SARTORIUS

Simplifying Progress

Putting the “D” in CDMO with Data Analytics and Ambr®

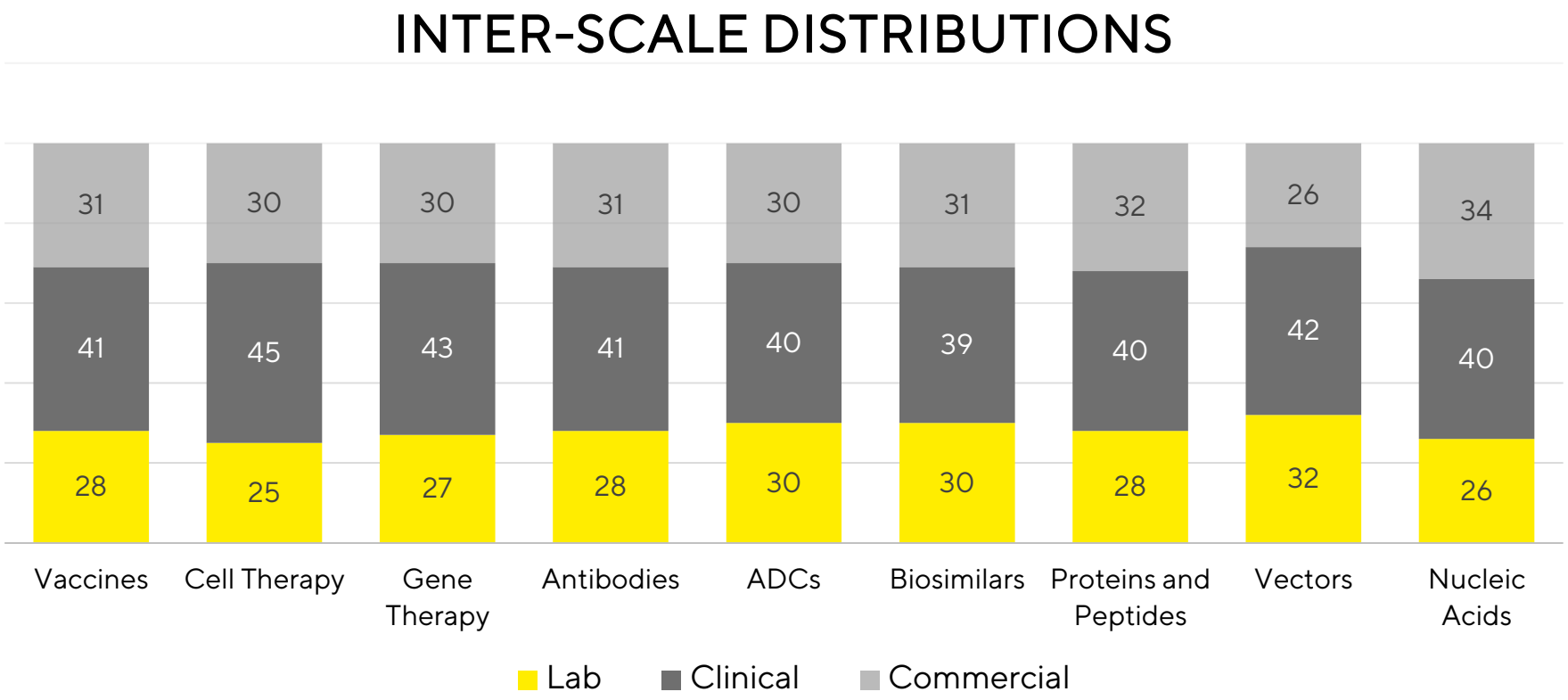
Tiffany McLeod

Kevin McHugh

Agenda

- Market Trends & Analysis
- CDMOs Pursuing QbD
- Technologies that Can Accelerate Process Development at CDMOs
  - Ambr® Systems Overview
- Why Ambr® and Data Analytics?

Biopharmaceutical CDMOs: Distribution of Biologics by Operations



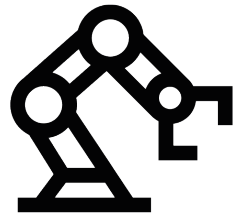
- Lab and Clinical operations make up a majority of the CDMO operations
- 57% of lab scale, 56% of clinical scale operations have been occupied by vaccines, antibodies, and proteins and peptides

Roots Analysis, Biopharmaceutical Contract Manufacturing Market (3rd Edition) 2019-2030 (2019)

Bioprocess Development Technology Trends

In-Silico Experimentation This disruptive technology influencing all industries including Pharma and Biotech and the hype is real. In-silico-based tools are part of drug targeting, screening and discovery, clinical studies and predictive analytics related to any risk involved.

High-throughput Process Development Involves the miniaturization, automation, and parallelization of process development activities – proving for a systematic approach for time- and resource-efficient workflow.



Continuous Bioprocessing The intensification of both upstream and downstream operations will requires higher levels of control during PD and presents new scale-up challenges.

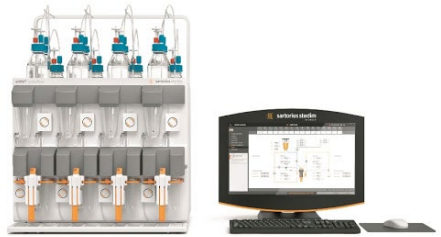
Bioprocess Development Technology Trends

In-Silico Experimentation

Soft Sensor

Digital Twin

High-throughput Process Development



Continuous Bioprocessing

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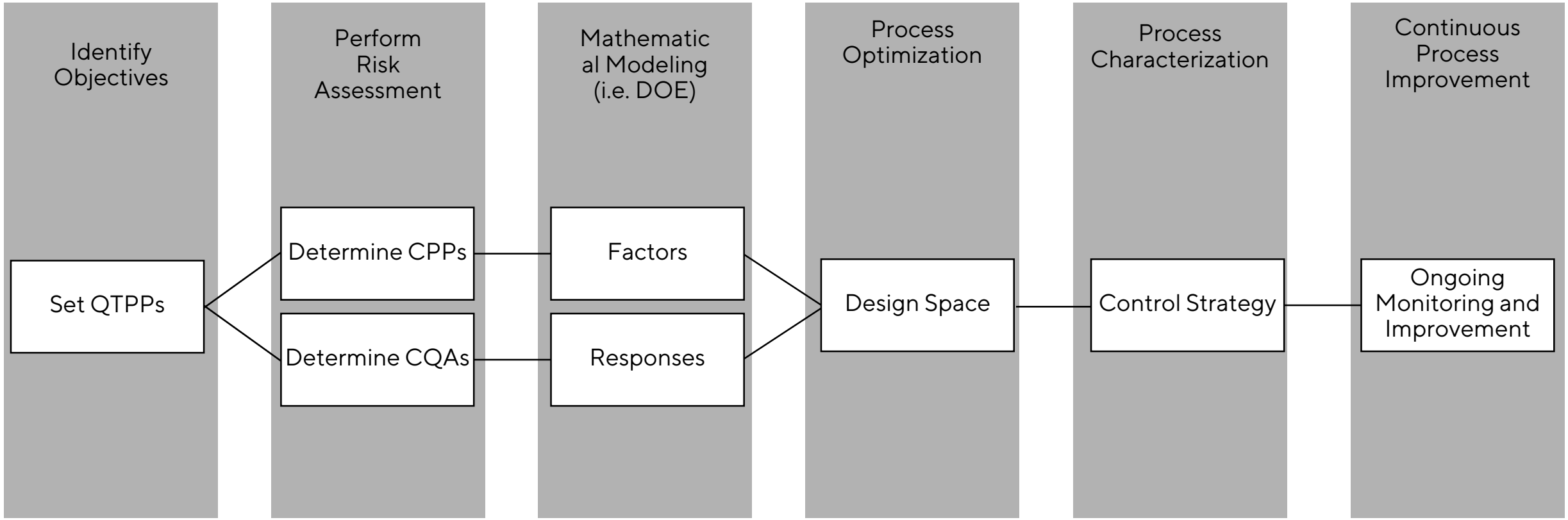
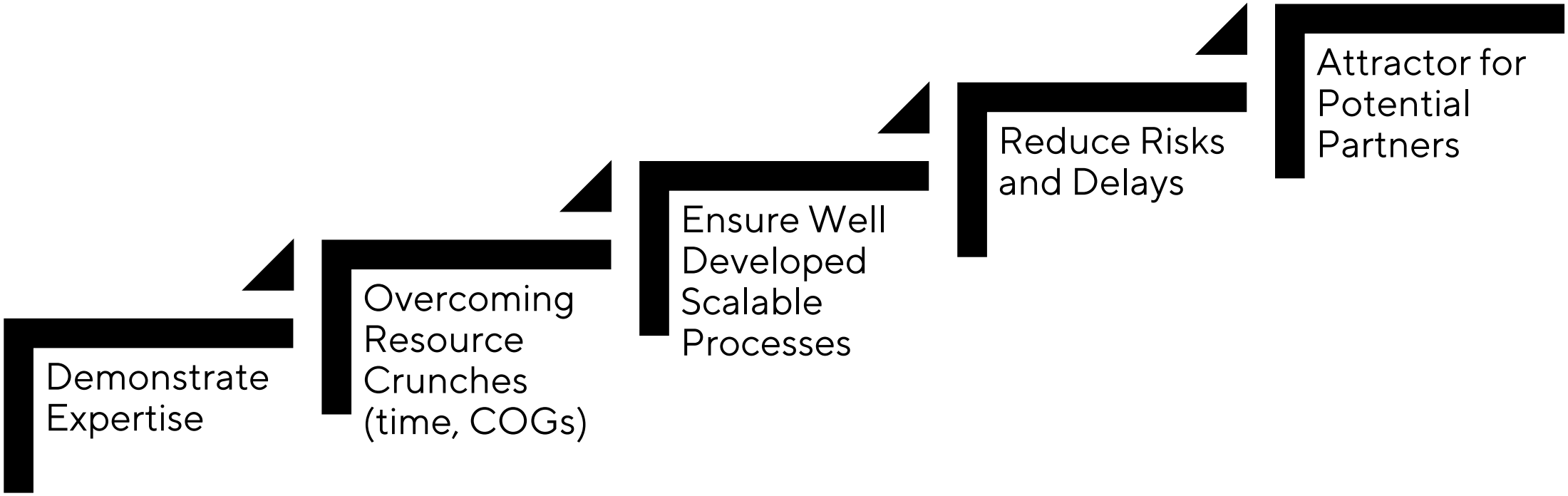
Why Regulatory Agencies are Pushing Quality by Design (QbD)

