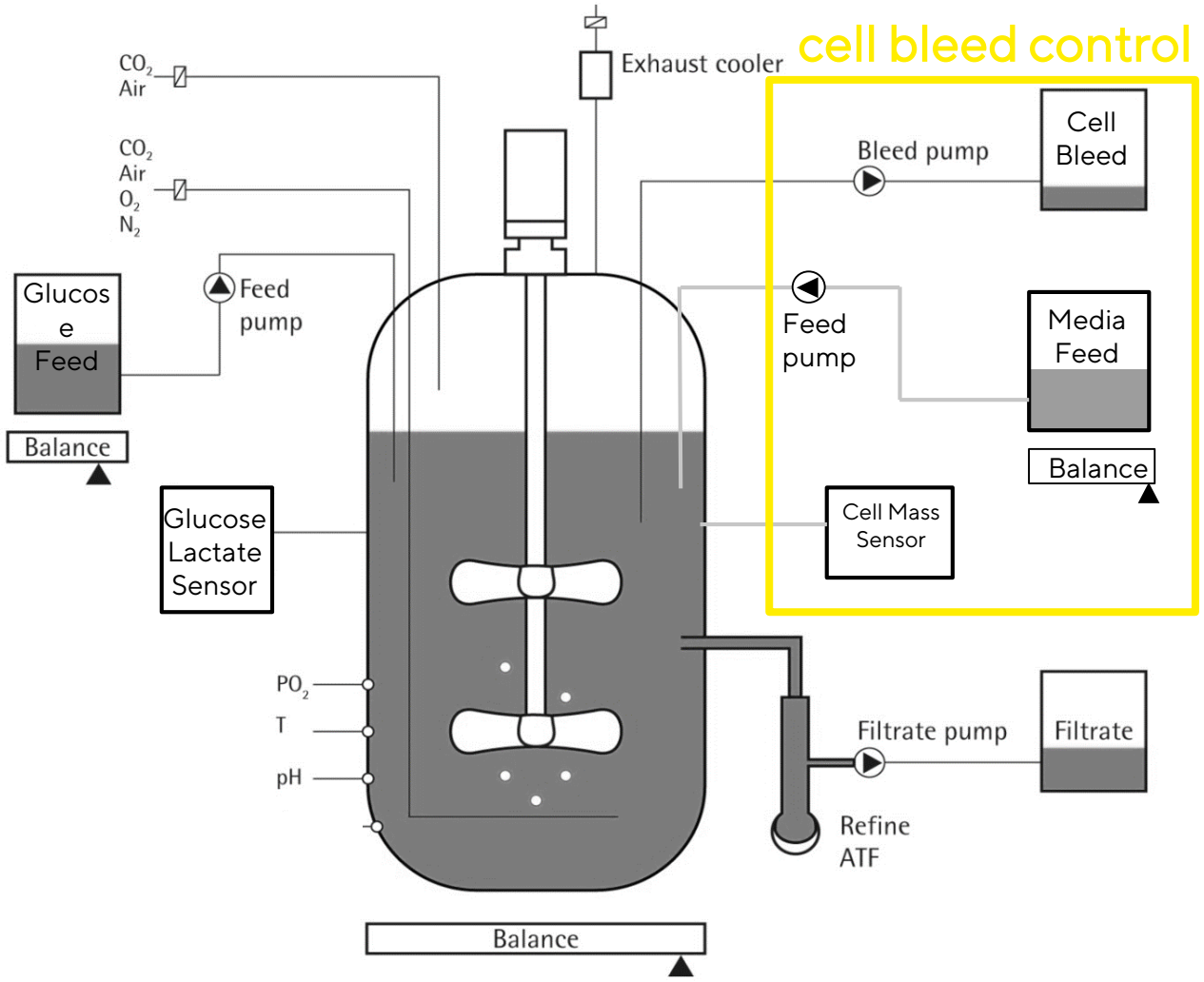
Advantages of perfusion

- 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

Cell bleed control is fundamental to perfusion processes



