Biologics production today and beyond our next steps to our journey to the facility 4.0

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With Content from
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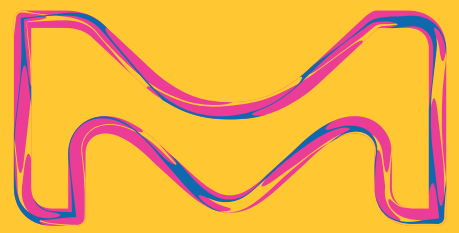
Prof. Dr. Michelangelo Canzoneri, Merck KGaA



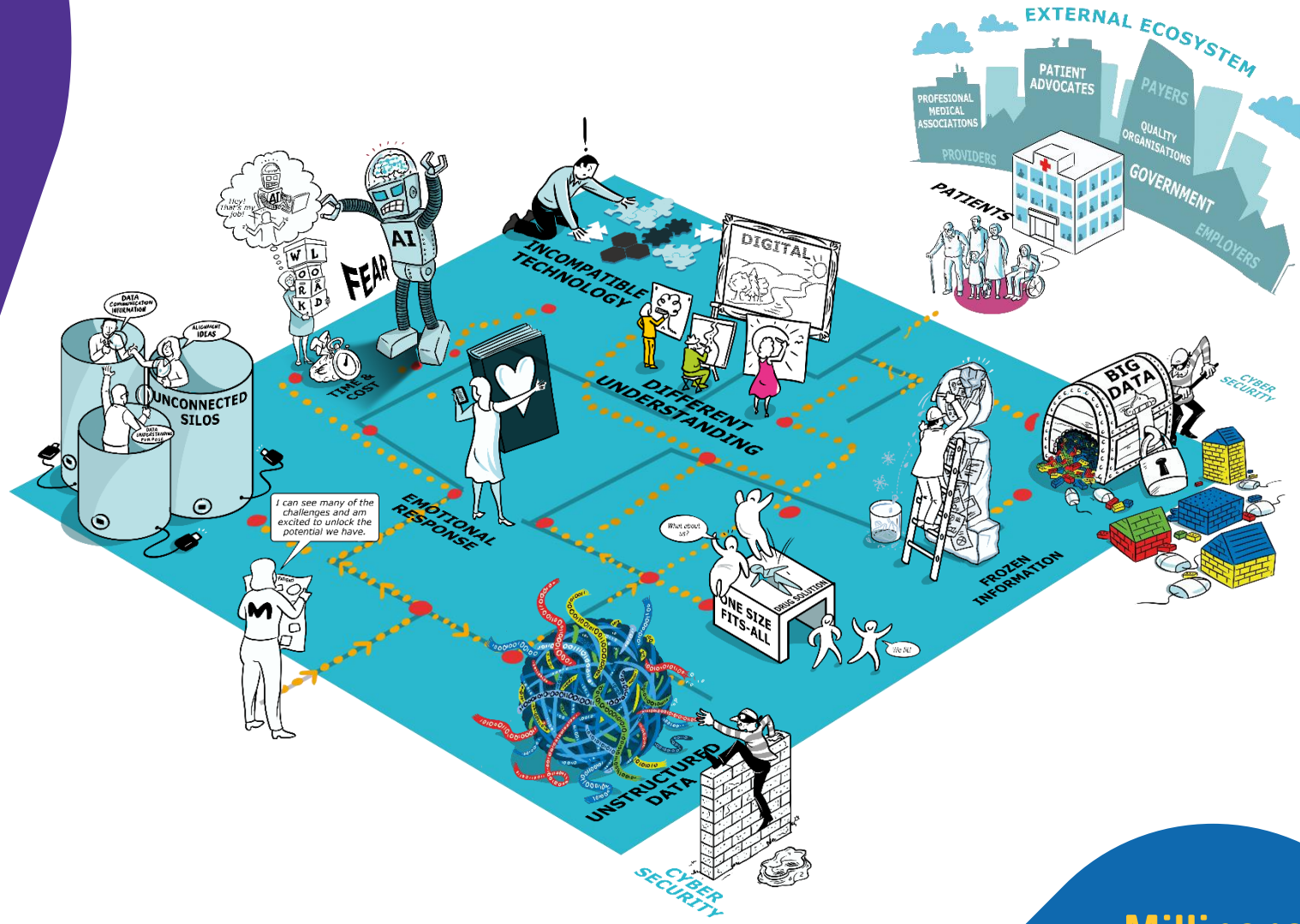
Millipore®

Preparation, Separation,
Filtration & Monitoring Products

plant of the future
or-
what do we have today?

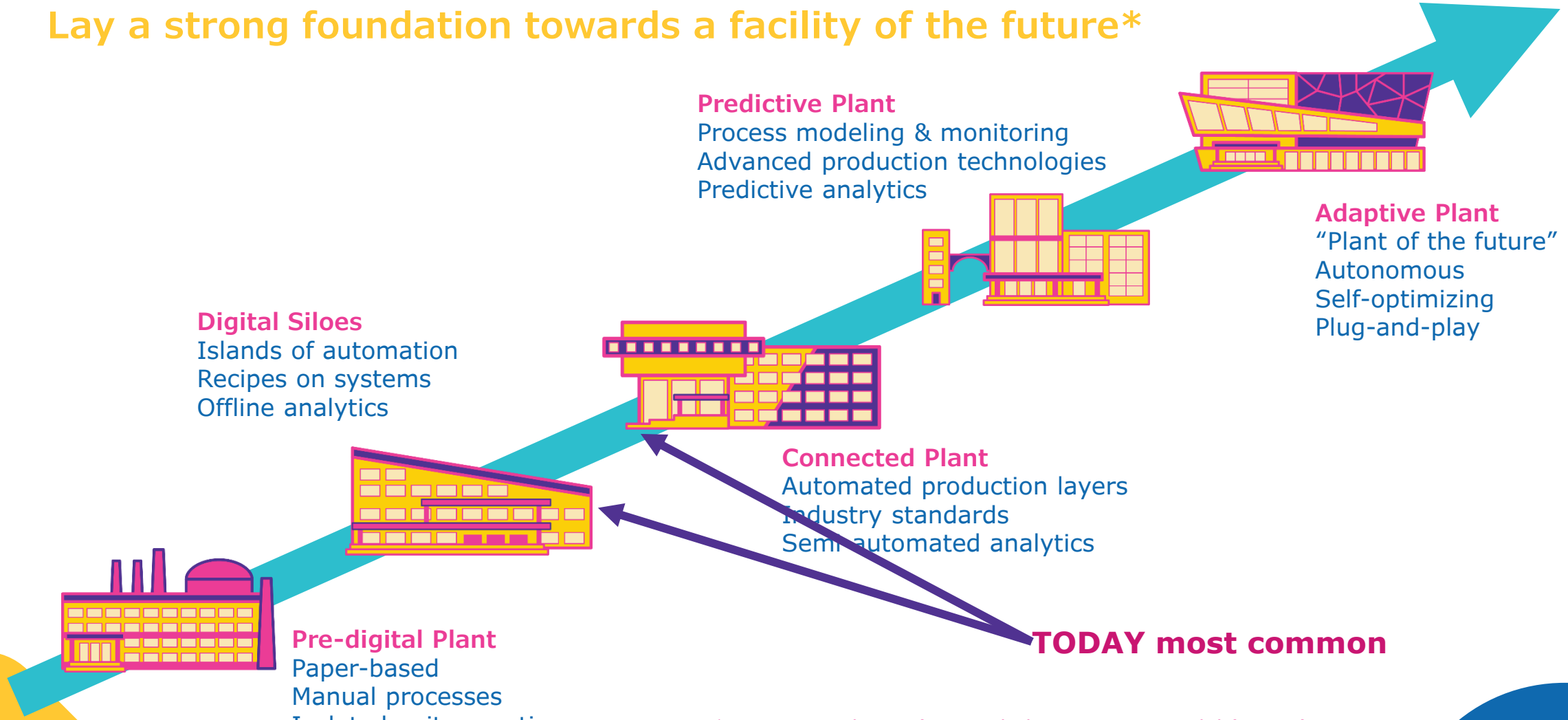
current state of industry

Siloed work on digital solutions to answer individual business questions **without scaling** & unlocking the full potential of our data assets



Begin Your Digital Transformation

Lay a strong foundation towards a facility of the future*



Predictive Plant
Process modeling & monitoring
Advanced production technologies
Predictive analytics

Adaptive Plant
"Plant of the future"
Autonomous
Self-optimizing
Plug-and-play

Digital Siloes
Islands of automation
Recipes on systems
Offline analytics

Connected Plant
Automated production layers
Industry standards
Semi-automated analytics

TODAY most common

Pre-digital Plant
Paper-based
Manual processes
Isolated unit operations

*source: BioPhorum's Digital Plant Maturity Model (DPMM)

90% less footprint

90% Less capital

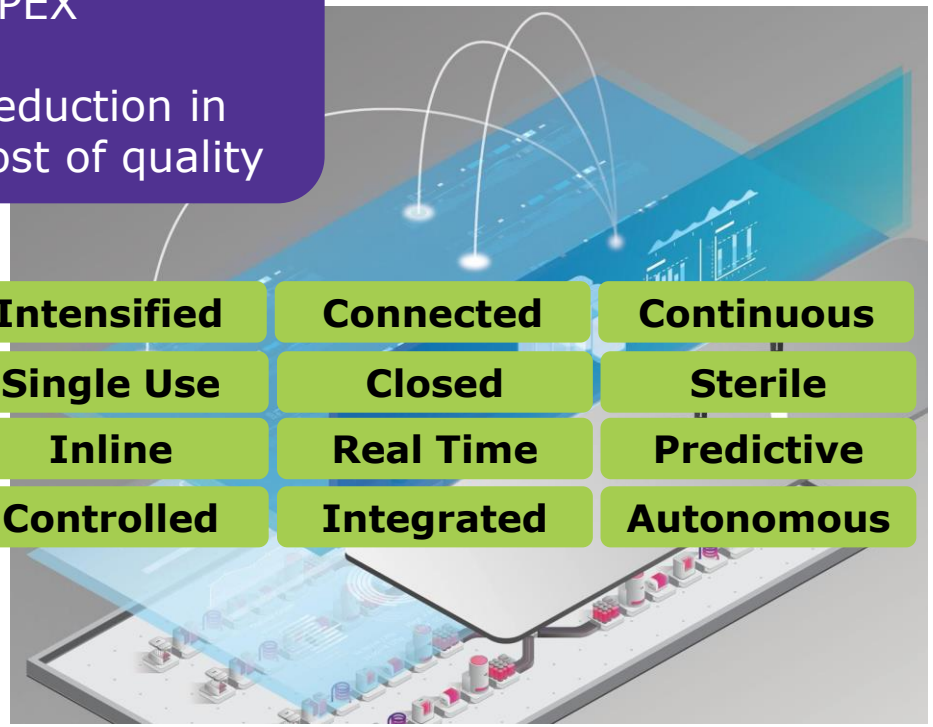
70% reduction in construction time

60% reduction OPEX

90% Reduction in cost of quality

Paradigm Shift:

The Factory of the Future will require a transformation in how biologics are developed and manufactured



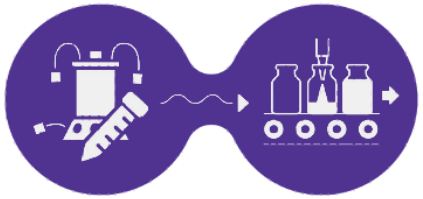
Process	**Intensified**	**Connected**	**Continuous**
Format	**Single Use**	**Closed**	**Sterile**
Analytics	**Inline**	**Real Time**	**Predictive**
Digital	**Controlled**	**Integrated**	**Autonomous**

How Do We Address The Need for Paradigm Shift?