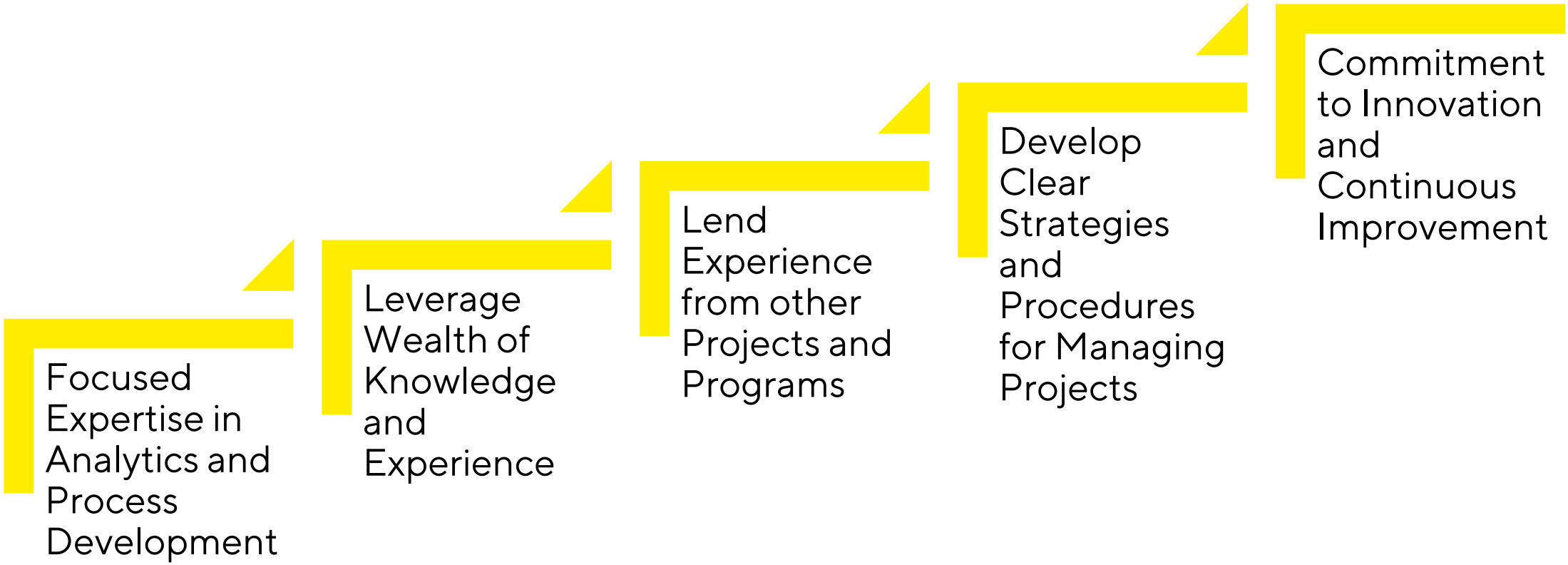


"QbD means designing and developing manufacturing processes during the product development stage to consistently ensure a predefined quality at the end of the manufacturing process." ICH Q10, FDA 2006

Why Should CDMOs Have Strong QbD Packages?



How Can CDMOs Develop Strong QbD Packages?



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Fully Scalable Range of Single-Use Bioreactors from 15 mL to 2000 L Following Conventional Stirred Tank Design Principles

Ambr® 15 Cell Culture

More representative

Predictive

- Clone selection
- Media and feed screening
- Early process optimization
- Batch, fed-batch and perfusion mimic

- Transient transfection studies
- Mammalian and insect cell lines
- Suspension cell lines and adherent cell lines on microcarriers (e.g 293, Vero)
- Applications ranging from recombinant protein vaccines to viral vectors and mRNA

Ambr® 15 Generation 2 Workstation Features and Functionality

New Liquid Handler improves precision

New Culture Station design improves temp. control and increases stirrer speed range

New Flexible deck layout allows more process flexibility

New Large tip bin expands tip capacity

24 or 48 vessels arranged in 2 or 4 culture stations

Active cooling option

New Rapid vessel drain allows removal of culture or spent media from microbioreactors

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Enabling Simple Consistent Clone/Strain Selection

Currently the selection of the top clones or strains is performed upon visual inspection of specific quality parameters or one number readout (e.g. max titre or IVCC)

The selection process is user dependent and the full power of using all available data with a balanced tool to give a robust priority selection is **not fully utilized**

Achieve a **better** and **more robust** clone selection in a **standardized** way using a balanced priority of CQA's

Ambr® 250 High Throughput: the Fast Track to Intensified Cell Culture Process Development

This next-generation bioreactor system can enable and enhance your perfusion process development in these key areas:

- Reduce complexity and setup time with single-use perfusion bioreactors
- Increase experiment capacity and data consistency with a fully automated parallel system
- Gain predictive, scalable results with the industry standard Ambr® 250 bioreactor
- Increase cost effectiveness due to media and labor cost savings
- Improve development timelines and performance with larger studies and perfusion DoE

Ambr® 250 High Throughput Workstations

12 Vessel

Analysis Module

Chilled sample storage with an option for freezer positions

24 Vessel

Automated system for aseptic bolus addition and sampling

13 feet

Bed locations for pipette tips and stirred bed location for 1 L and 175 mL bottles

12 or 24 bioreactors
4 pumps each

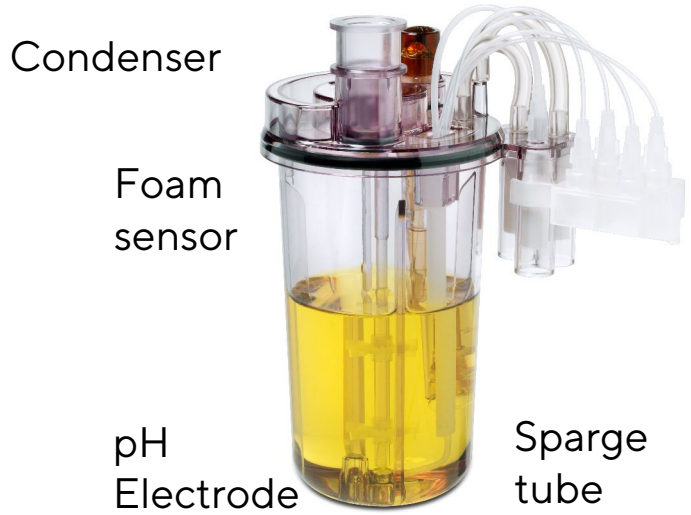
Perfusion Option

Class II equivalent BSC

Perfusion pump towers and filters

Ambr® 250 High Throughput Vessels

Single-Use Vessel



Micro Carrier
Vessel

30mm Rushton
Microbial Vessel

Ambr® 250 High Throughput Perfusion Option– Key Features

- Fits into the existing footprint of a standard ambr®250 high throughput system
- Fully capable of operating in either fed-batch or perfusion modes
- ATF & TFF consumable includes a single-use perfusion filter and single-use pump chambers
- Includes a high efficiency sparger for enhanced oxygen transfer and capable of supporting high cell densities
- Single-use bleed and permeate bags
- Medium exchange of 0.5 - 4 VVD
- Integrated automation