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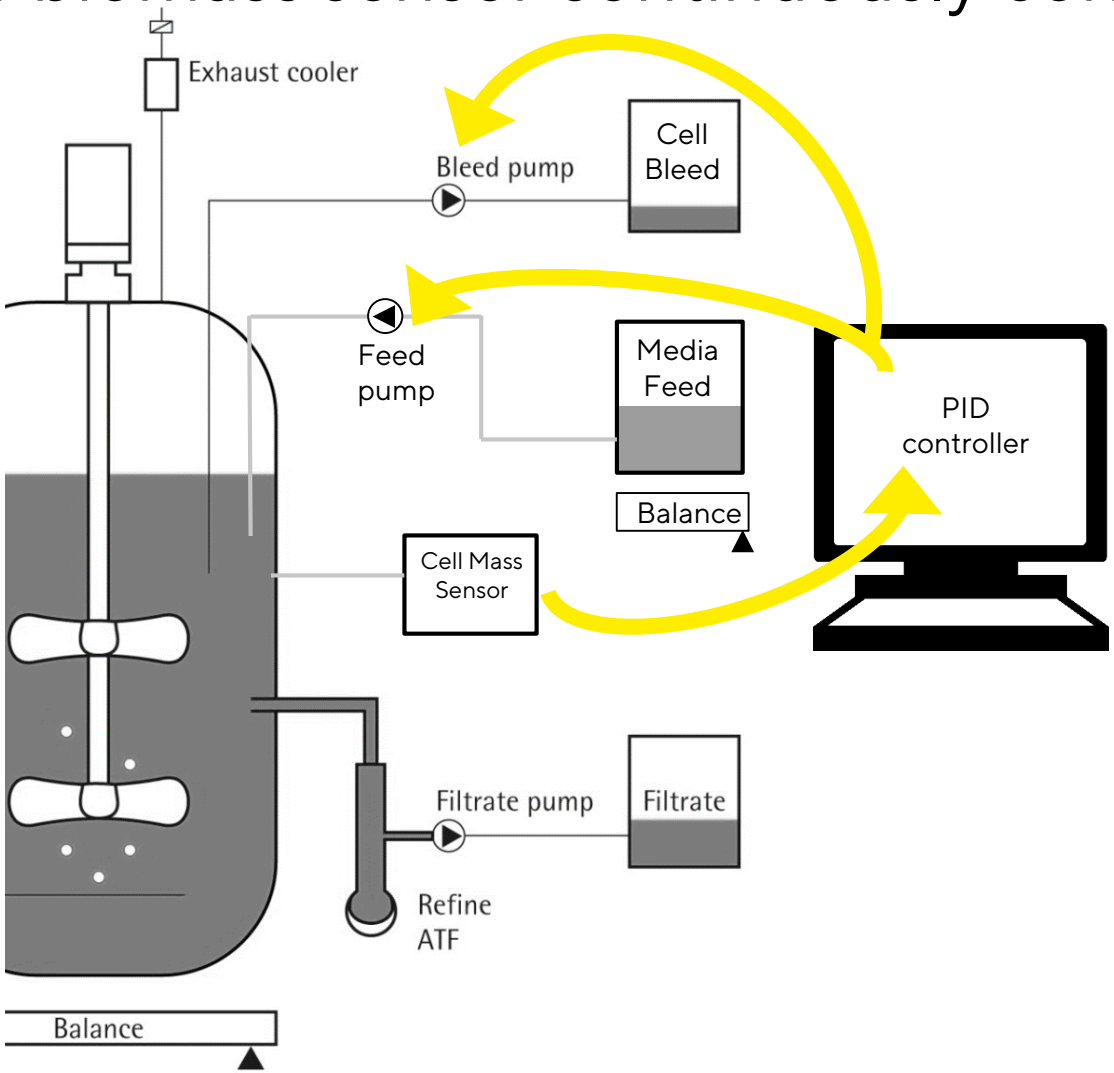
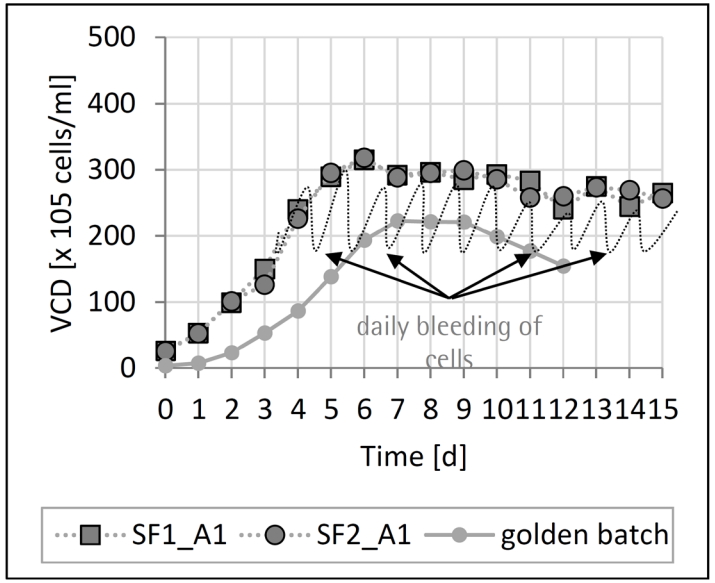
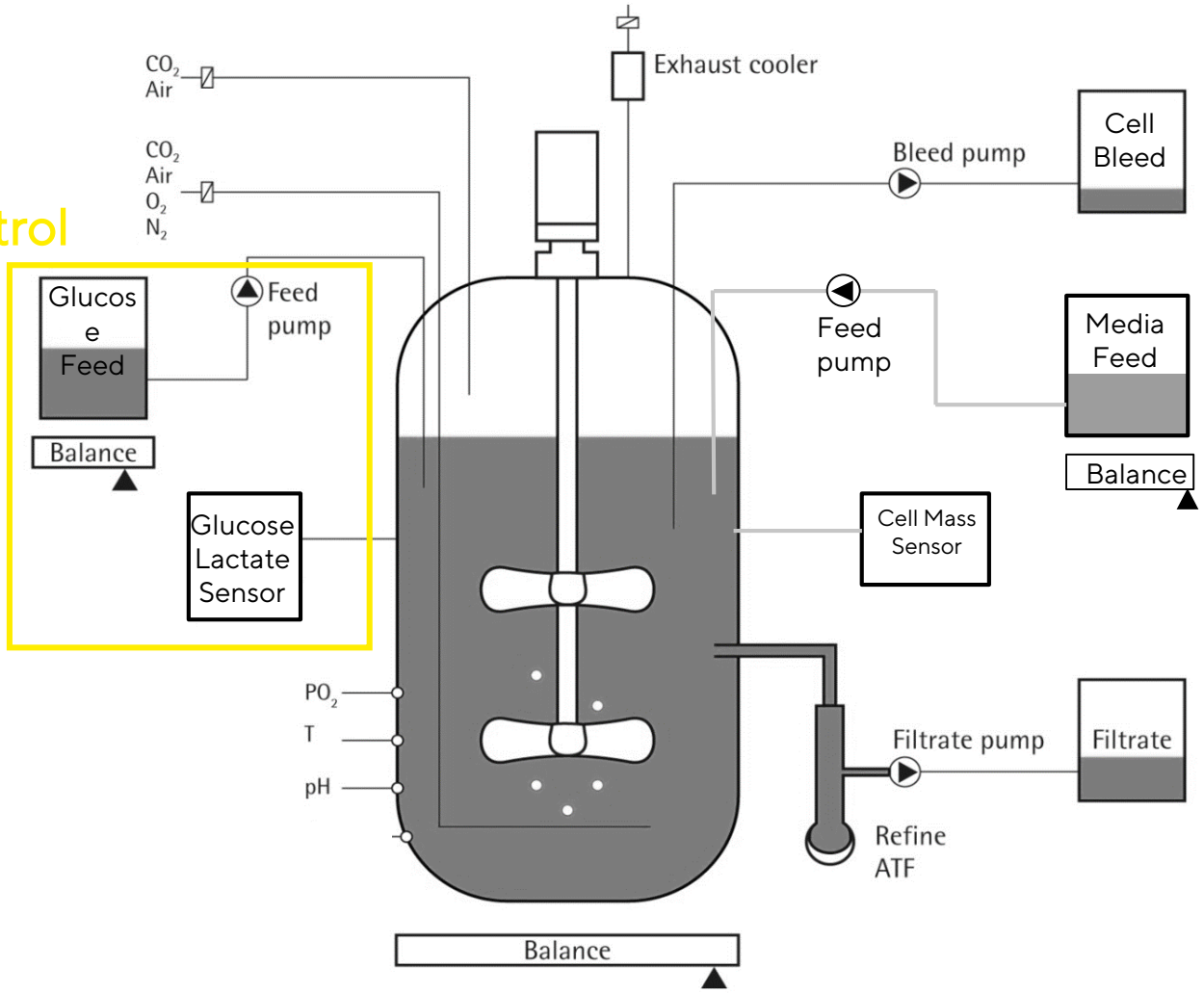
An inline biomass sensor continuously controls the cell bleed