Convergence of Evolving Process, Analytics & Digital Technologies

END-STATE

Continuous



Real-time

Process Simulation

Predictive Analytics

Electronic Batch Record

MID-TERM

Intensified

On-line

Orchestration Process

Process Analytics

Data Analytics

Our actuall state: In Progress

TODAY

Batch

Off-line

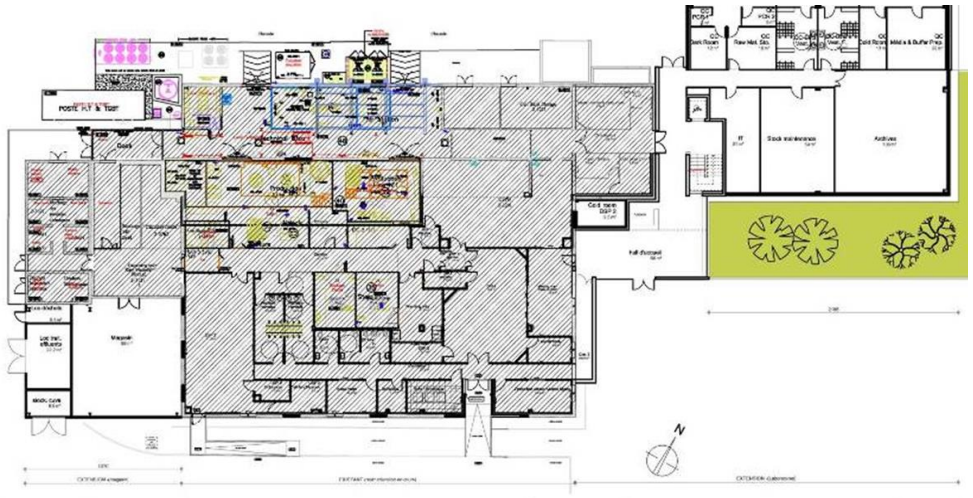
Harmonized Unit Operation Control

Process Technologies

Process Analytical Technologies

Digital Technologies

Full dedicated Biotech plant



Ballroom concept: "A large manufacturing area that has no fixed equipment and minimal segregation due to the use of functionally closed systems."

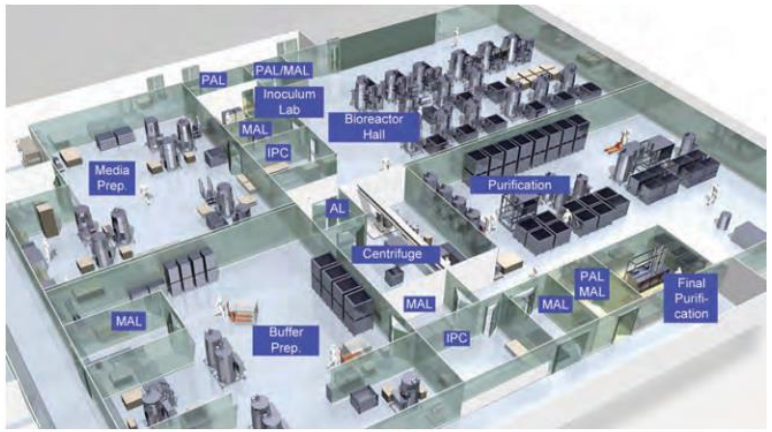


Figure 1. 3D model of a ballroom type facility.

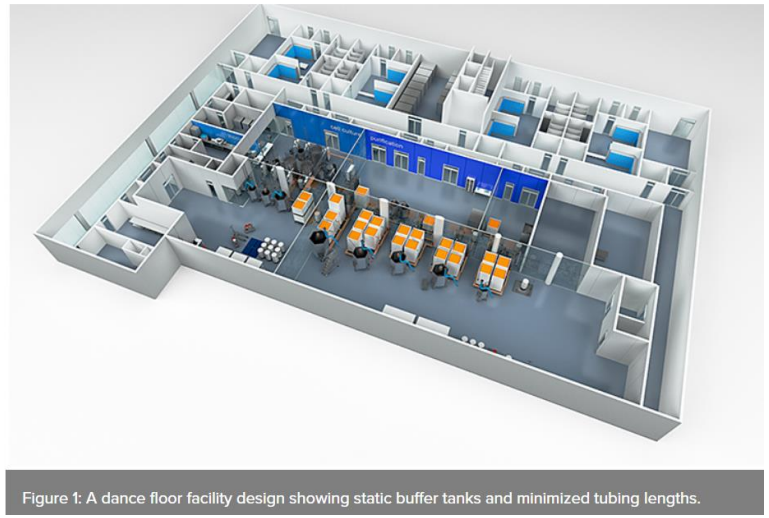


Figure 1: A dance floor facility design showing static buffer tanks and minimized tubing lengths.

Dance floor concept: "Mix of static elements like buffer tanks/Bags with flexible, SU based manufacturing technologies. Movement of liquids is done with small volumes only"

Parenteral Formulation plant

Source: ISPE; Pharmaceutical Engineering July August 2014. D. Wolton/A. Rayner; ISPE Online Nov 2019/2020 D. Wolton/ T. Rohrer

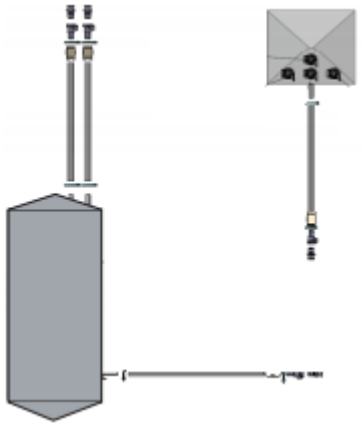
9 buffer and product storage

Single-use storage Solutions

Mobius® bins, drums & 2D containers

Mobius® drums	Collapsible Bins	Stainless Steel Bins	3D Large Liquid Transport Bins	2D Container Cart
• Storage of process fluids in 3D single-use bags • Top & bottom container ports • Supported by an optional dolly • Available in 50, 100 and 200L	• Storage of process fluids in 3D single-use bags • Stackable & Collapsible • Available in 100,250, 500 and 1000L	• Storage of process fluids in 3D single-use bags • Single large door facilitates easy operator access and bag installation • 304/304L ss and optional 316 ss • Stacking guides on bins • Tray design with slide-out capability • 200L and above • Pallet jack & fork lift compatible	• fluid management solution that enables users to safely move large liquid volumes of media, buffers, process intermediates and bulk drug substance between different sites, via road or air • Bag working volumes of 100L to 500L, aseptic and non-aseptic versions, PF+ film • 304L stainless steel • ISTA 3E shipping validation, 2°C to 45°C • Stackable up to two units high	• Storage of process fluids in 2D single-use bags • Supports up to six process containers in 10 L, 20 L and 50 L sizes • Mobile with a small footprint • Handle to tilt the racks for better drainage • Removable container cradles for easy loading and unloading

Single-use storage systems
Mobius® Storage Solutions



2D Bags	Drums Bags	3D Bin Bags
• Available in 50mL to 50L • Standard and custom options available	• Available in 50, 100 and 200L • Standard and custom options available	• Available in 200L to 2000L as standard • Large volumes available as custom

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product sterilization – filtration

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Final Filtration

Definition of a Sterile Filter

"A filter which, when challenged with the bacterium Brevundimonas diminuta, at a minimum concentration of 10^7 CFU per cm^2 of filter surface area, will produce a sterile effluent."

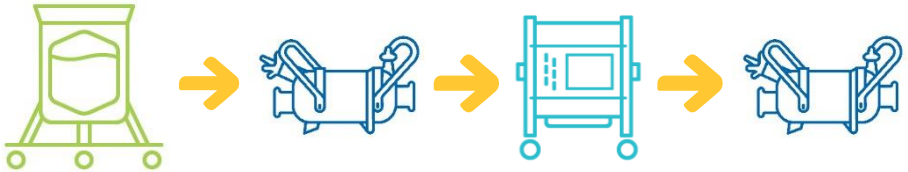
"Sterilizing Grade" designation is not pore size rating dependant, it is a functional definition.

References

Standard Test Method **ASTM** F838-05
FDA Aseptic Processing Guideline, 2004
PDA Technical Report 26 1998
EMEA, Annex 1, 2020

There is no one common filtration set up!
Process specific, based on risk/benefits considerations.

Final Filtration
Design Options

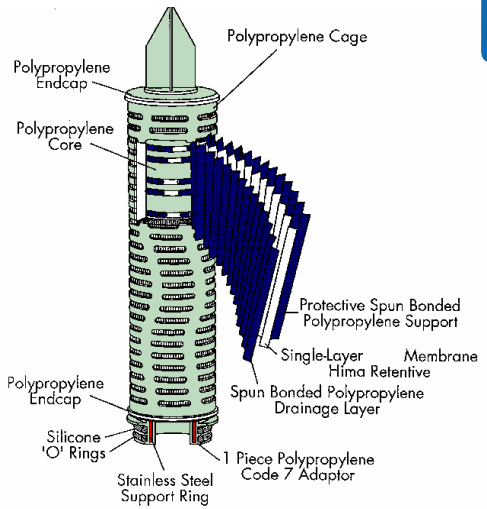
Filtration Process Design Options	Filter Configurations	Benefits	Drawbacks
	**Single Filter** Sterile Filtration	• Compliance with regulatory guidance for <10 cfu/100 ml • Minimum hold-up volume • Minimum flushing requirements • Ease of handling and operation • Lower cost	• No back-up in the event of primary filter failure • Feed bioburden control • Filter plugging
	**Bioburden Filter** Bioburden – Sterile Filtration	• Compliance with regulatory guidance for <10 cfu/100 ml • Very low plugging risk for primary filter	• No back-up in the event of primary filter failure • Higher hold up • Higher cost • Higher system complexity
	**Dual Filters** Sterile Filtration – Hold – Sterile Filtration	• Compliance with regulatory guidance for <10 cfu/100 ml • Very low plugging risk for primary filter	• No back-up in the event of primary filter failure • Higher hold up • Higher cost • Higher system complexity
	**Redundant Filters** Sterile Filtration – Sterile Filtration	• Compliance with regulatory guidance for <10 cfu/100 ml • Very low plugging risk for primary filter • Potential batch recovery if one filter fails IT	• Higher hold up • Higher cost • Highest system complexity