Ambr® 250 Modular System

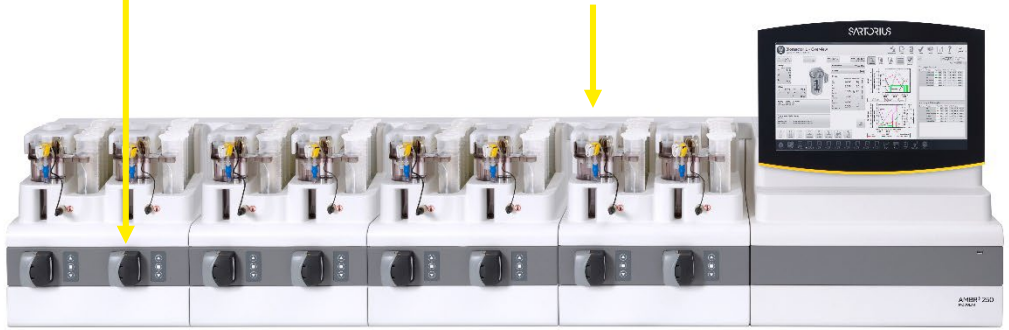
Single-Use Vessel

Integrated off-gas analyzers available for CO_2, and O_2 Measurement, as well as OUR, CER, and RQ calculation

Workstation

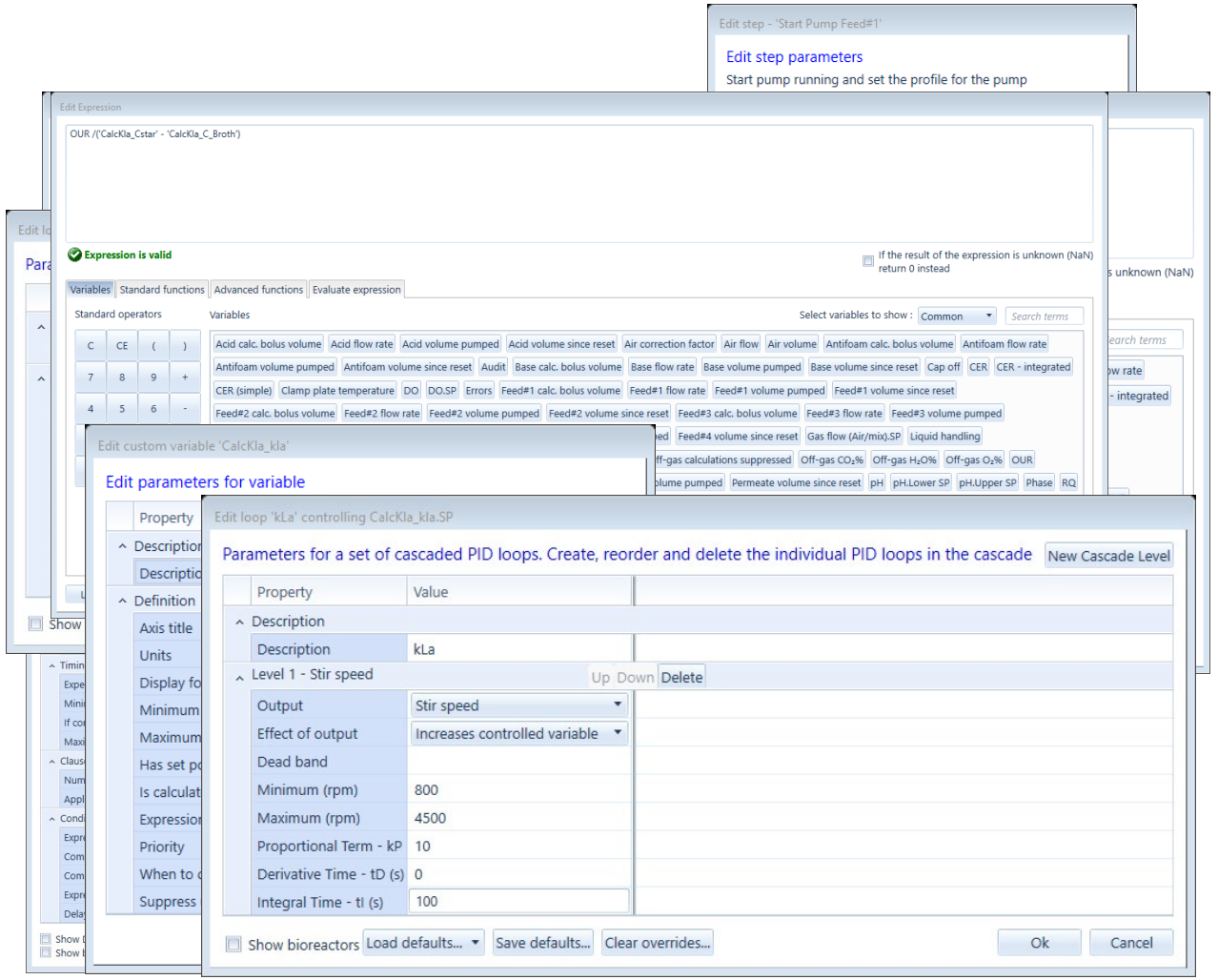
Variable speed ‘x pump’ allows for flexible use and quick reactor harvesting.

Simple and efficient pH and gassing, and agitation connections



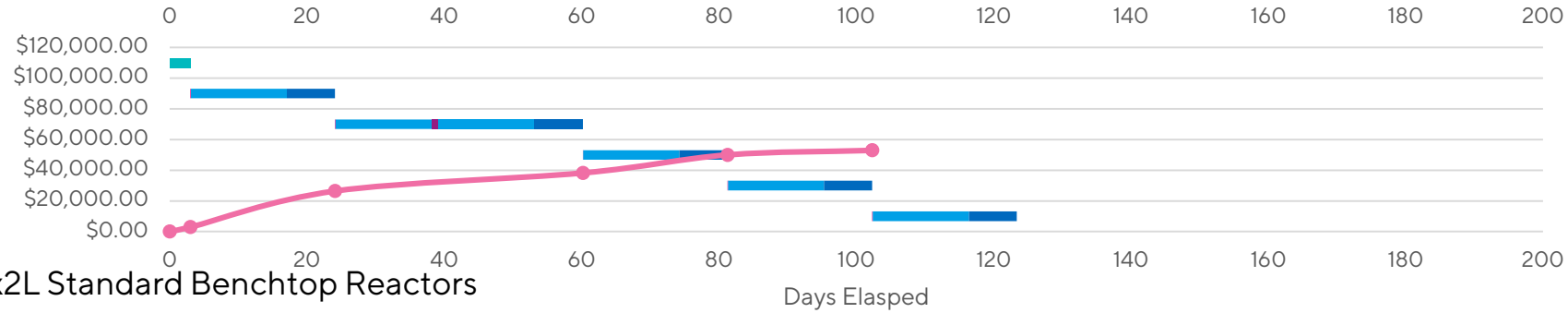
Easily Develop Advanced Control Strategies

- Flexible Control Strategies:
  - Setpoints can be based on a value, equation, profile, or even OPC input.
  - Not just for pumps but also process parameters
- Easy to use Triggers
  - Variety of options available to easily automate the transition between phases of a process
- Flexible Control Loops:
  - Any process parameter or calculated value can have a setpoint and an output can be assigned to control it
  - Implement advanced control strategies like DO-Stat in just a few clicks
- Calculated Variables
  - Equations can be developed to calculated values based on various sensors and inputs
  - Can be used as triggers, controlled variables & PID terms

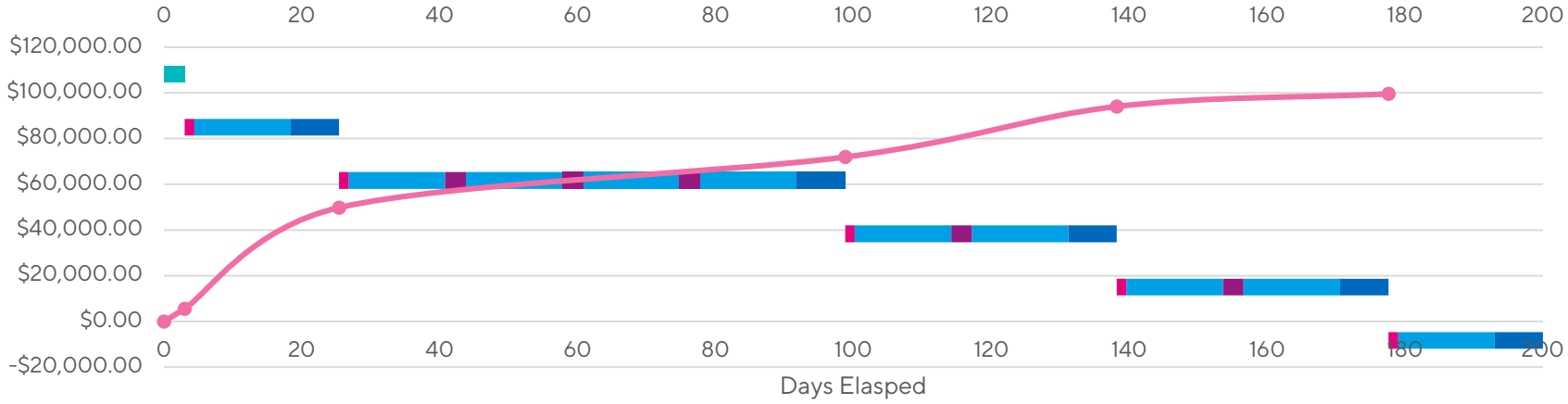


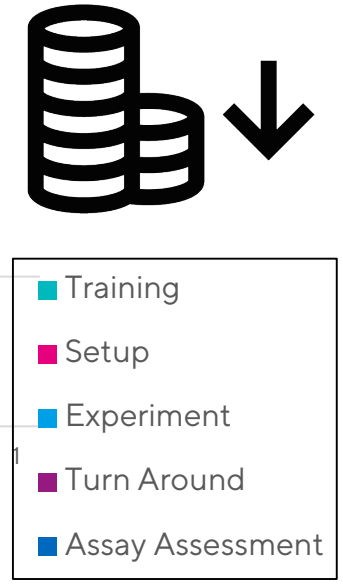
High Throughput Upstream Process Characterization Platform Development– Cost and Time Saving Comparison With Traditional Approach

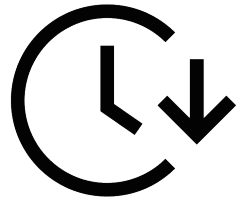
- Ambr® 250 – 24 Vessel Configuration



- 12x2L Standard Benchtop Reactors







Scalable, Automated At-Line and Real Time Process Monitoring and Control

From 15 mL to 2000 L SU bioreactors

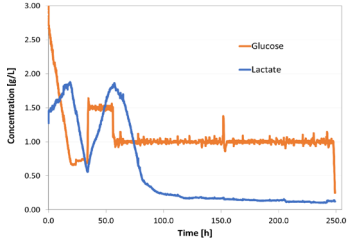
Guidance for Industry
PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

PAT facilitates the implementation of QbD!