Nutrient control is fundamental to perfusion processes

low glucose control



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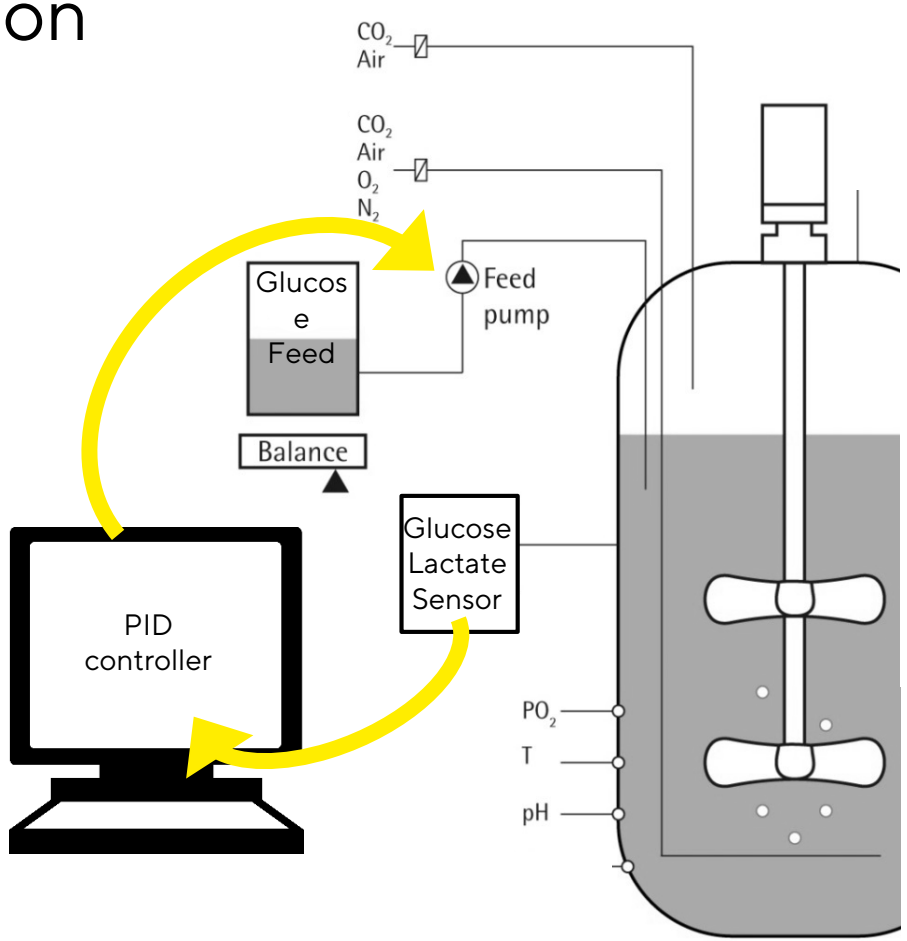
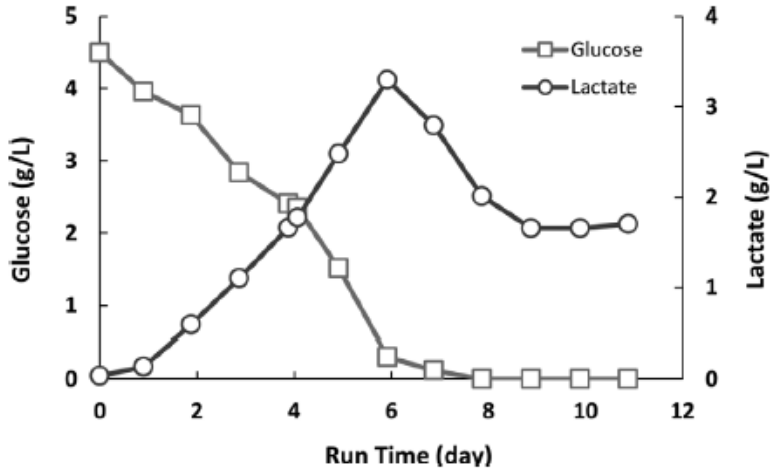
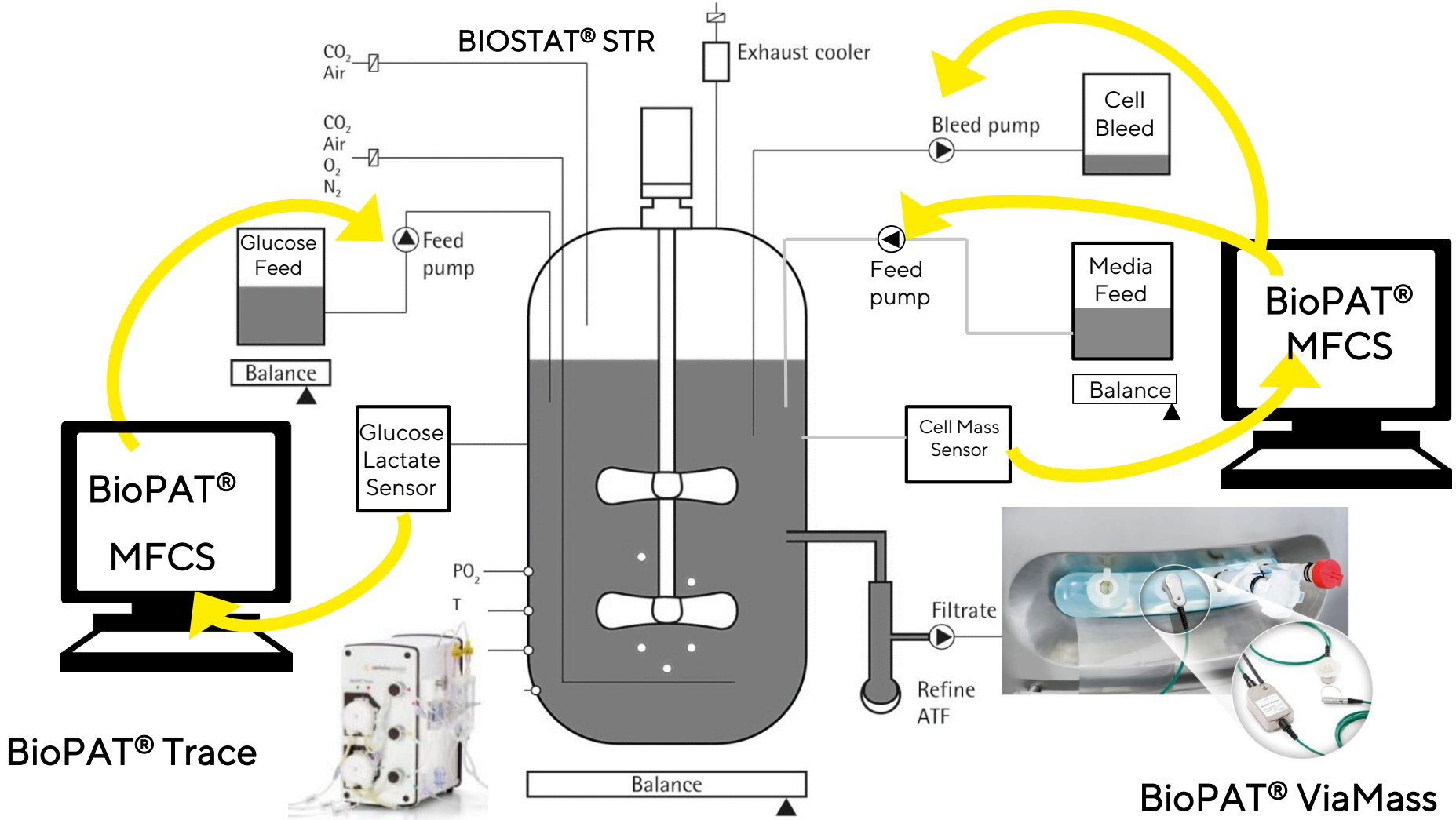
An integrated glucose/lactate sensor can control a low glucose concentration