Final Filter Options

Best option for final filtration

1 Pleated Membrane

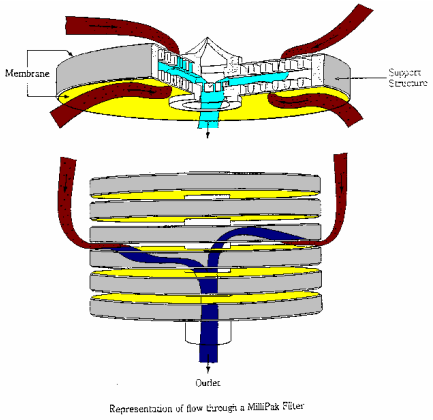
- Available in PES of PVDF
- Pleated membrane enable higher filtration flow rate
- Available from XL150 to XLT 30”
- Good forward & reverse pressure resistance



Preferred for **high flow**

2 Stacked disk

- Available in PVDF
- Stacked disk enable low hold up volume & increased product recovery
- Available from 100cm² to 1000cm²
- Low resistance to back pressure



Preferred for **low hold-up volume**

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Millipak® Final Fill

The Clear Choice for Final Fill

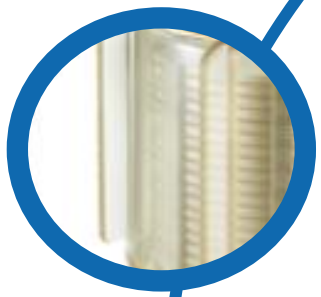
MERCK

Transparent polysulfone housing

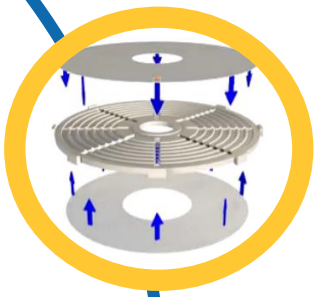
Filter Assembly Integrity Testing Video

Flow direction

Assembly setup with handle



Easy to stabilize



Stacked Disk with Durapore® Membrane Flat Disk Design

GS1 2D barcode

Aseptic Multi Purpose Port

Risk Reduction

Product Recovery

Millipore®

Millipak® Final Fill

The Clear Choice for Final Fill

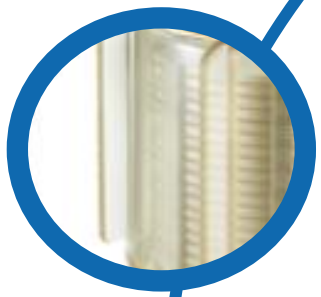
MERCK

Transparent polysulfone housing

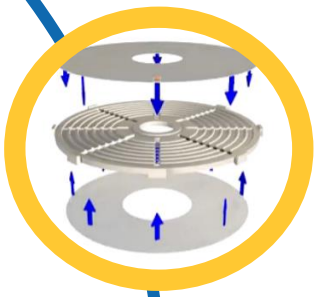
Filter Assembly Integrity Testing Video

Flow direction

Assembly setup with handle



Easy to stabilize



Stacked Disk with Durapore® Membrane Flat Disk Design

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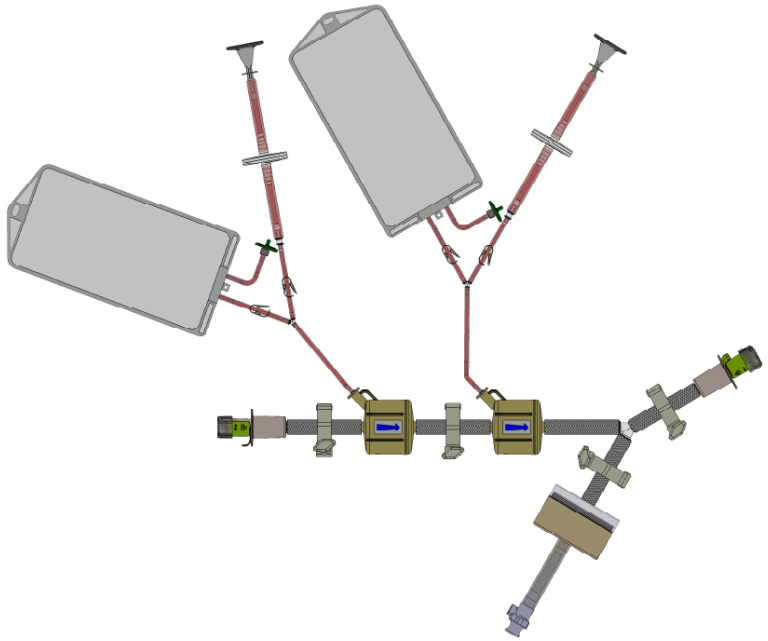
Aseptic Multi Purpose Port



Risk Reduction

Product Recovery

Millipore®

Integritest 5

Integrity Testing Made Simple

- Easy-to-use touch screen operation
- Fast, proven, full set of filter test algorithms that reduces test time and simplifies test creation
- Easy set up with Staubli quick connectors for inlet and outlet that are different
- Standard model offers all networking functions, including multi-unit management and synchronization
- Windows 10 operating system
- Unlimited test storage
- Comprehensive context sensitive help
- Upgraded sensors
- Internal Thermal Printer
- Barcode reader capability
- WiFi, Bluetooth, Ethernet ready

YouTube Video Instructions Link:

I speak 8 languages

Only 10 kg!

MERCK

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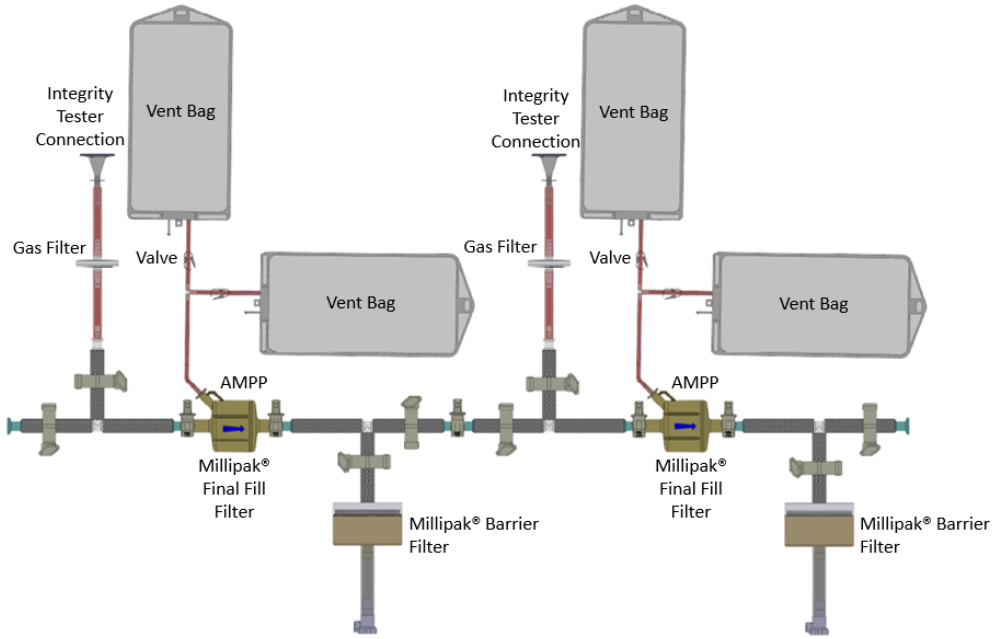
Redesigned Port Offers Flexibility in SU System Design

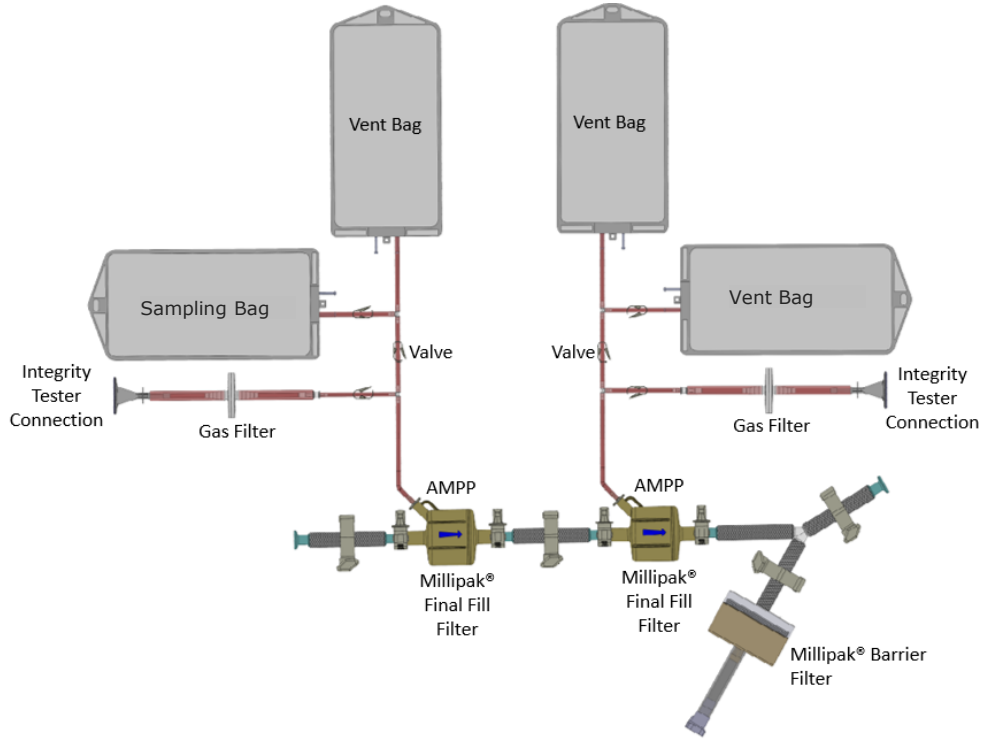
Traditional SURF System



Flow Direction

- IT through inlet
- Multiple connections

Streamlined SURF System



Flow Direction

- IT connections through AMPP
- Streamlined connections

Aseptic connector benchmark

Multiple technologies exist

Peal Strip (membrane) devices

- Easy to use
- Membrane cannot be tested
- Do not pass Aerosol test
- Risk of contamination if not performed in controlled environment.

Tube Welders

- Multiple connection / deconnection possible
- Capital investment
- Floor space required
- Equipment needs maintenance.
- Compatible with very few tubing.