NOVA Flex II with ESM

Off-gas and Foam Sensors

ViCell XR



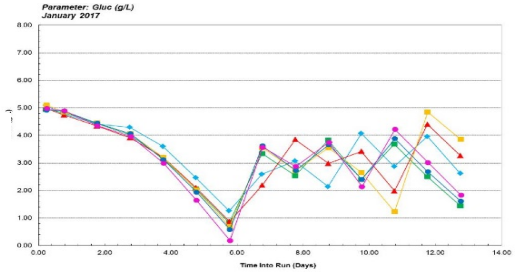
BioPAT® Trace

BioPAT® X-gas

BioPAT® Foam

Analysis Module w/ BioPAT Spectro

Online Biomass



BioPAT® Viamass

EC/SU pH

BioPAT® Spectro

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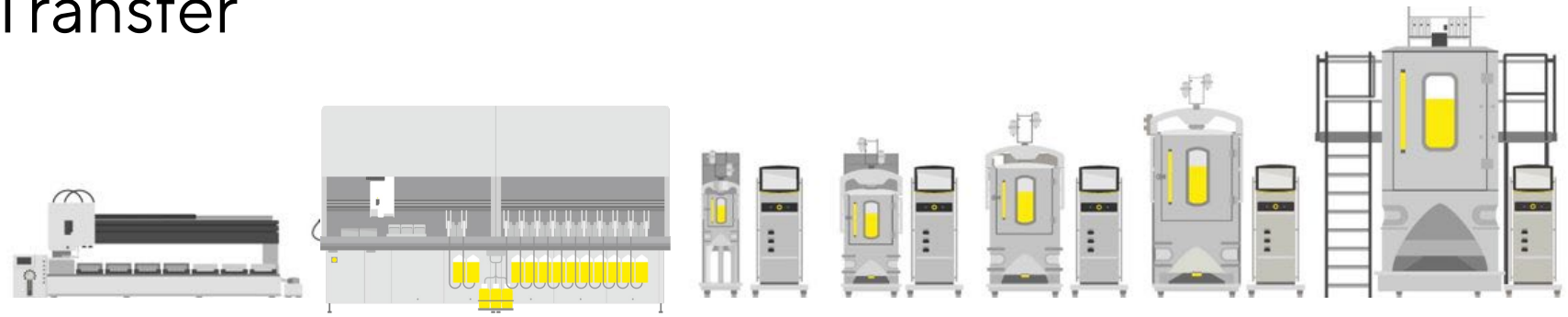
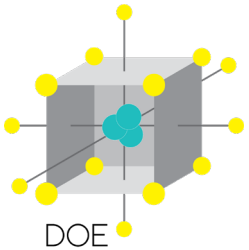
Spectroscopy Platform across Scales enabling straight-forward Model-Transfer

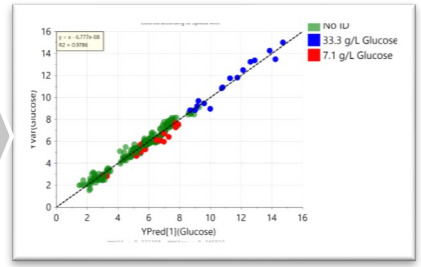


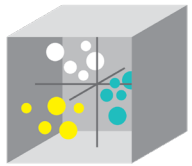
Rowland-Jones, RC, Graf, A, Woodhams, A, et al. Spectroscopy integration to miniature bioreactors and large scale production bioreactors–Increasing current capabilities and model transfer. *Biotechnol Progress*. 2020;e3074. https://doi.org/10.1002/btpr.3074

1. Model Building		2. Process Development		3. Model Transfer	4. Production
Enhanced Model building in small scale	Model validation in small scale	Model application in small scale	Model application in pilot scale	Model validation in larger scale	Model application in SU production scale bioreactors

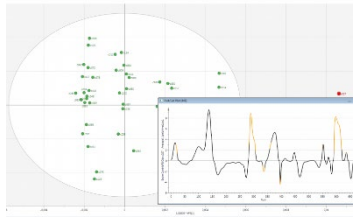


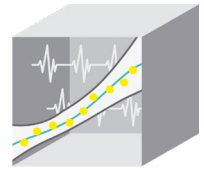
DOE
Design of Experiments



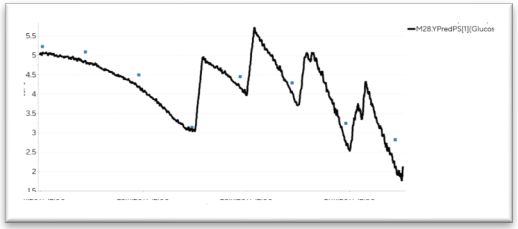


MVDA
Multivariate Data Analysis





MVDA
Online Multivariate Data Analysis



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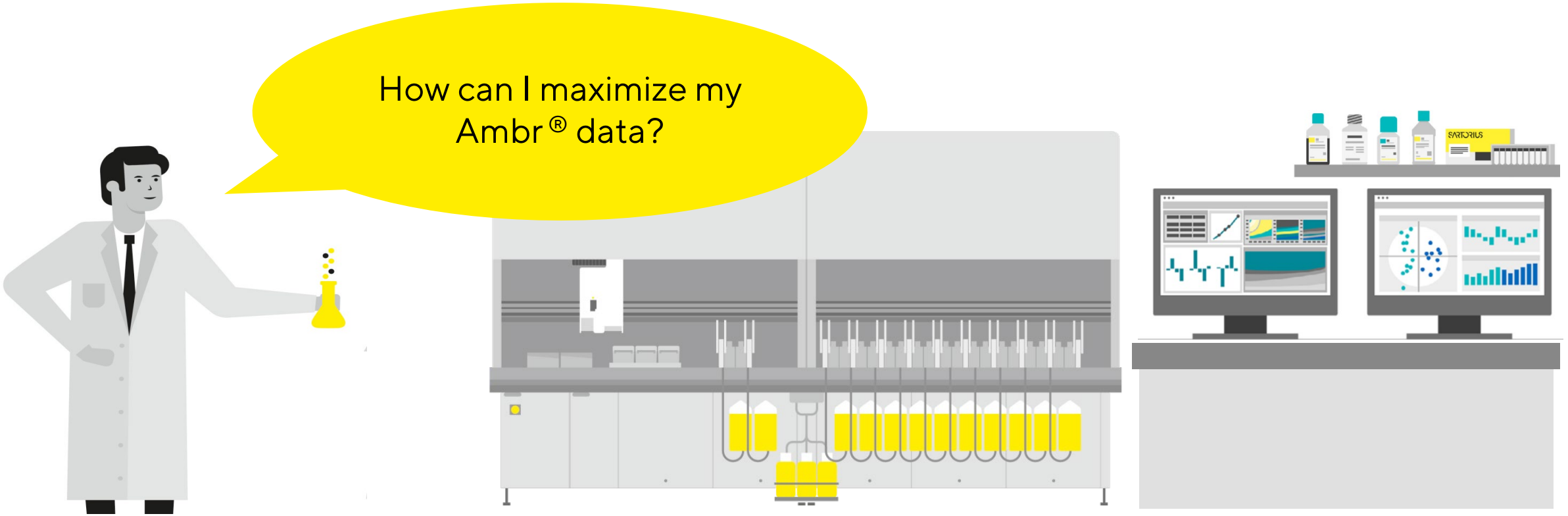
Ambr® and Data Analytics: The Perfect Match