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

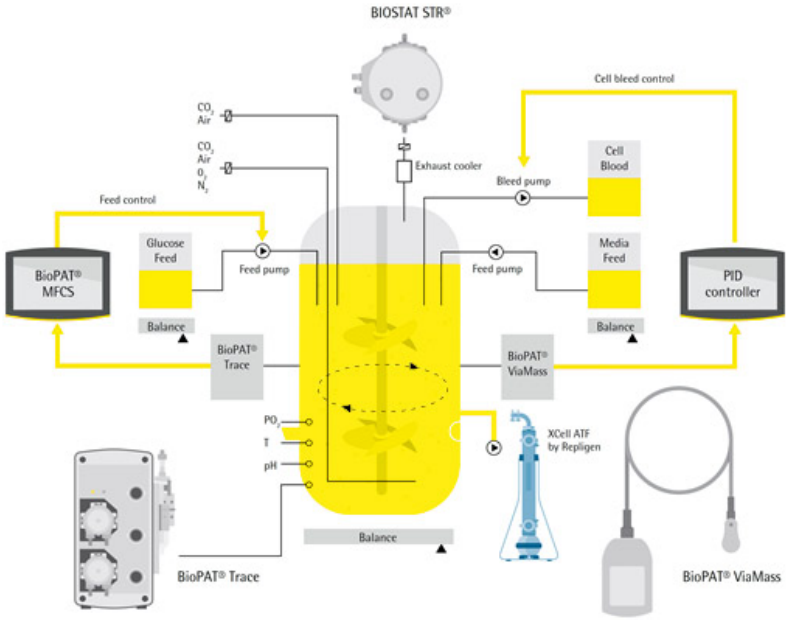
The integrated advanced analytics allow automated process control



Integrated Modular End-to-end (Upstream & Downstream) Platform(s)