Sterile Chamber Devices

- Robust device
- 100% integrity testing in manufacturing
- Validated for use in ANY environment
- Size (only for reconnection)

Millipore®

A variety of connectors to meet your fluid transfer needs

Lynx® Connector Family

MERCK

Click to Navigate to Section

Lynx® ST — Steam-To

Enables Hybrid Systems

- Connects steamable hard-piped processing systems to sterilized disposable flow paths
- Available in a variety of sizes and configurations: ¼”, ½”, 1”
- Multiple actuations
- SIP, autoclave and gamma compatible

Lynx® S2S — Sterile-to-Sterile

True Sterile Connector

- Enables a single connection between two single-use flow paths
- Robust sterility validation (minimum of to 10^6 CFU/device)
- Available in three sizes: ¼”, 3/8”, ½”
- Autoclave and gamma compatible

Lynx® CDR — Connect, Disconnect, Reconnect

First Reconnectable Device

- Offers multiple (up to 6) sterile connections, disconnections, and reconnections wet, under pressure
- Enables processing efficiency and flexibility when multiple aseptic connections are needed
- Simple and fast actuation
- Available in sizes from 3/8” to 1”

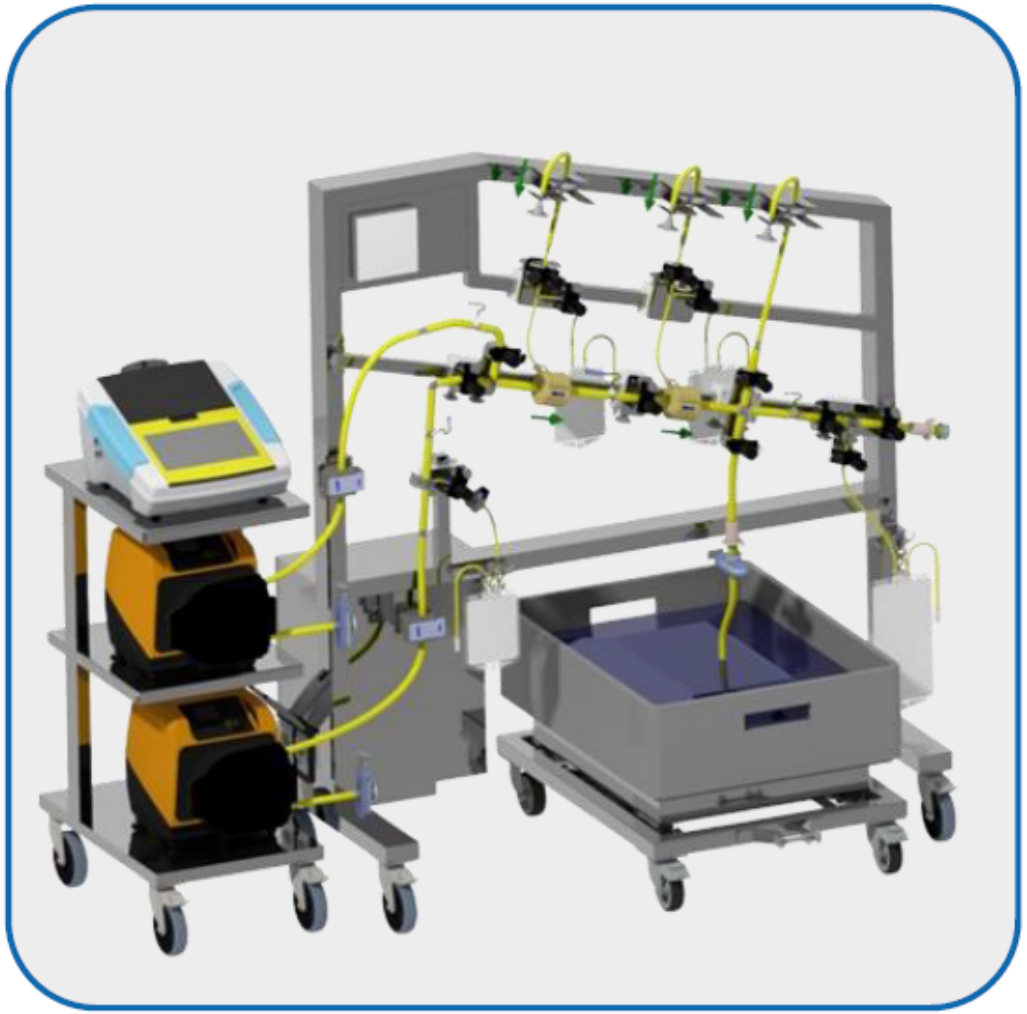
NovaSeal

Sterile Disconnect

- Aseptically disconnects single-use flow paths
- Crimps and cuts pinch-pipe & tube with one simple motion
- Offering includes two tools to disconnect four tube sizes from 3 mm ID x 6 mm OD to ¾-inch OD tubing

Millipore®

Manual PUPSIT Skid
Configurable Options



IT5
- Easy-to-use
- Full set of filter test algorithms
- Networking functions

Filter
- Single or redundant filtration
- Multiple size available MPFF20 to XL10

Pump
- Pump provided by customer
- Separate WFI inlet (option 2)

Automation options
- Measurement / display (flow, speed, weight)
- Recorder
- Full auto / Dummy Skid
- Signal exchange (option 11)

Sensor
- Additional P° sensor (option 9)
- Additional T° sensor (option 4)

MISC
- Flush bag (option5a) and weight scale (5b)
- Product Flush bag (option8a) and weight scale (8b)

Automated PUPSIT Skid
Configurable Options

❑ IT5

- Easy-to-use
- Full set of filter test algorithms
- Networking functions

❑ Filter

- Single or redundant filtration
- Multiple size available MPFF20 to XL10

❑ Pump

- Separate WFI inlet (option 2)

❑ Automation options

- Full auto
- Dummy Skid
- Signal exchange (option 11)

❑ Sensor

- Additional P° sensor (option 9)
- Additional T° sensor (option 4)

❑ MISC

- Dedicated product flush bag on load cell (option5)
- Additional sampling point (option 8)
- Additional N2 supply line (option 10)

NovaSeptum® GO Sampling Systems

Selection of available sampling units

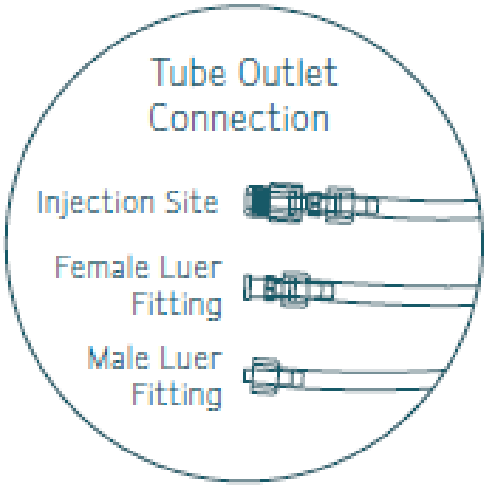
NovaSeptum® GO Sampling Systems

High purity application

- PureFlex® bag TPE tubing
- Three piece luer on outlet tubing
- 2 mm needle
- Single or manifold

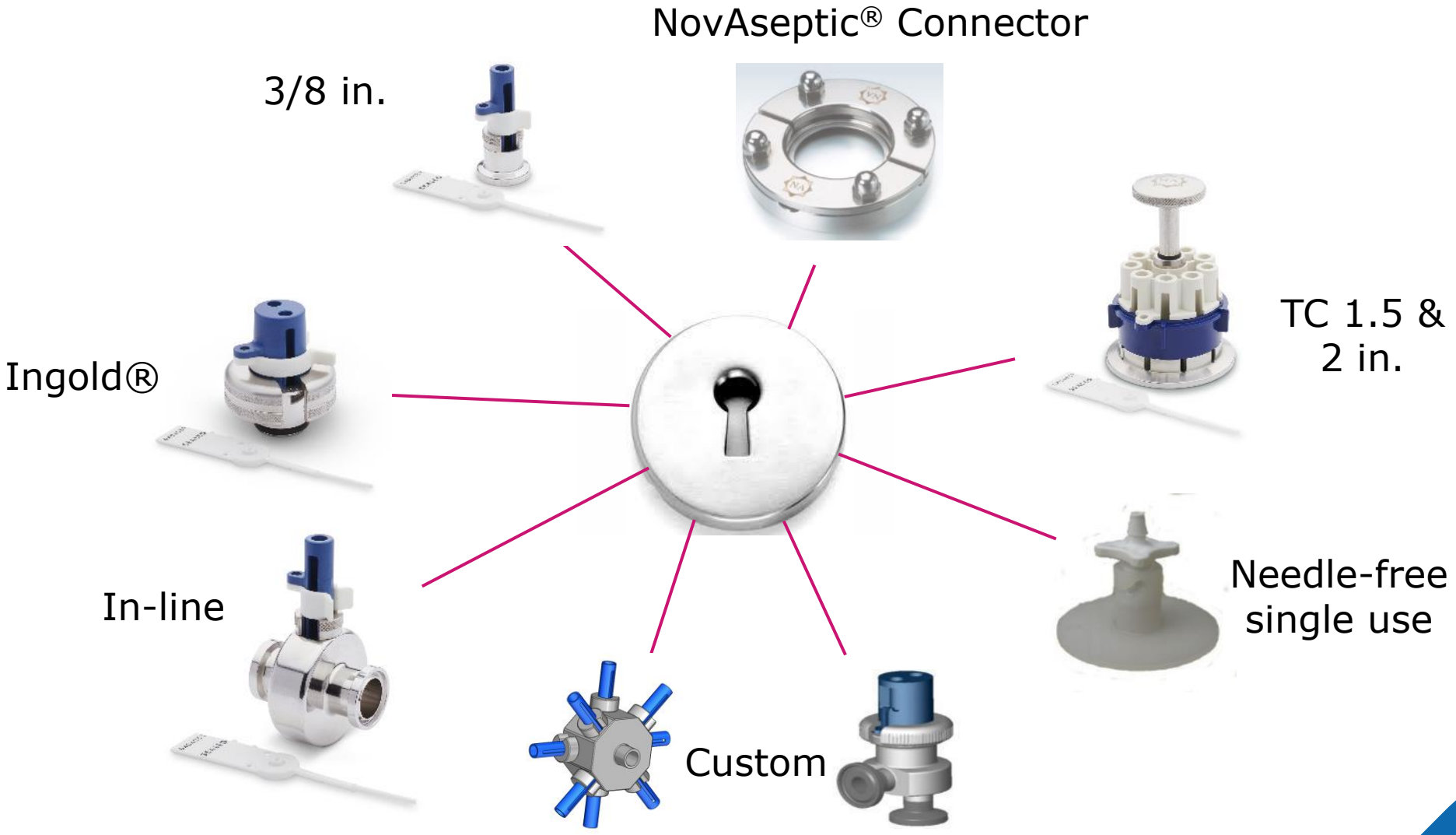
Available sizes
- 50, 100, 250 and 1000 mL

Multiple sampling unit
- 1 flush bag and 5 sampling units (50, 100 or 250 mL)



Selection of available holder

NovaSeptum® GO Sampling Systems



Website

Sterile sampling – New marketing page

Home > Biopharmaceutical Manufacturing > Drug Substance > Sterile Sampling > NovaSeptum® GO Sterile Sampling System

The NovaSeptum® GO Sterile Sampling System

Explore NovaSeptum® GO Sterile Sampling

Continuing to set the sampling standard, NovaSeptum® GO Sterile Sampling System provides you with the flexibility and safety you need to sample throughout your entire process. Its closed design maximizes security and reduces the risk of cross contamination for consistent, representative samples.