From Data to Decisions

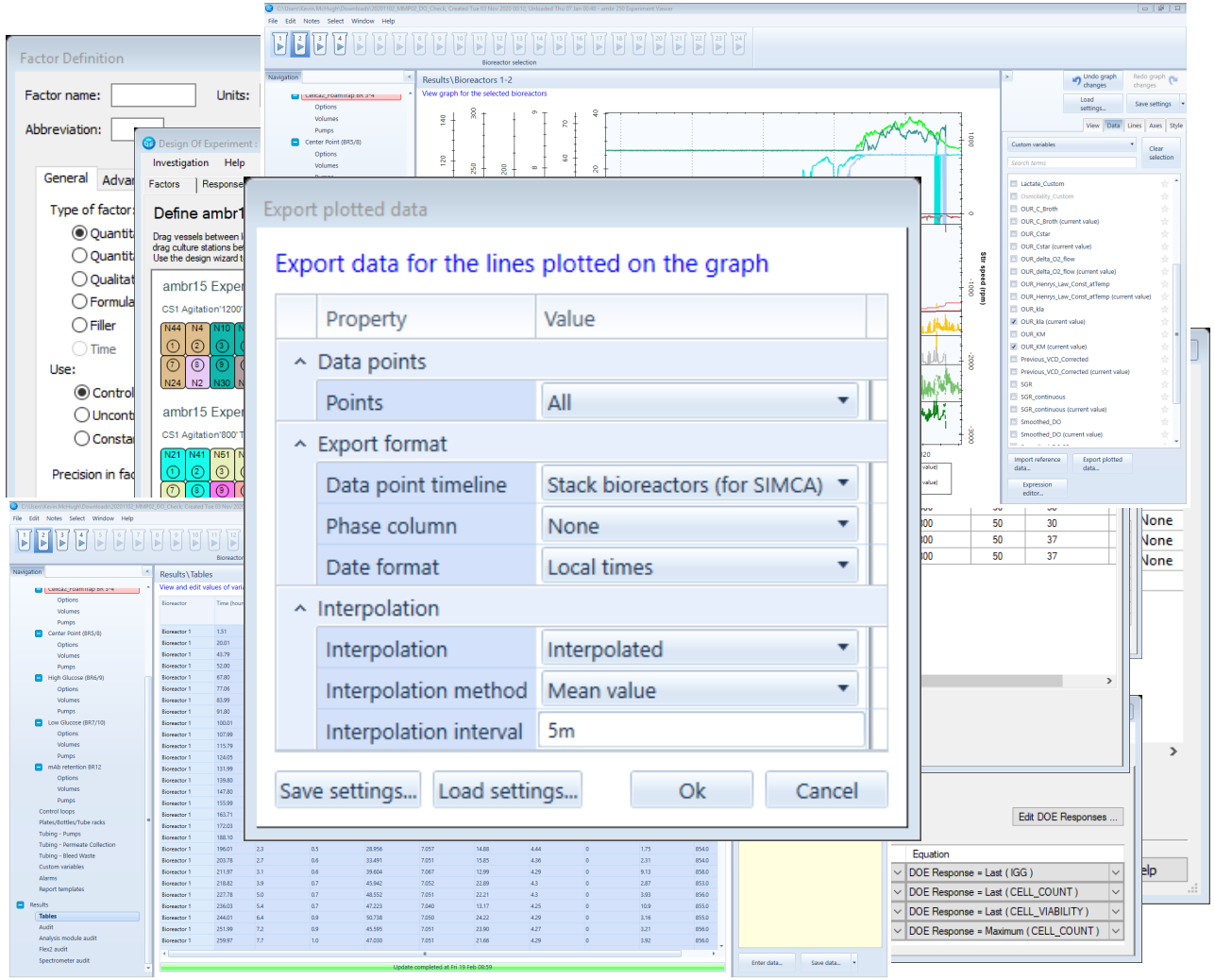
Sartorius Data Analytics tools examine large amounts of data to uncover hidden patterns.

MODDE®

SIMCA®

Design, Execute and Analyze Experiments Quickly and Easily

- MODDE® Design of Experiments
  - Familiar interface for defining factors and responses.
  - Functionality to automatically import setpoints and extract responses from ambr15 experiments
    - Not only end point but min, max, timepoints, etc.
  - Software automatically accounts for system type (12, 24, 48 & culture station limitations)
- Experiments and Results Viewer
  - Quickly and easily explore pervious experiments and campaigns
  - Quickly generate tables and charts
  - Investigate experiment audit trails
  - Combine and visualize data from multiple experiments
- Easy to Use SIMCA® Data Export
  - Quickly and easily export online and at-line sequential batch data for an experiment or entire campaign
  - Interpolate data as needed



DOE vs MVDA for Ambr® Experiments

MODDE® DOE

Media Component Screening

Cell Line and Clone Screening

Bioreactor Condition Optimization

Feed Strategy Optimization

Bioreactor Characterization

Scale-up/down Model Development

VS

SIMCA® MVDA

Bioreactor Condition Optimization

Feed Strategy Optimization

Spectroscopy Calibration Modeling

Scale-up/down Model Verification

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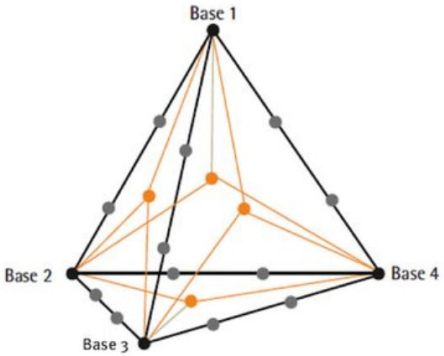
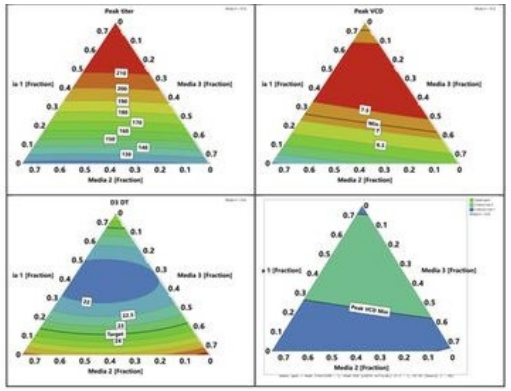
Ambr® DOE Examples

Media Component Screening





Challenge:

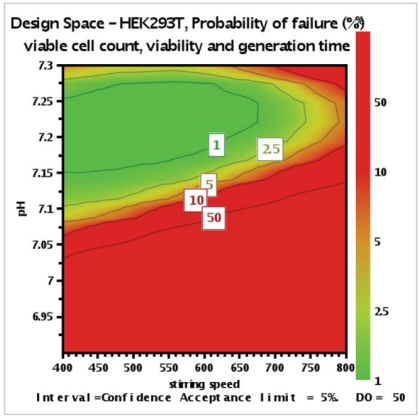
- Not all commercially available media supports every cell line, therefore in some cases additional supplements must be added to improve cell performance
- The classical approach to media component screening is time consuming and labor-intensive

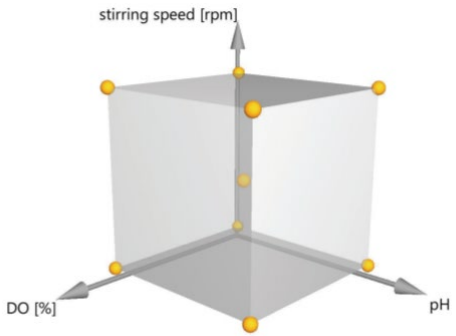
Data Driven Solution:

- Use DOE principals to systematically screen media components for productivity effects
- Recognize interactions and define them early in the process, setting optimum levels accordingly

How to Optimize Cell Culture Media to Speed Biopharma Development, Sartorius (2018)

Bioreactor Optimization and Characterization





Challenge:

- A significant challenge for developing viral vector gene therapies is that is well characterized and can be scaled-up

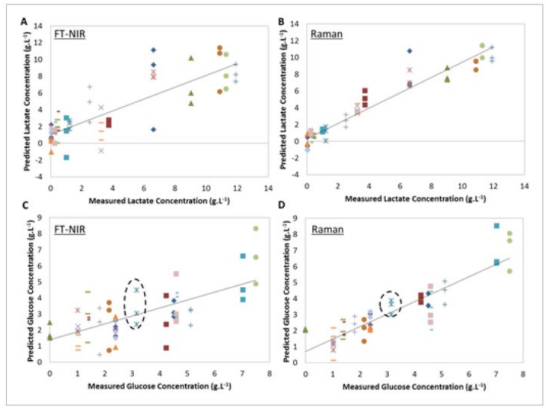
Data Driven Solution

- Use DOE principals to identify which process parameters impact product quality and yield
- Justify and adjust manufacturing operating ranges – control strategy - and acceptance criteria

Optimization of HEK293t Suspension Cultivation with DOE-approach in the Ambr 15 Micro Bioreactor, Bollman, Riethmuller, Johansson, Tappe, R&D Regenerative Medicine, Sartorius (2019)