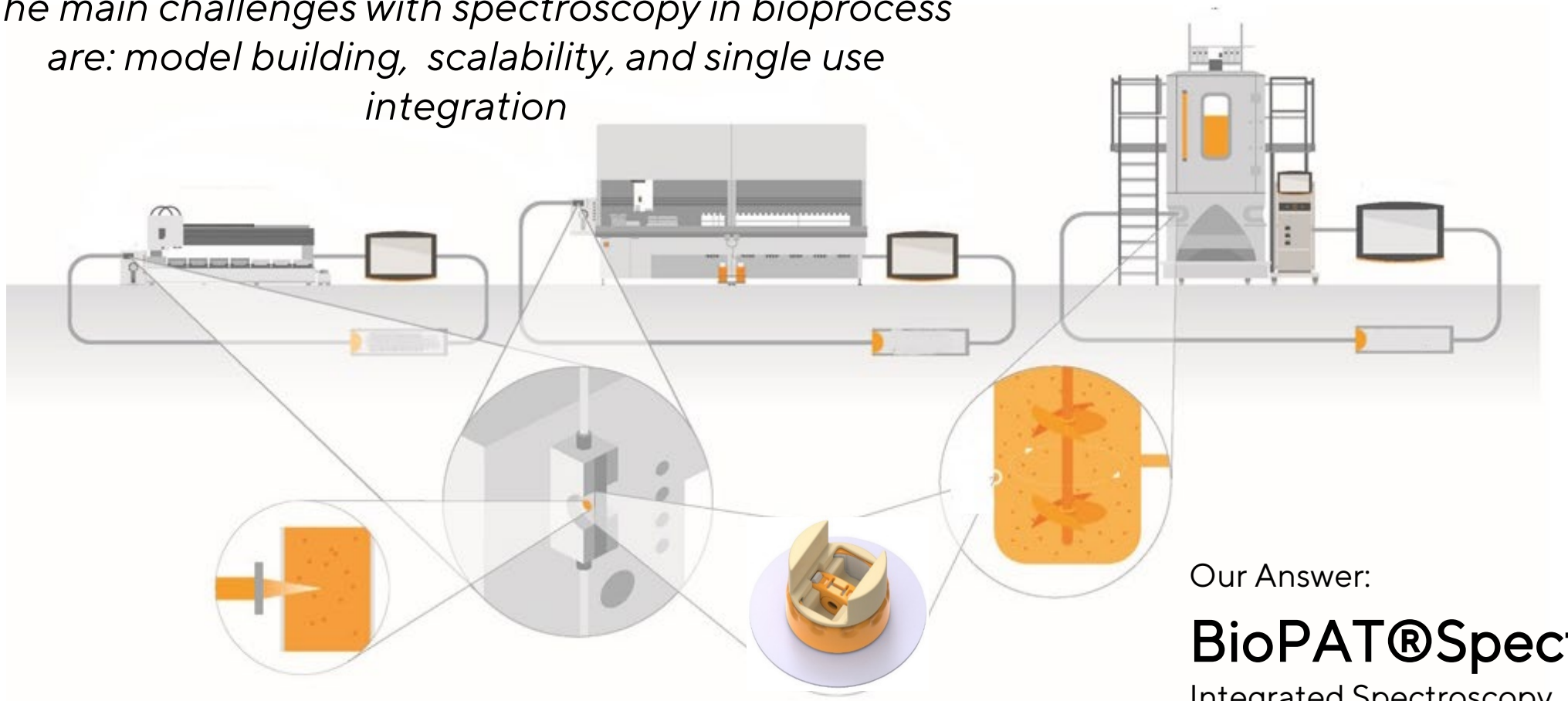
Advanced single use PAT and software enabling well understood and controlled processes to drive faster process development, consistent product quality and higher manufacturing efficiency with an exceptional user experience.

Intensified. Automated. Predictive.



Sartorius Spectroscopy Platform enables QbD in Ambr® and BIOSTAT® STR

The main challenges with spectroscopy in bioprocess are: model building, scalability, and single use integration



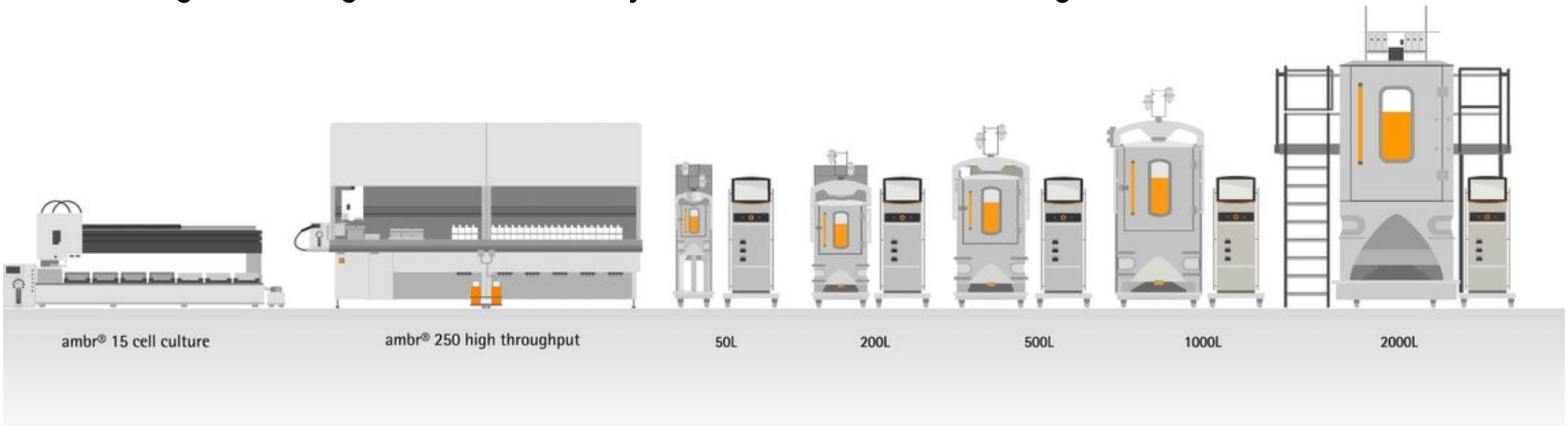
Our Answer:

BioPAT®Spectro

Integrated Spectroscopy Platform

BioPAT® Spectro was designed to meet three key requirements

- Enable Raman spectroscopy in high throughput process development
- Facilitate the model building process
- Full single-use integration and scalability for commercial manufacturing



BioPAT®Spectro - integrated in Ambr® 15 and Ambr® 250 high throughput

connection of a Kaiser Raman Spectrometer

connection of a Tornado Raman Spectrometer

BioPAT® Spectro single-use, inline integration in Biostat STR®

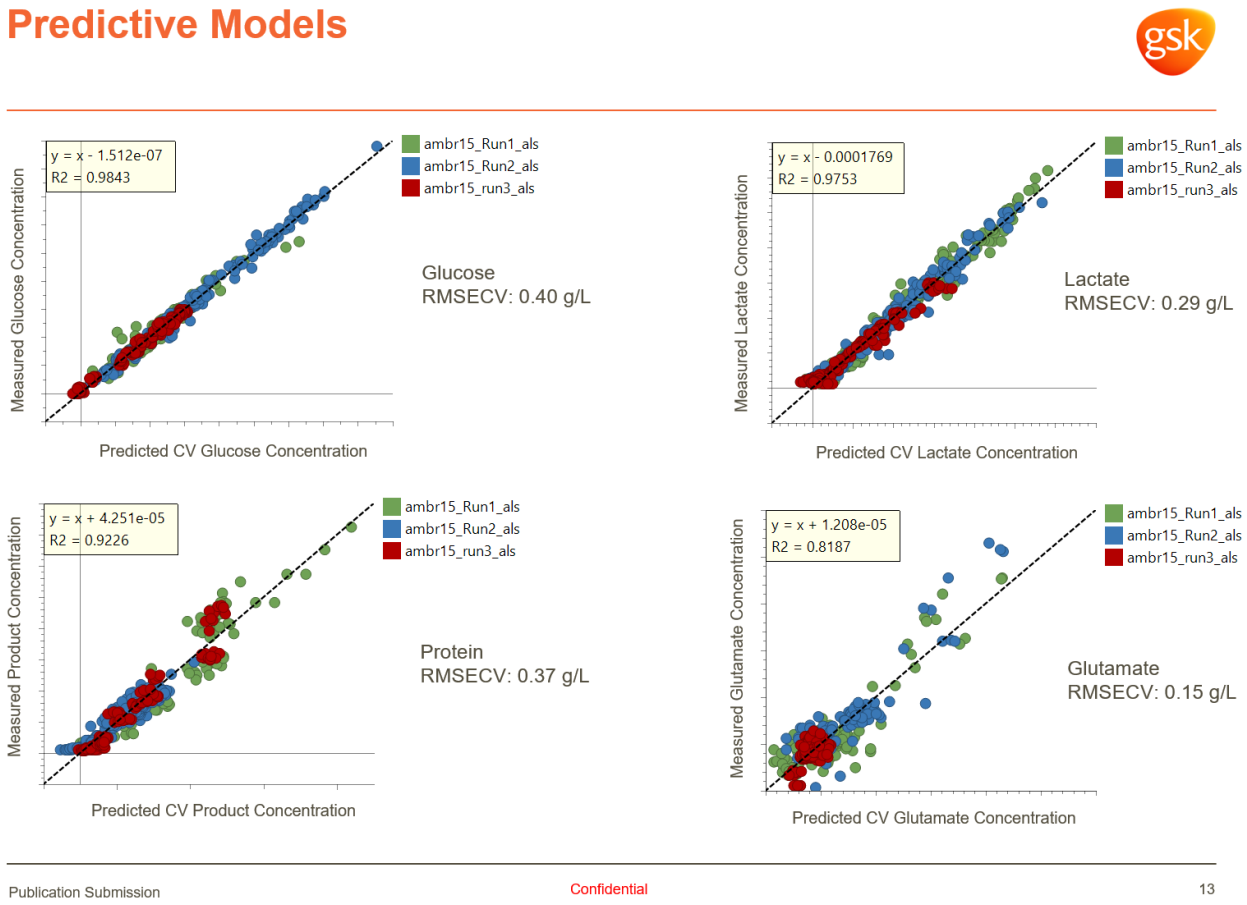
BioPAT® Spectro single-use port in BIOSTAT STR®

connection of a Tornado Raman Spectrometer

connection of a Kaiser Raman Spectrometer

standardized optical design: same probe for ambr® and BIOSTAT STR®

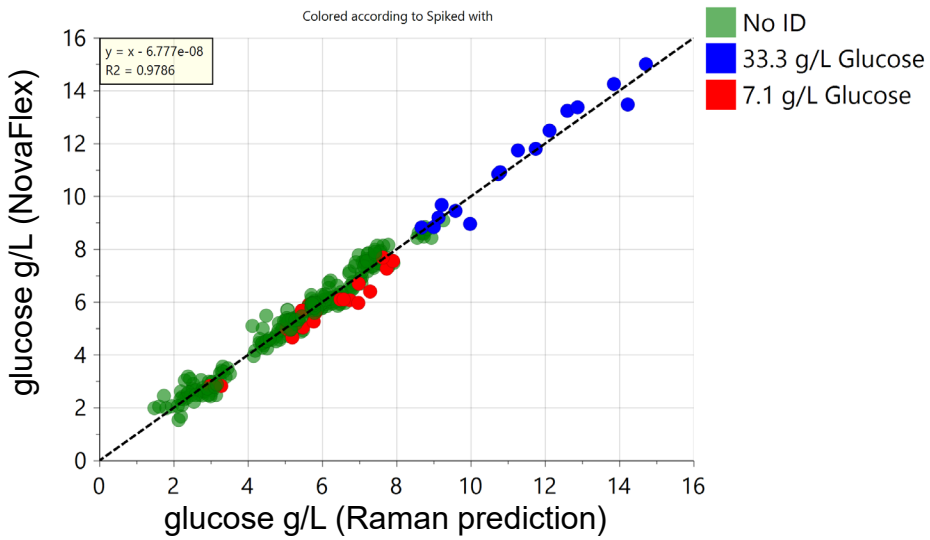
Publication (released) - GSK, model building in ambr® 15