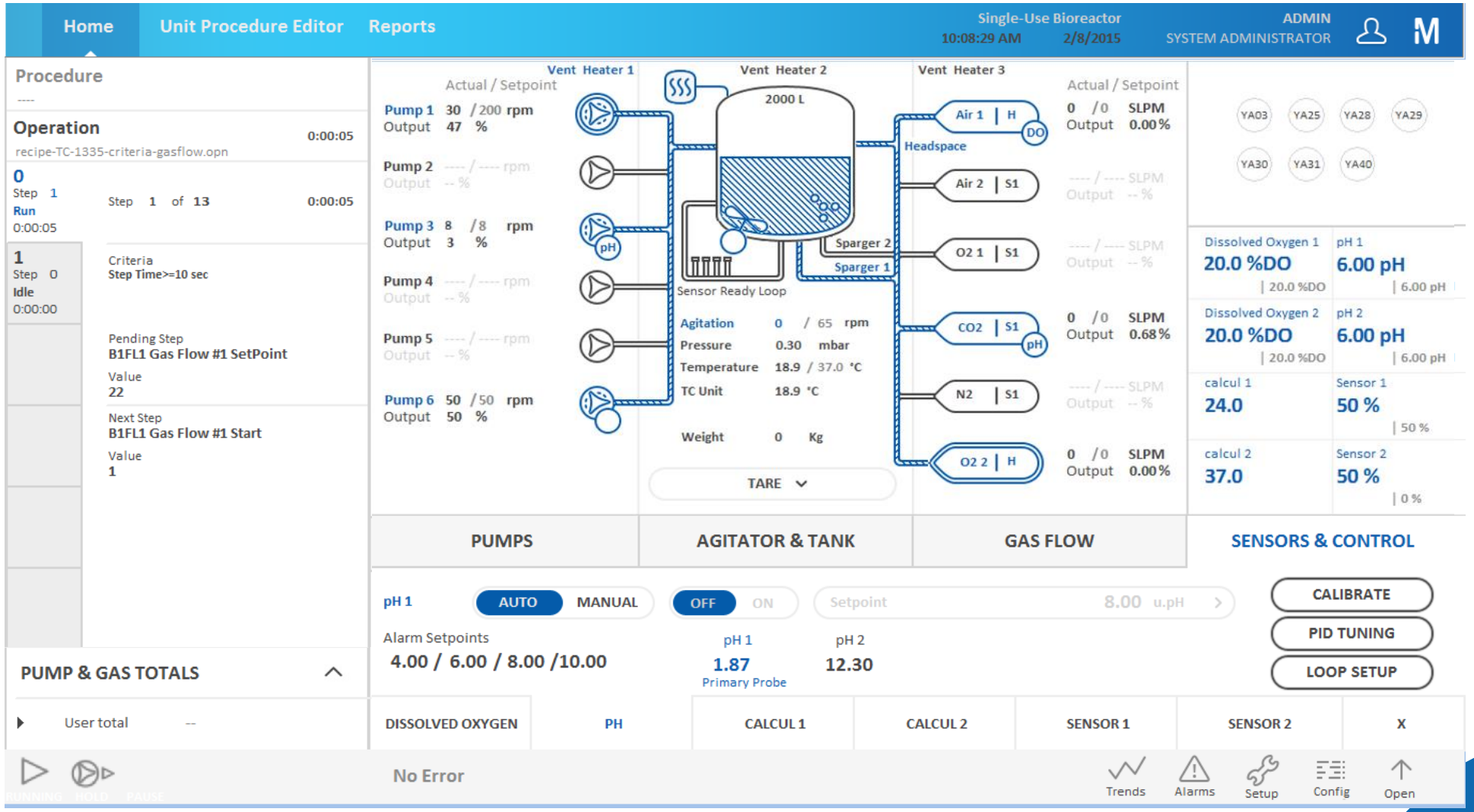
Our NovaSeptum® GO system has also been enhanced with a new locking mechanism that prevents accidental actuation, protecting your valuable product from exposure and ensuring accurate, reproducible results.

The NovaSeptum® GO system is designed to give you the control and flexibility to sample the way you want and where you want with confidence for reliable process monitoring and quality. We are committed to meeting your evolving processing needs with products that continue to drive more efficient drug production and delivery.

Media Preparation | Bioreactor | Bioburden Reduction | Chromatography | Sterile Filtration | Final Fill

CCP® Software: designed for intuitive navigation

Mobius® Single-Use Bioreactor Platform



Software solutions

CONTEXT

EMBEDDED SOLUTION

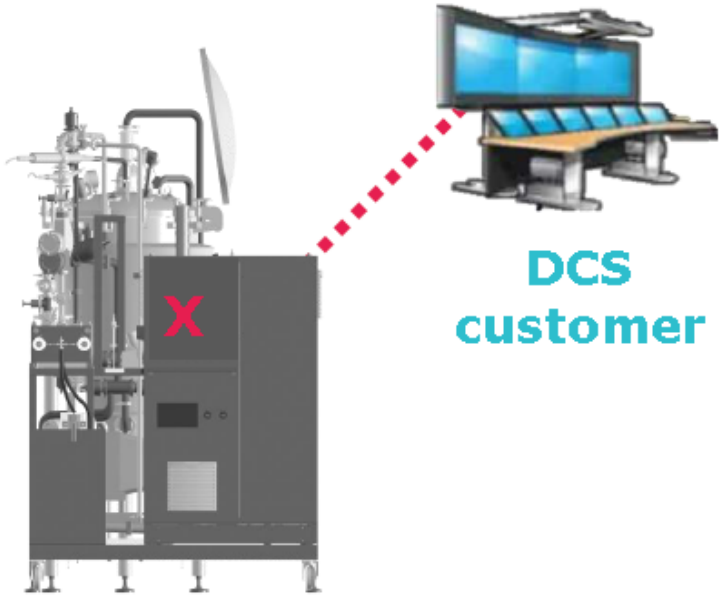
with supervision

(CCP / ACE /specific Siemens TIA)

DUMMY SYSTEMS

With DCS

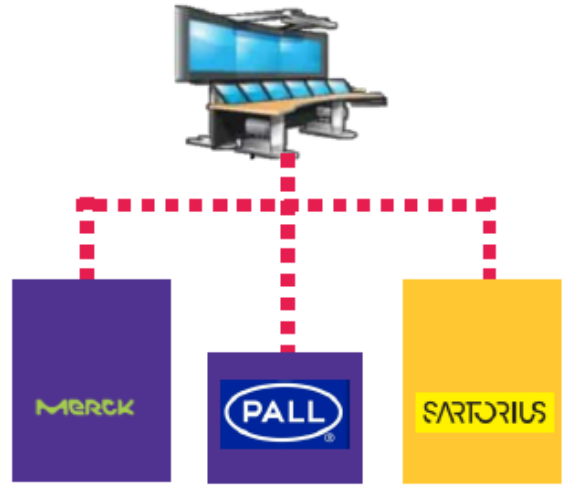
(Emerson DeltaV / Siemens PCS7 / …)



MERCK SKID

System limited to Hardware

Why customers want DCS?

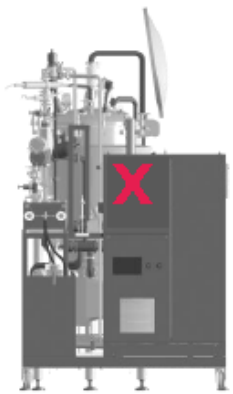


- Centralization of the controls
- Same interface for all systems whatever the brand
- Adaptation of the software to customer needs
- Simplify operator training
- Communication between the systems is easier
- 2 mains actors : Emerson DeltaV / Siemens PCS7

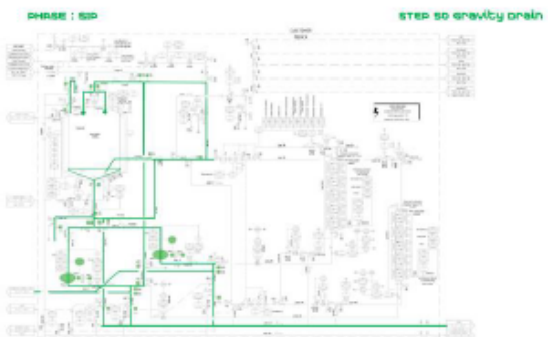
What is Merck proposal ?

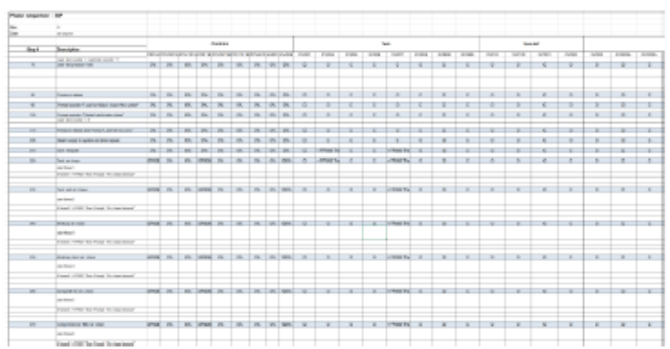
- A system limited to hardware called "dummy skid"