Ambr® MVDA Examples

Spectroscopy Calibration Modeling



Challenge

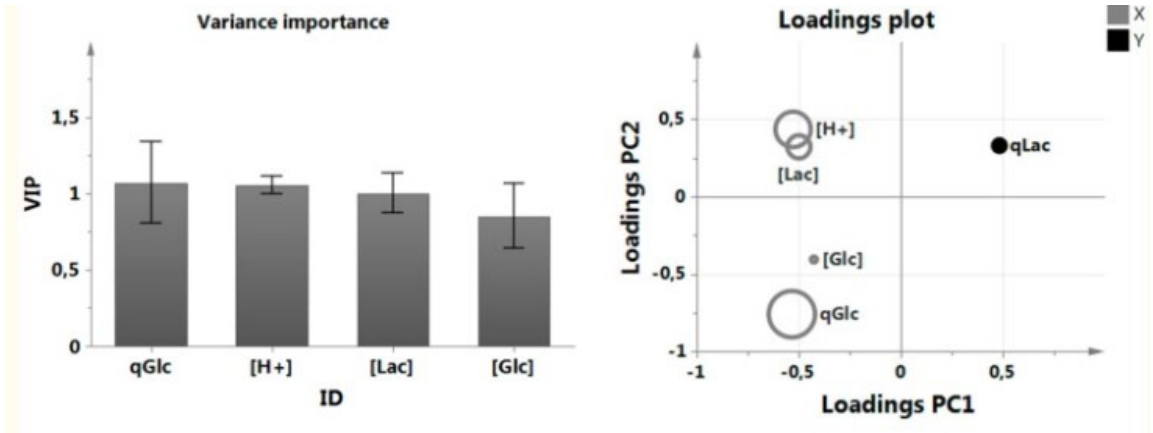
- PAT tools can (i.e. spectral devices, advanced sensors and analyzers) generate large amounts of complex data presenting a challenge when it comes to interpreting accuracy

Data Driven Solution:

- MVDA is a fast and flexible spectral calibration tool that can handle multiple types of spectral data (NIR, IR, Raman, Fluorescence, Mass-Spec)
- It provides accurate prediction models for analyte concentrations can be used to optimize monitoring and control of the culture

Comparison of Spectroscopy Technologies for Improved Monitoring of Cell Culture Processes in Miniature Bioreactors, Rowland-Jones, van den Berg, Racher, Martin, Jaques, Biotechnology Process Volume 33, Issue 2, GSK (2017)

Feed-Strategy Optimization



Challenge

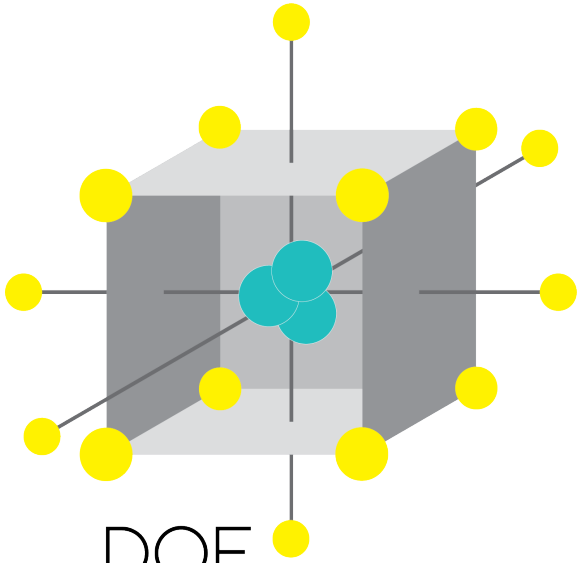
- A significant challenge in cell-culture cultivation is predicting the nutritional requirements of the culture so that an appropriate feeding strategy can be implemented

Data Driven Solution

- Use MVDA to identify and rank any potential inhibitors or promotors of cell-culture productivity in order to optimize feed strategy

Metabolic Control in Mammalian Fed-Batch Cell Cultures for Reduced Lactic Acid Accumulation and Improved Process Robustness, Kanokovsky, Clemens, Müller, Bechmann, Berger, Schlatter, Herwig, Boehringer Ingelheim, Vienna Institute of Technology, Bioengineering Basel (2016)

Combining the Best of Both Worlds for Ambr® Scale-down Modeling



DOE

Design of Experiments

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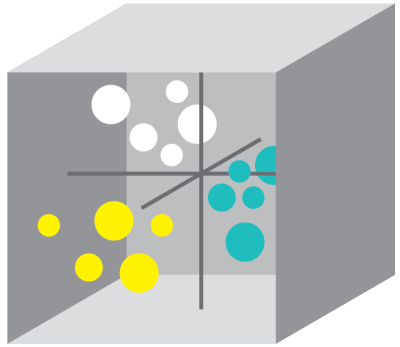


MVDA

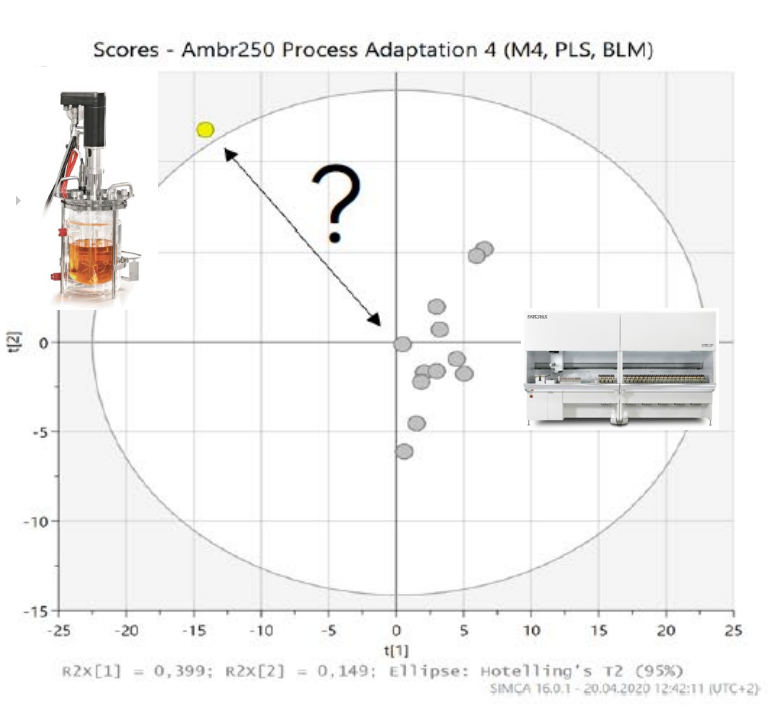
Multivariate Data Analysis

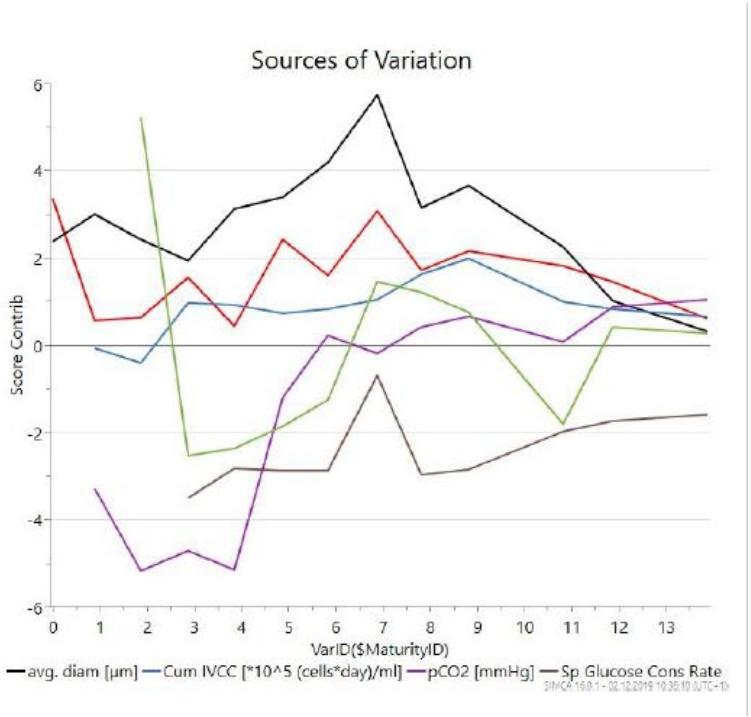
=

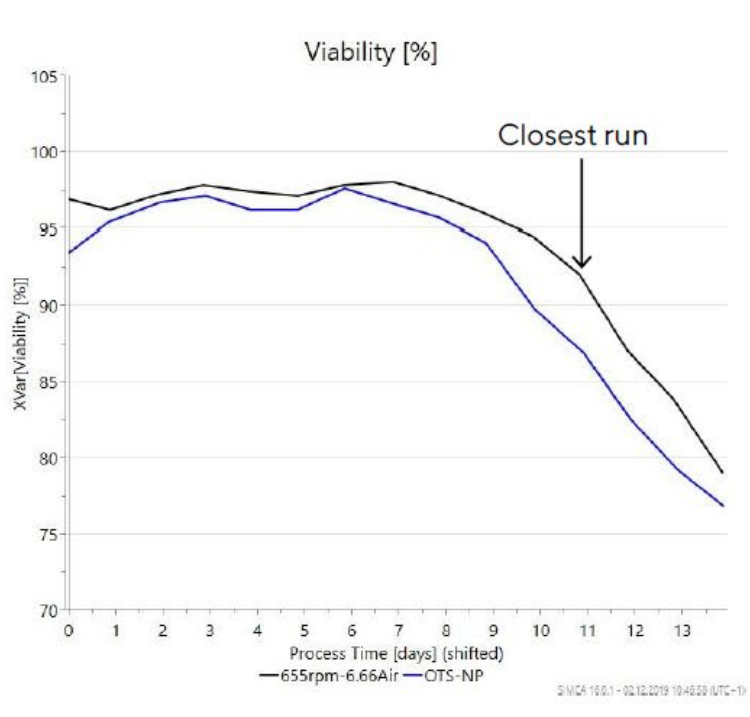
Combine multi-objective optimization criteria (DOE) with quantitative ranking (MVDA)