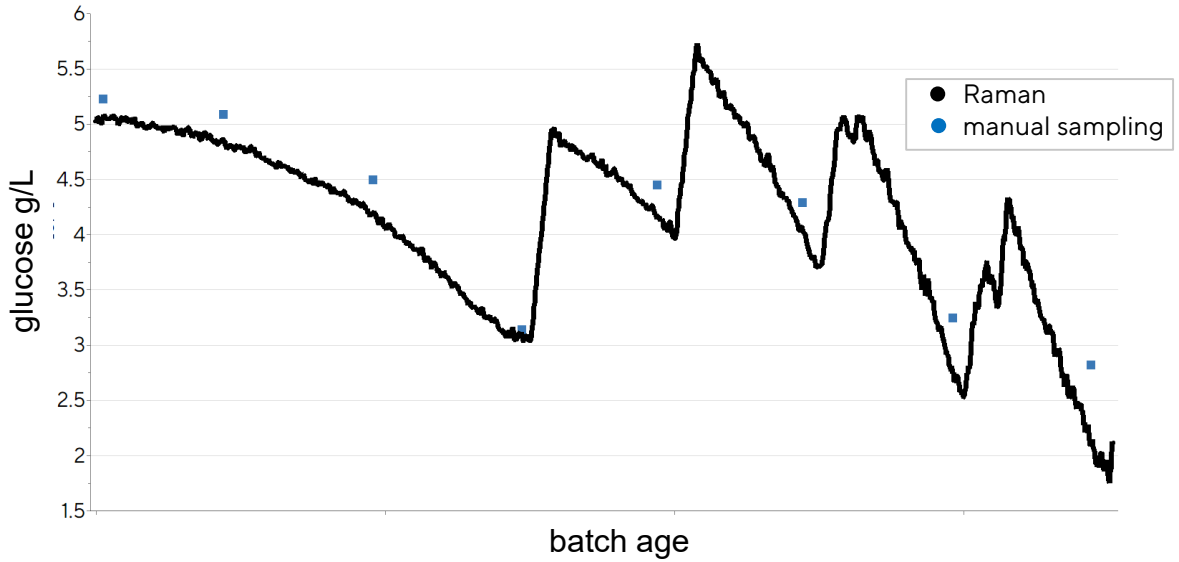


Data source: GSK Stevenage, Performed with a prototype spectroscopy integration and a Tornado Raman spectrometer.

https://aiche.onlinelibrary.wiley.com/doi/full/10.1002/btpr.3074

Easy model transfer due to platform approach





model building in ambr® 250

- glucose model built using two ambr runs of eight vessels each
- spiking two glucose stock solutions
- RMSEcv = 0.34 g/L

direct model transfer to FlexSafe STR® 200L

- STR and ambr runs happened at different sites
- different seed train & media lot and reference method was used
- the raw ambr model was used without any additional data from an STR
- offset correction was performed based on first reference measurement

Data source: ambr® 250 high throughput & BIOSTAT STR® 200, with Kaiser Raman spectrometer and probe; Marek Hoehse and Mike Sibley, Sartorius