  Automation hardware (IO, controller) can be supplied as an option

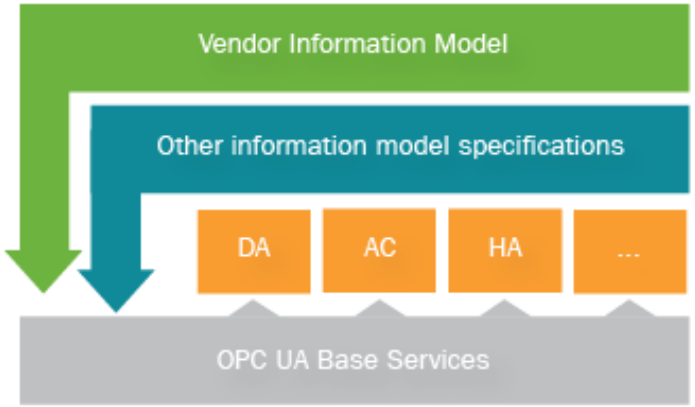


- Support on process : **Functional Specifications**



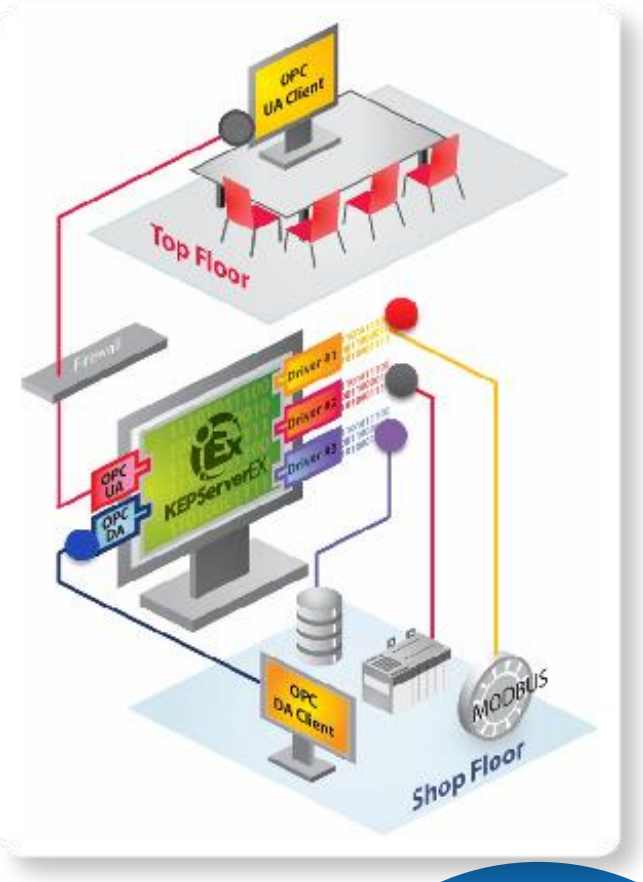


OPC UA : the unified version



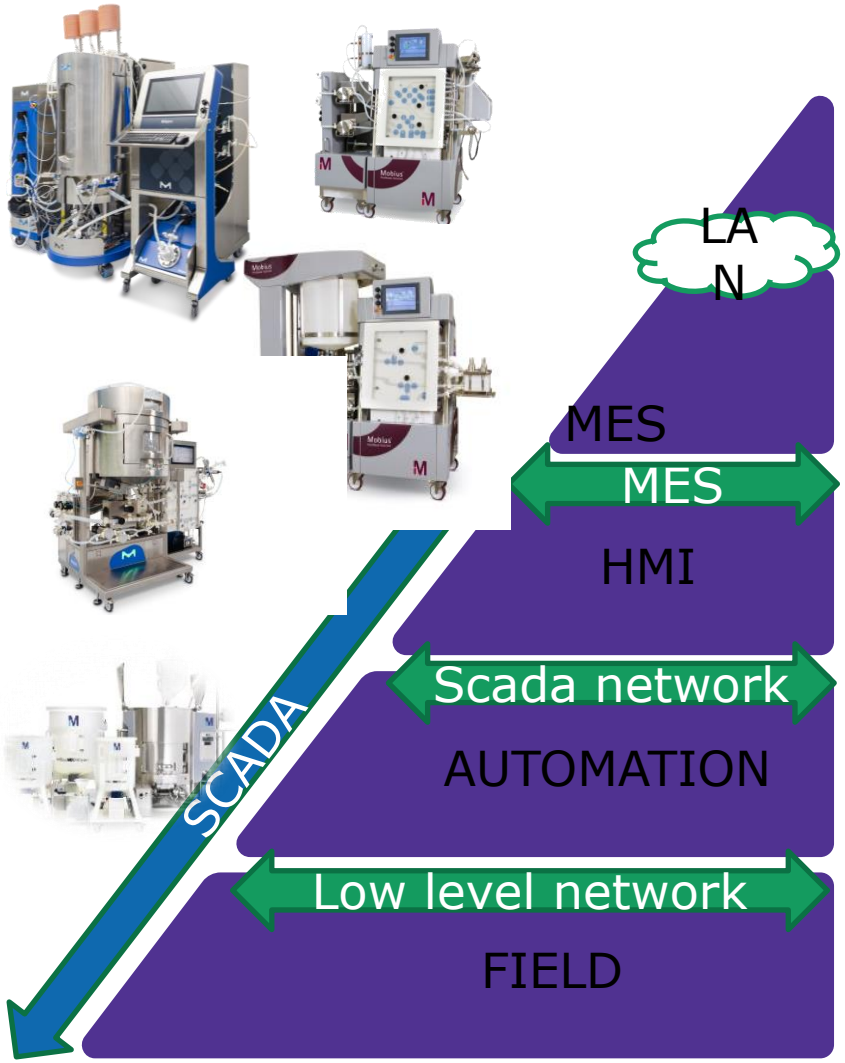
OPC UA in few words:

- First OPC not relying on proprietary technology (available for Apple, Linux (JAVA), Microsoft…).
- possibility to use structures or models
- Adding context information
- It is a protocol based on Ethernet networking
- So far OPC UA are mostly used for bridging between different OPC servers, this is called tunneling



Automation & Software background

Standard architecture: Goal



ERP (Enterprise Resource Planning)

Interconnections with the rest of the world ! (other company departments, WWW…)

Manufacturing Execution System (MES)

Shared functions for multiple SCADAs (reporting, recipe management, ….)

HMI (Human Man Interface) system level & DCS (Distributed Control System)

Friendly interfaces for operating the lower levels /gathering data from lower levels.

Automation level

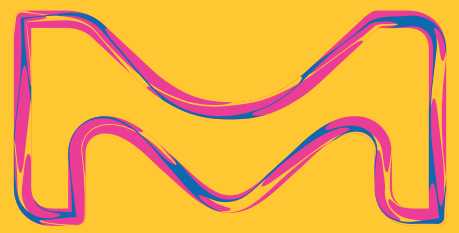
PLCs, controlling the lower level

Field level

Actuators, Sensors, linking electrical and automation worlds

Introduction to MAST® System (Modular Automated Sampling Technology)

Shawn Bates, Senior Product Manager, IS&S



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01

automated sampling enables biopharma 4.0

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Preparation, Separation,
Filtration & Monitoring Products

Towards Industry 4.0

The industry demands tools that support evolving manufacturing and quality control processes in traditional biologics

Market Drivers

- Market Growth
- Uncertainty
- Cost Pressure
- New Product Classes

Customer Needs

- Greater Facility Flexibility
- Multi-Product Facilities
- Cost Control

BioPharma 4.0

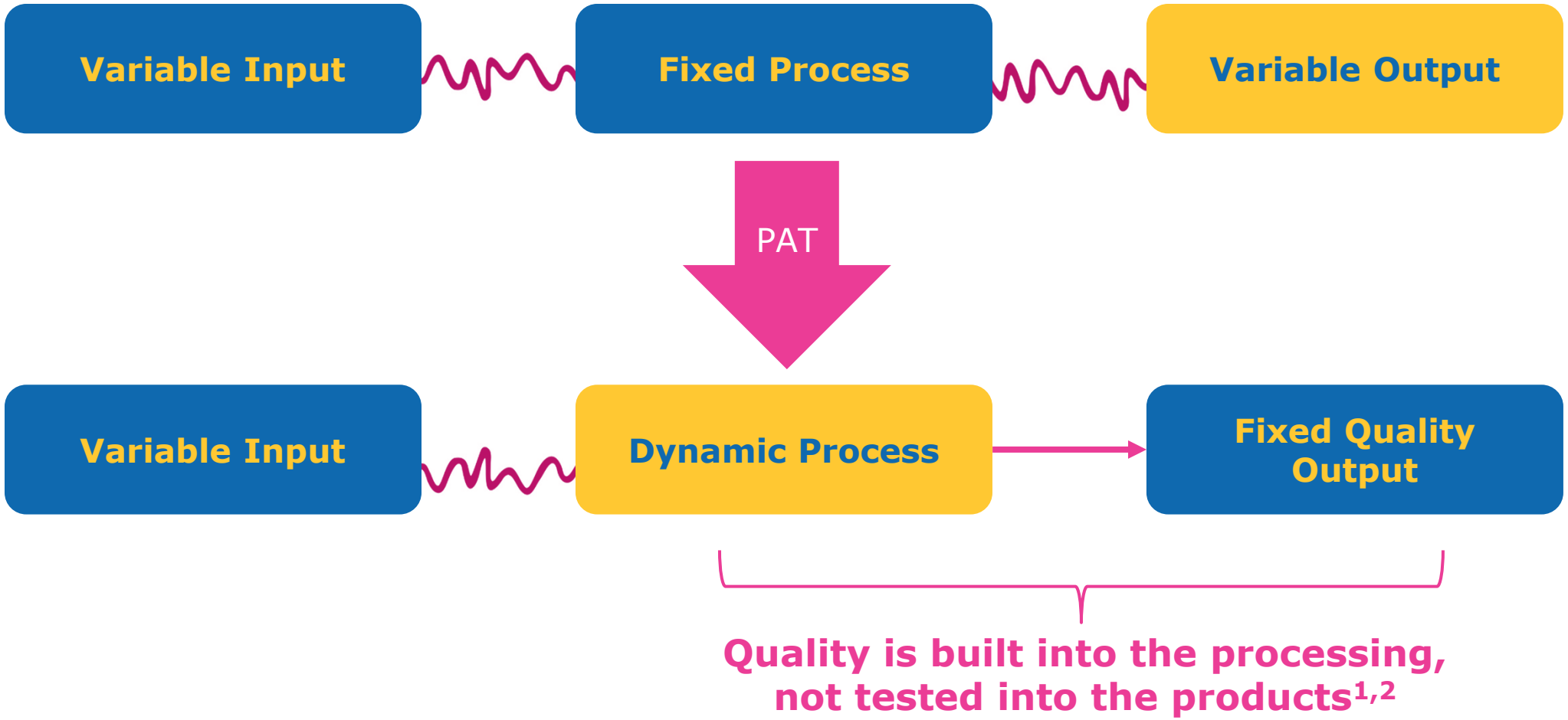
- Process Analytical Technology (PAT)
- Digital Technologies & Data Management
- Process Technologies

Analytical Evolution

Standard QC Methods → Rapid QC Methods → At-line → Inline/Real-time Sensing

Dynamic Manufacturing Process

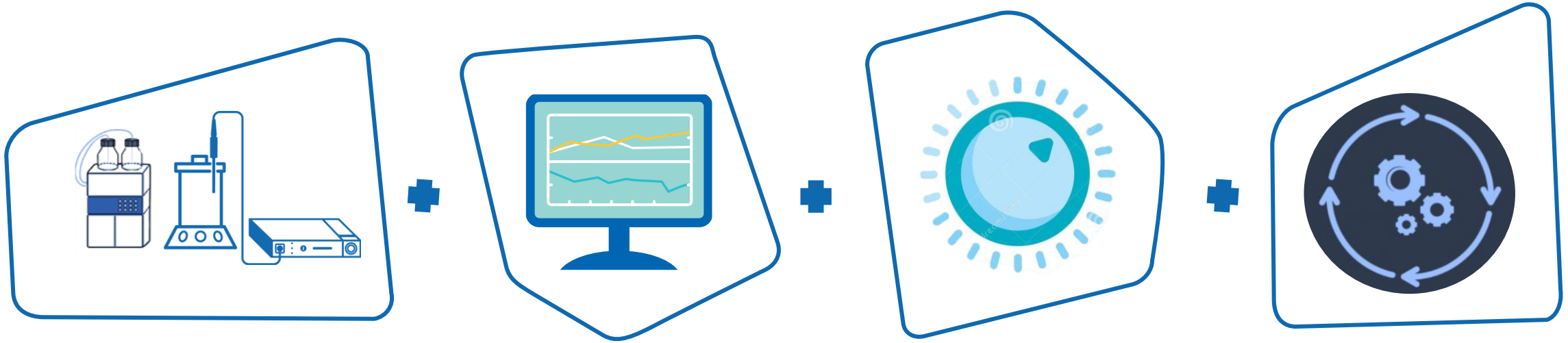
A dynamic process requires inline/real-time analytical analysis



1. Snee, R. D. Quality by design: Building quality into products and processes. in: Zhang, L. (Ed.), *Nonclinical Statistics for Pharmaceutical and Biotechnology Industries*, Springer International Publishing; 2016, pp. 461–499.
2. Abu-Absi, S. F. et al. Defining process design space for monoclonal antibody cell culture. *Biotechnol. Bioeng.* 2010, 106, 894–905.