Squeeze all the value from the data you have

DOE and MVDA for Ambr® Scale-down Modeling





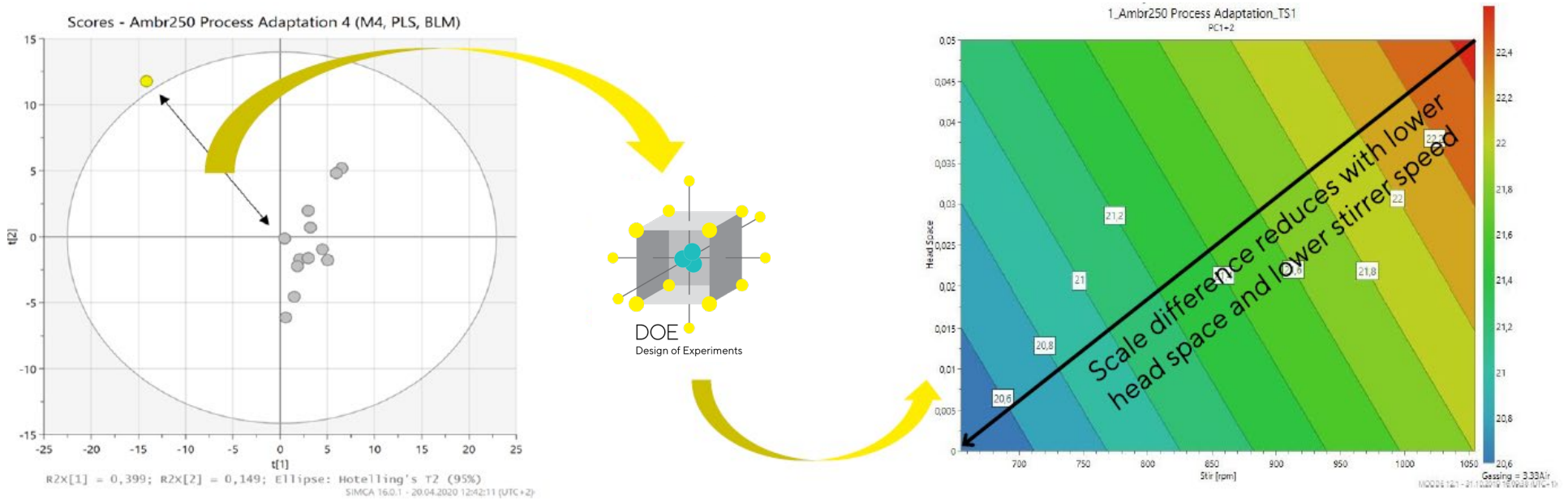


MVDA Used to Evaluate Major Sources of Variability Between Ambr ® and 5L Reference Scale

DOE Establishment of Scale-down Bioprocess Models for Ambr Using Clustered Multivariate Analysis, Timo Schmidberger, Thomas Krieg, Sartorius (2020)

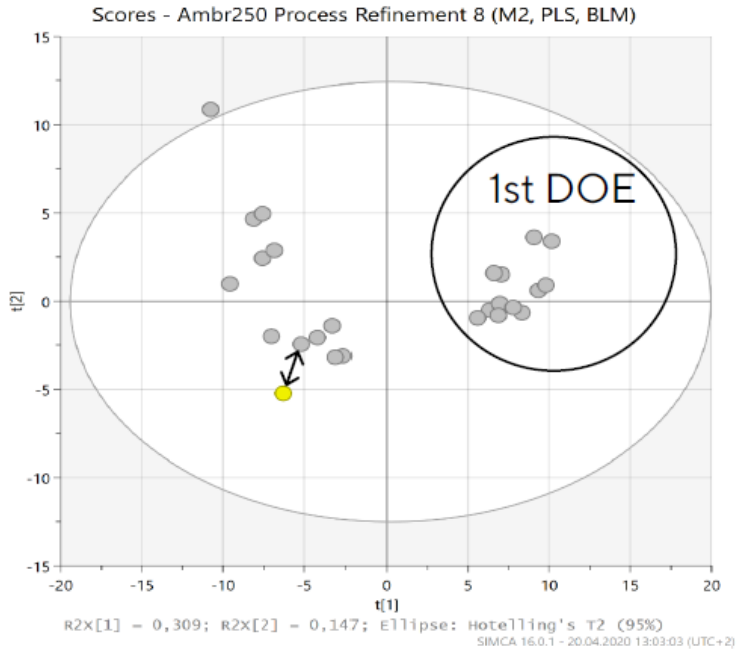
DOE and MVDA for Ambr® Scale-down Modeling

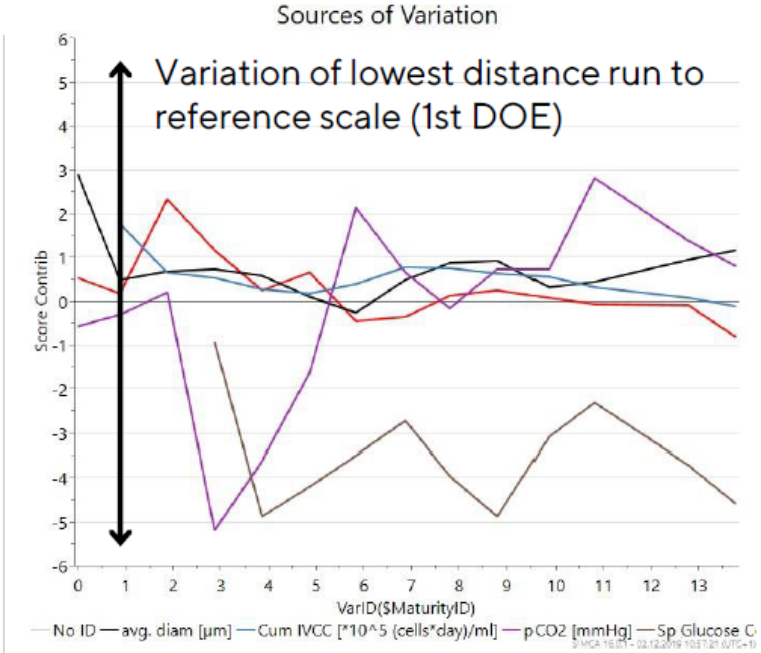
- The goal in scale-down modeling is to decrease the distance between the scaled-down runs and the target scale
- To do this we can use MODDE® DOE to evaluate the length ⟷ and give suggestions as to how to change operating parameters to reduce scale difference

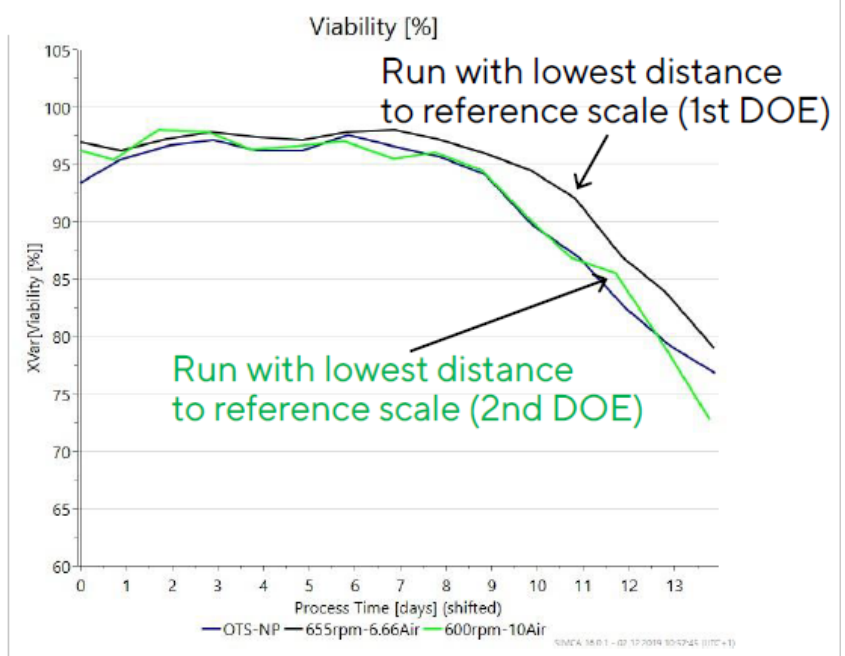


DOE Establishment of Scale-down Bioprocess Models for Ambr Using Clustered Multivariate Analysis, Timo Schmidberger, Thomas Krieg, Sartorius (2020)