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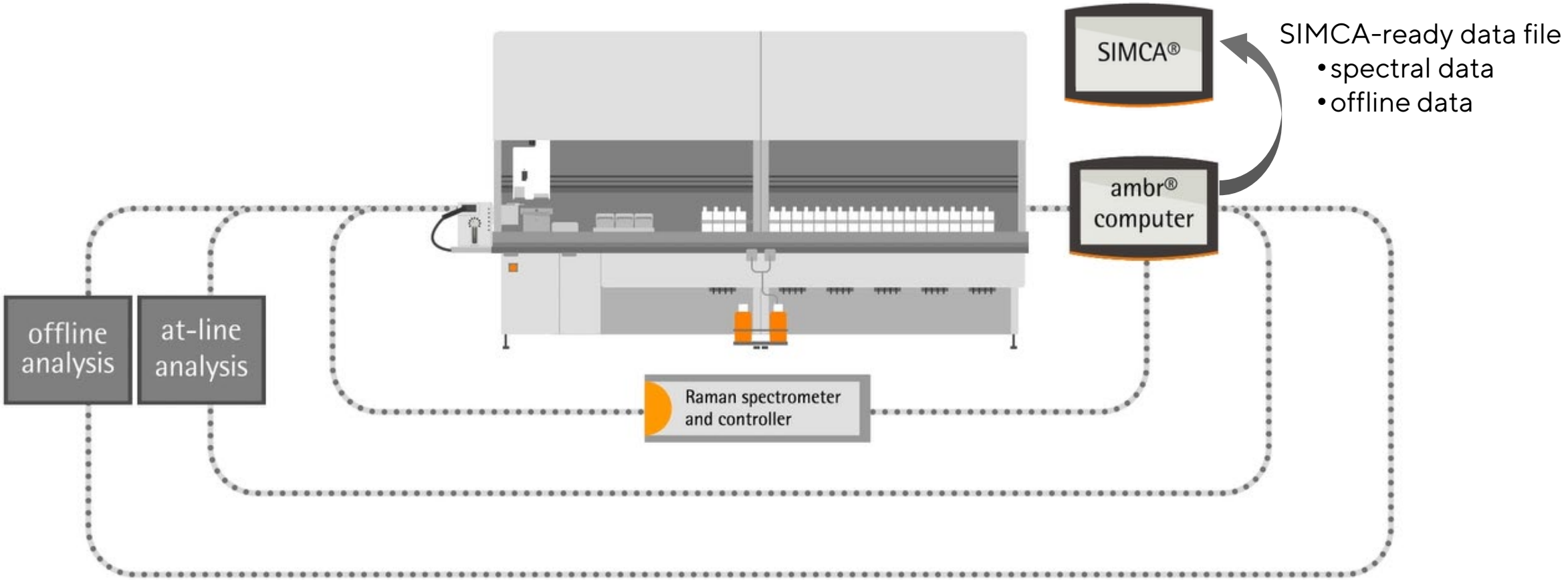
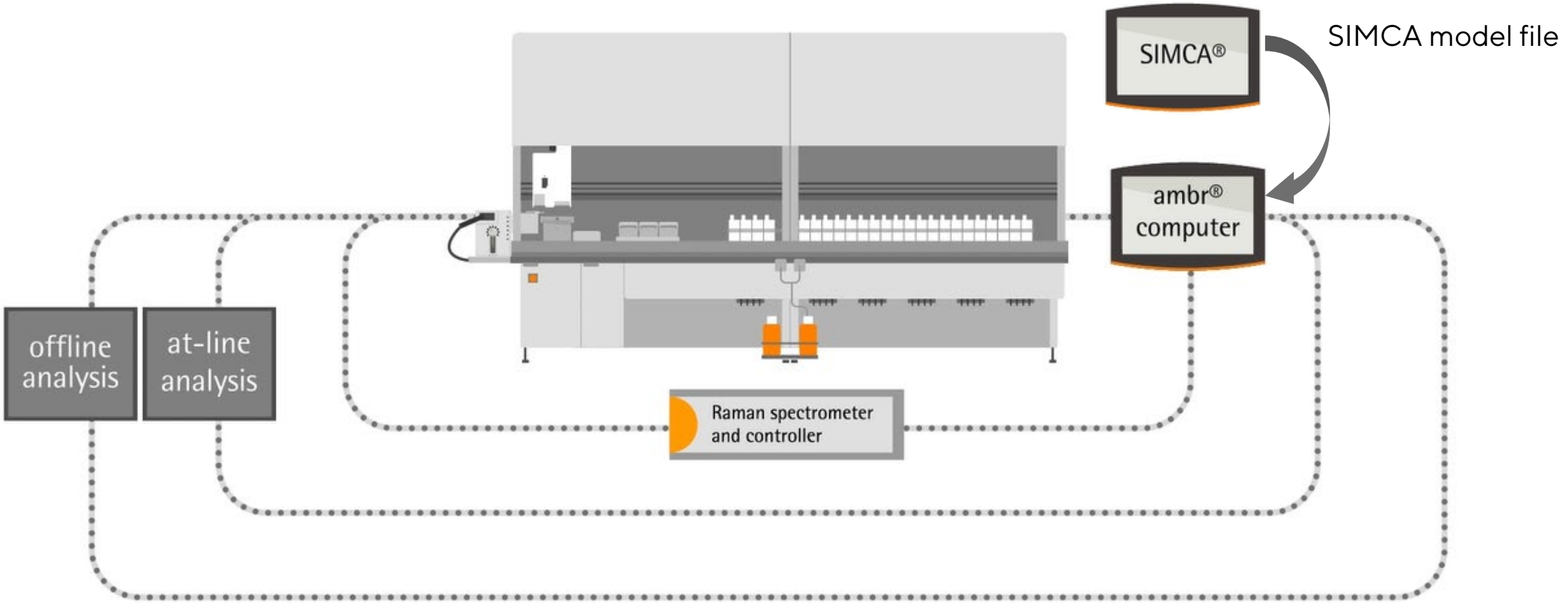
Data acquisition and consolidation is fully automated in ambr®



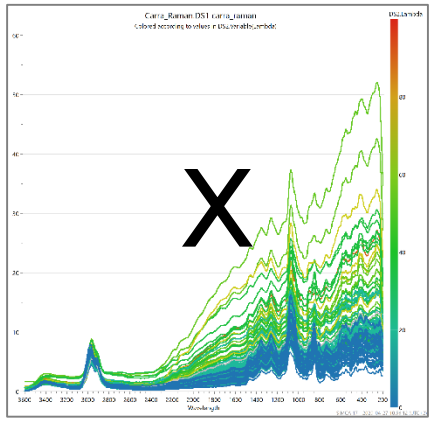
Data acquisition and consolidation is fully automated in ambr®



Building a calibration models in SIMCA®

- Experiment(s) run to generate good calibration data
  - DOE strategy for spiking of samples
- Data exported from BioPAT® Spectro
  - Digitized spectra
  - Concentration measurements of analytes
- SIMCA® is used to create calibration model
  - PLS or OPLS regression used
- SIMCA® model(s) exported back to BioPAT Spectro
  - One calibration model for each analyte
- Development or manufacturing application
  - BioPAT Spectro use Raman spectra to predict analyte concentration

Spectra



PLS
OPLS

Concentrations

Glucose
2.740
2.010
3.750
3.750
3.690
3.690
3.690
3.690
5.230

Y

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Demo of SIMCA®

Creating a Glucose calibration model for BioPAT® Spectro

SIMCA® and how to learn more

- SIMCA® is a powerful data exploration tool based on multivariate correlation
- Versatile – Works on any type of multivariate data
- Provides
  - Data overview and pattern recognition
  - Classification and quantitative regression
  - Data driven trouble shooting and deviation analysis
- Visualize hidden trends and patterns not seen in univariate analysis
- Free webinars on many data analytics topics
  - www.sartorius.com/umetrics

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Thank you!
Time for Q&A

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