PAT Implementation

The application of PAT involves analytical monitoring, data acquisition & analysis, process control, and continuous optimization



1

Analytical process monitoring techniques (sensors + sampling) to measure CPPs and CQAs

2

Data acquisition and mechanistic/data-driven modeling of the generated data

3

Process control to facilitate real time release

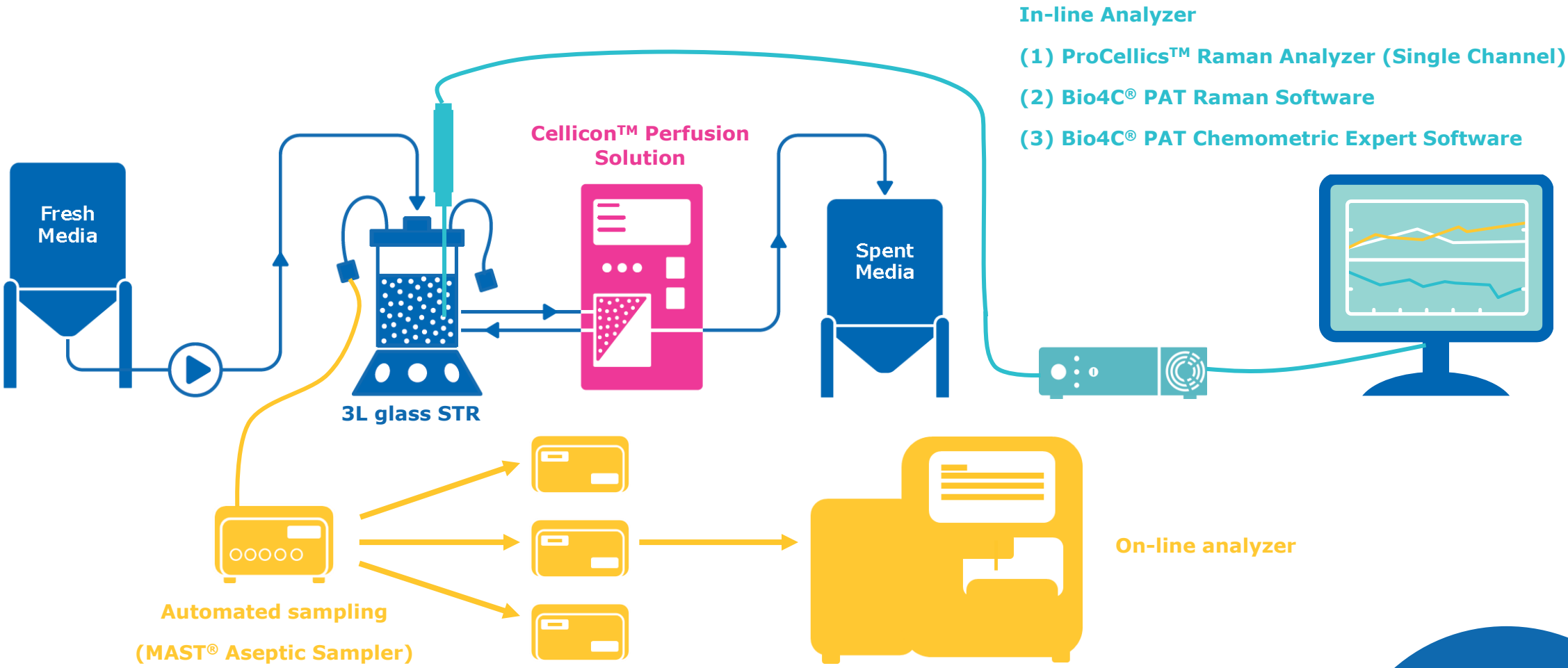
4

Continuous process optimization and knowledge management

Monitoring Tools

Implementation of automation technology for integrated PAT

Integration of in-line and on-line analytics via automated sampling



Automated sampling expands capabilities for automated measurement of CPP & CQA in combination with in-line sensors

	In-Line		On-/At-Line
	Traditional Sensors	Raman	Automated Sampling
Temperature	√		
Pressure	√		
Conductivity	√		√
Gases (DO, CO2)	√		√
pH	√	√	√
Cell density/biomass	√	√	√
Titer		√	√
Aggregation		√	√
Nutrients/Metabolites		√	√
Vitamins & amino acids		√	√
HCP		*	√
DNA		*	√
Glycans		*	√
Charge Profile		*	√
Fragmentation		*	√
Endotoxin			√

Reduce manual burden and improve accuracy with in-line technologies through automated calibration & model development

Integrate with a broad range of analyzers to enable automated measurement of parameters that cannot be measured in-line

* Investigating Potential

Automated sampling

Enabling technology to automate the upstream process and reduce time for data acquisition of CPPs & CQAs

Manual Workflow

Bioreactor & Inline Analysis

Manual Sampling

At-line Sample Analysis

Sample Storage

Offline Sample Analysis

Automated Workflow

Bioreactor & Online Analysis

Automated Sampling

- ✓ Sample removal & delivery
- ✓ On-line sample analysis, replacing at-line & some offline analysis
- ✓ Sample storage

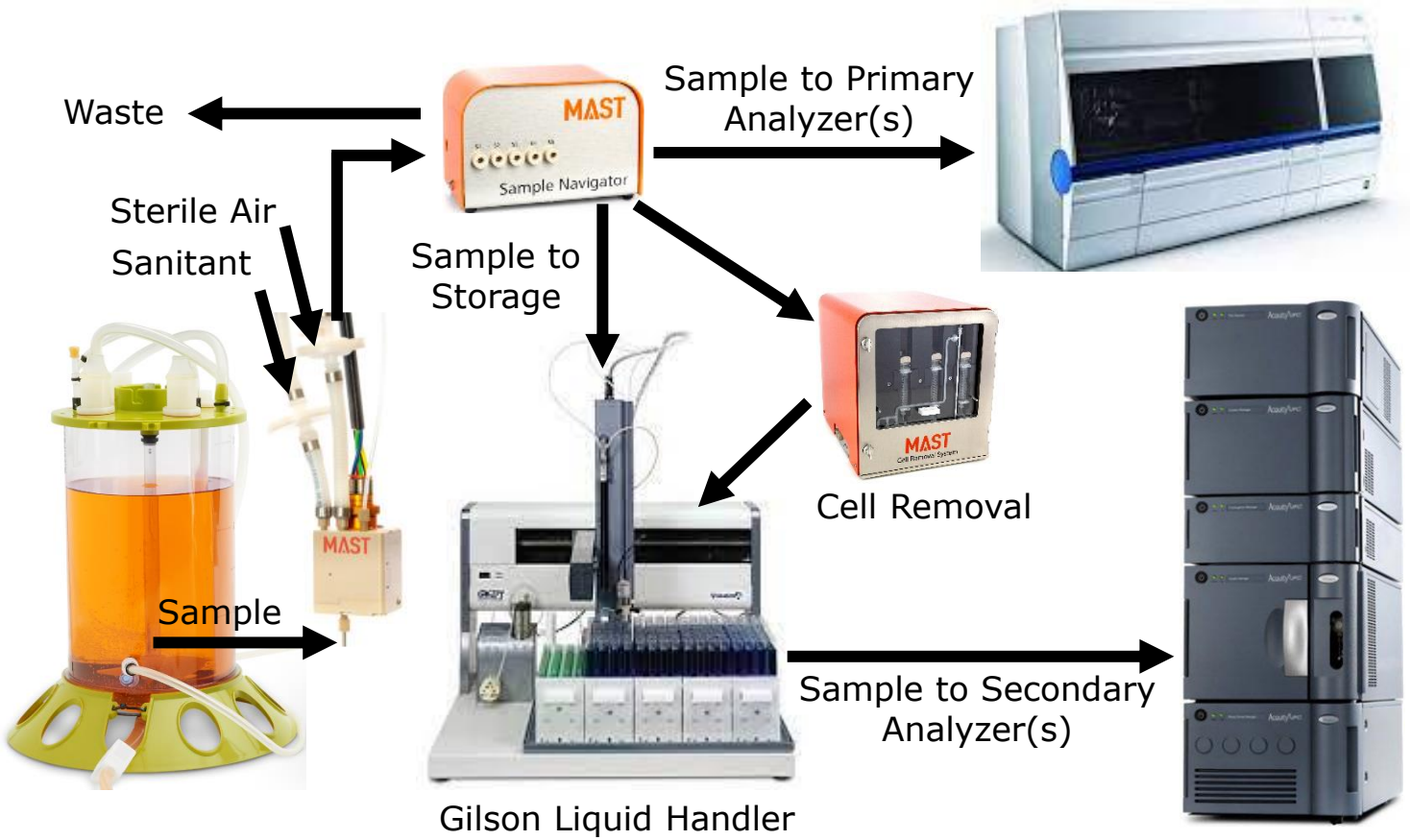
02 MAST® Technology

MERCK

Millipore®

Preparation, Separation,
Filtration & Monitoring Products

MAST® is an integrated system for the automation of sampling and sample management



Integrations:

- Gilson liquid handler
- Nova BioProfile FLEX & FLEX2
- Roche Cedex BioHT
- Waters Acquity Systems via Empower
- ThermoFisher LC Integration via Chromeleon
- Agilent LC Integration via ChemStation
- Cary 60 UV/Vis Analyzer

Controllers & Software Interface

The MAST® Product Portfolio Includes Hardware, Software, Consumables, and Services

Hardware

- MAST® Controller
- Sample Pilots

Sample Pilot devices

- Sample Navigator

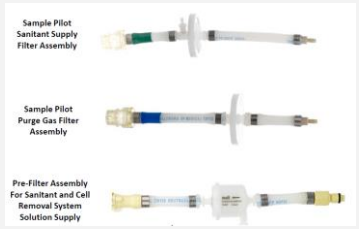
- Analytical Navigator
- Cell Removal System
- Gilson Liquid Handler
- Sanitant Stations

Software

- Controller Software
- Integrated Software with Analytical Equipment
- Sample Planning