DOE and MVDA for Ambr® Scale-down Modeling

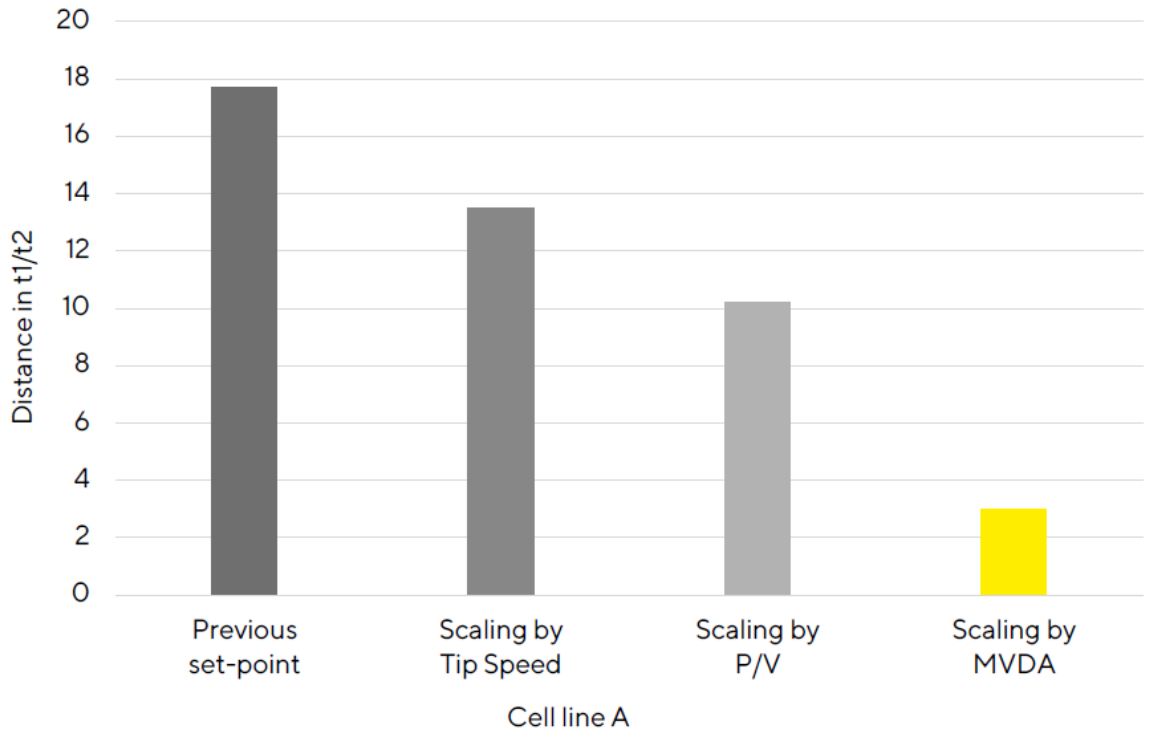


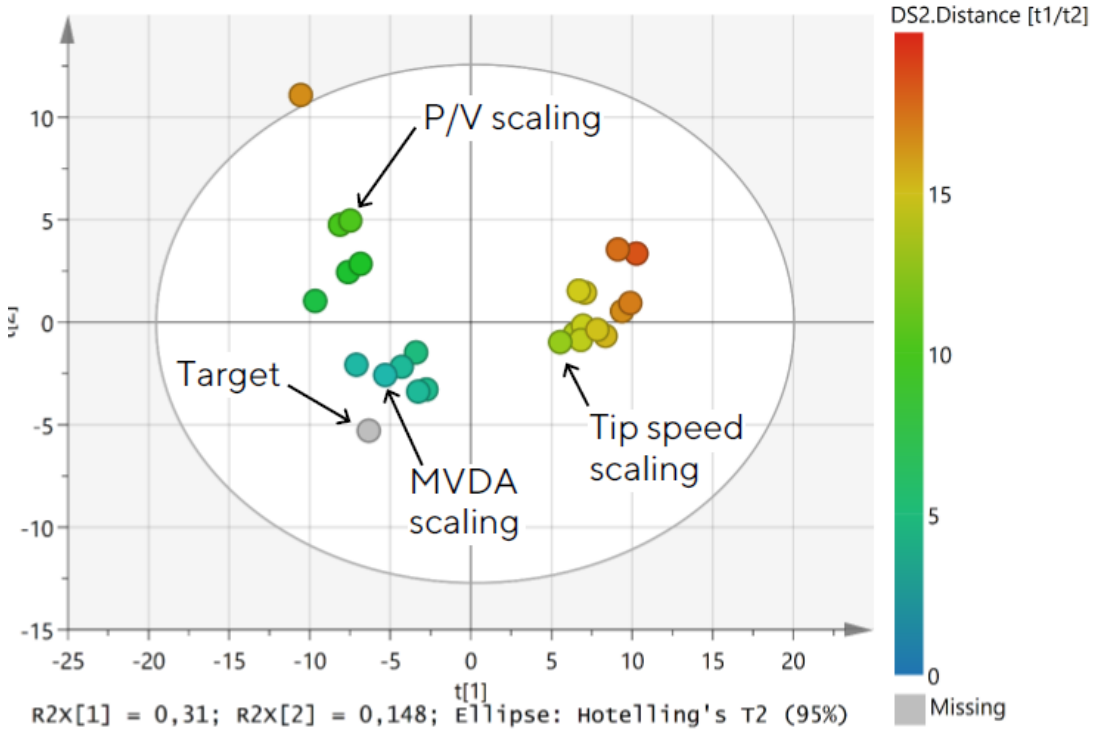




DOE Establishment of Scale-down Bioprocess Models for Ambr Using Clustered Multivariate Analysis, Timo Schmidberger, Thomas Krieg, Sartorius (2020)

DOE and MVDA for Ambr® Scale-down Modeling Method Conformation





DOE Establishment of Scale-down Bioprocess Models for Ambr Using Clustered Multivariate Analysis, Timo Schmidberger, Thomas Krieg, Sartorius (2020)

DOE and QbD are Key for CDMO Success

“The most successful CDMOs, therefore, have identified strategies for completing process development projects efficiently and effectively while incorporating DOE and QbD approaches that provide increased process understanding and lead to optimal processes.”

Greg Flyte, GSK, CMO Alliance and Program Management

Putting the “D” in CDMO with Advanced Process Development, American Pharmaceutical Review, Greg Flyte, GSK (2016)

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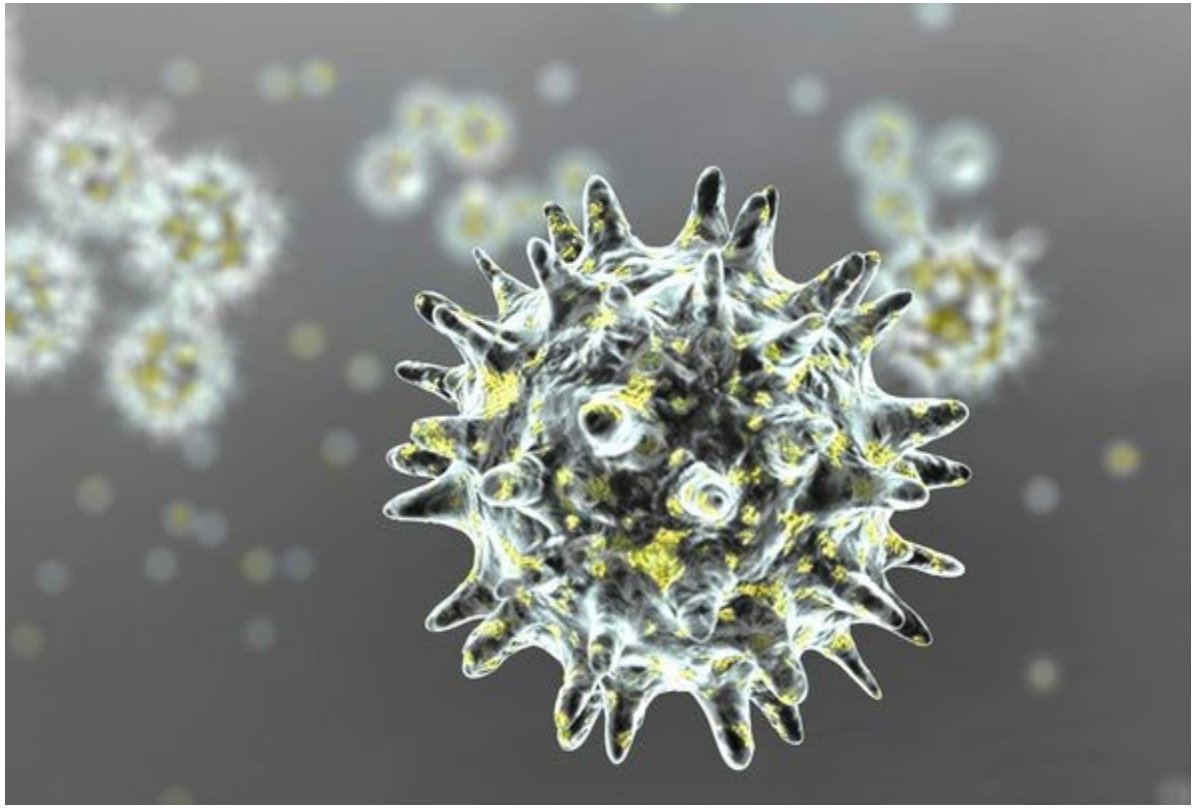

Thank you!

Tiffany McLeod
Kevin McHugh

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