Consumables

- Sanitant & Air Filter Assemblies



- Cell Removal Cassettes

- Spare Parts

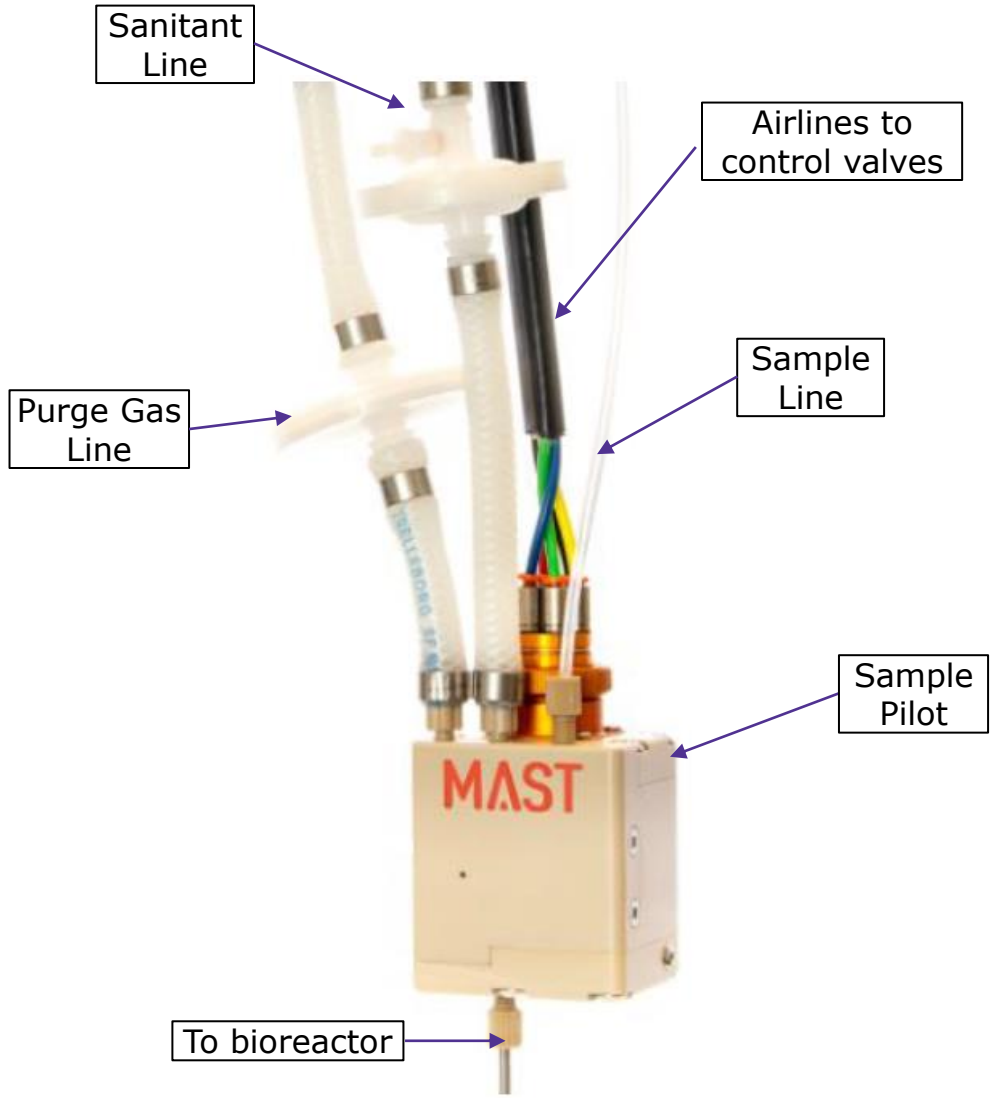
Services

- Hardware PM
- Software Maintenance

How Does MAST® System Work?

The MAST® Sample Pilot Uses Positive Pressure Unlike Other Autosamplers

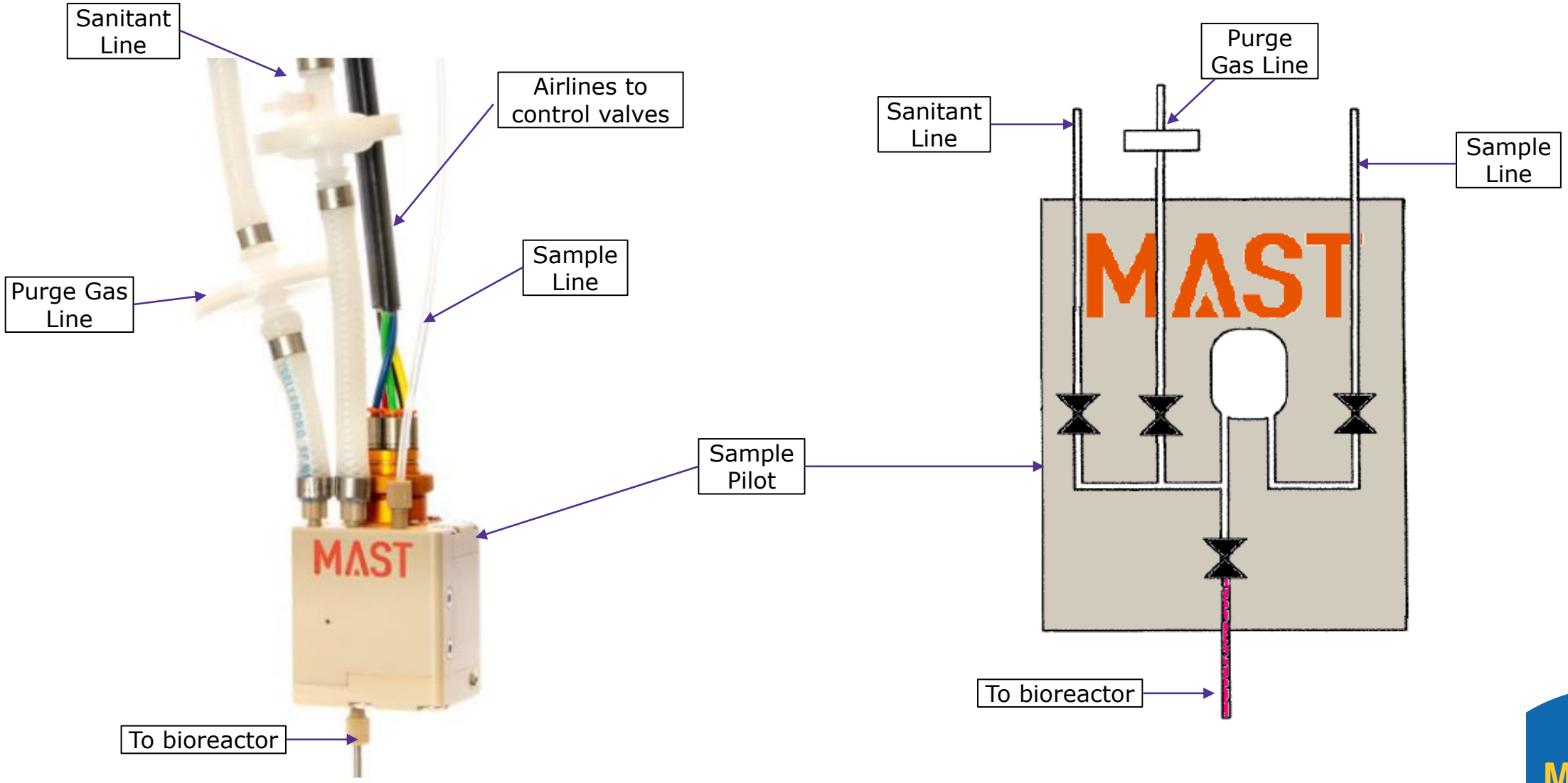
SP200



- Other autosamplers attempt to draw the sample which is limited to 15 psi of suction
- We push the sample and can apply pressures as high as 70 psig
- SP100 unit has pushed thick microbial sample 80 feet to its destination

How Does MAST® System Work?

A Zoomed In View Shows the Various Lines in the Sample Pilot



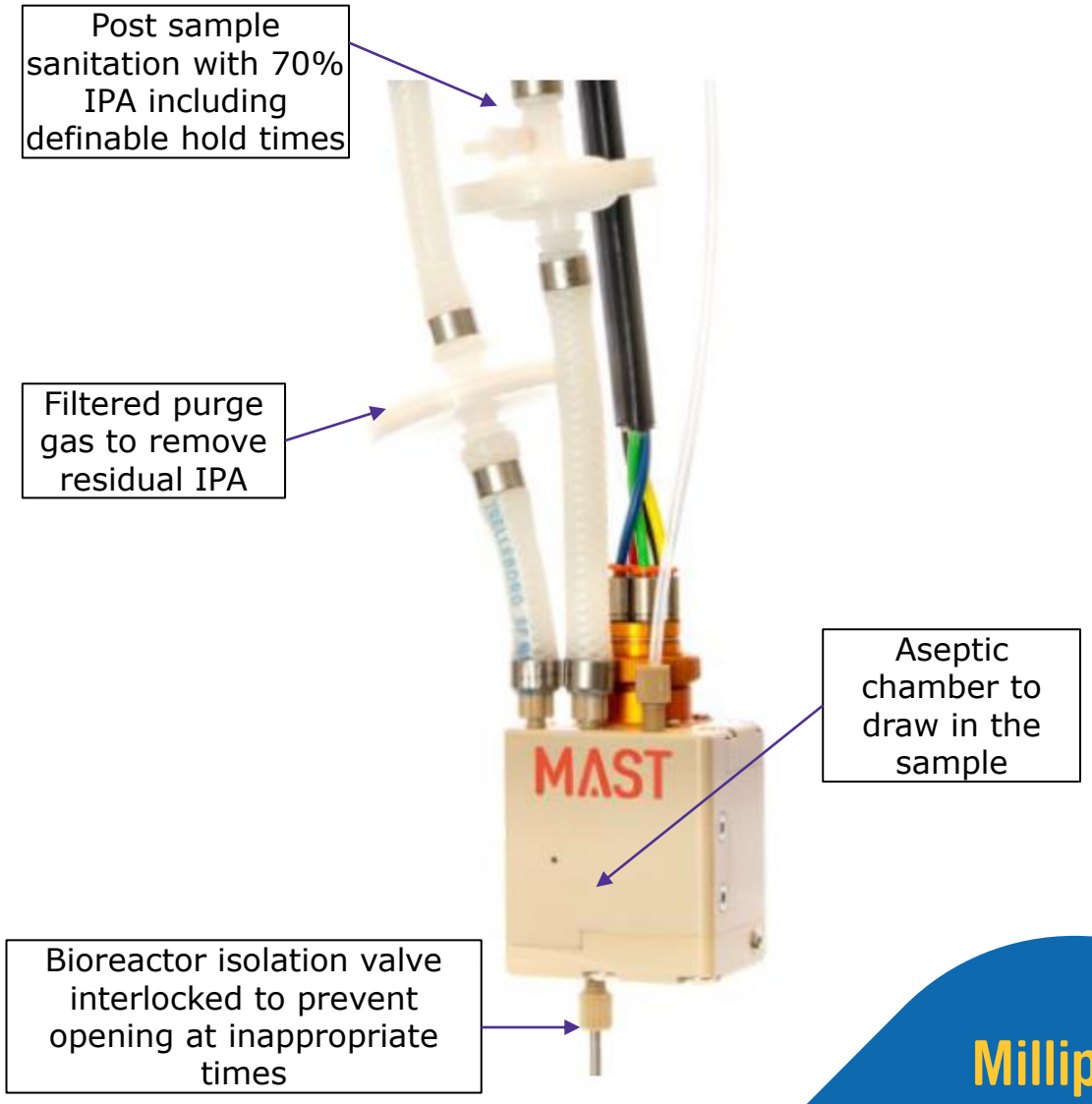
Concerned About Autosampler Contamination?

MAST® System Offers Three Phases of Sterility Protection

1. Sample Pilots are autoclaved sterilized

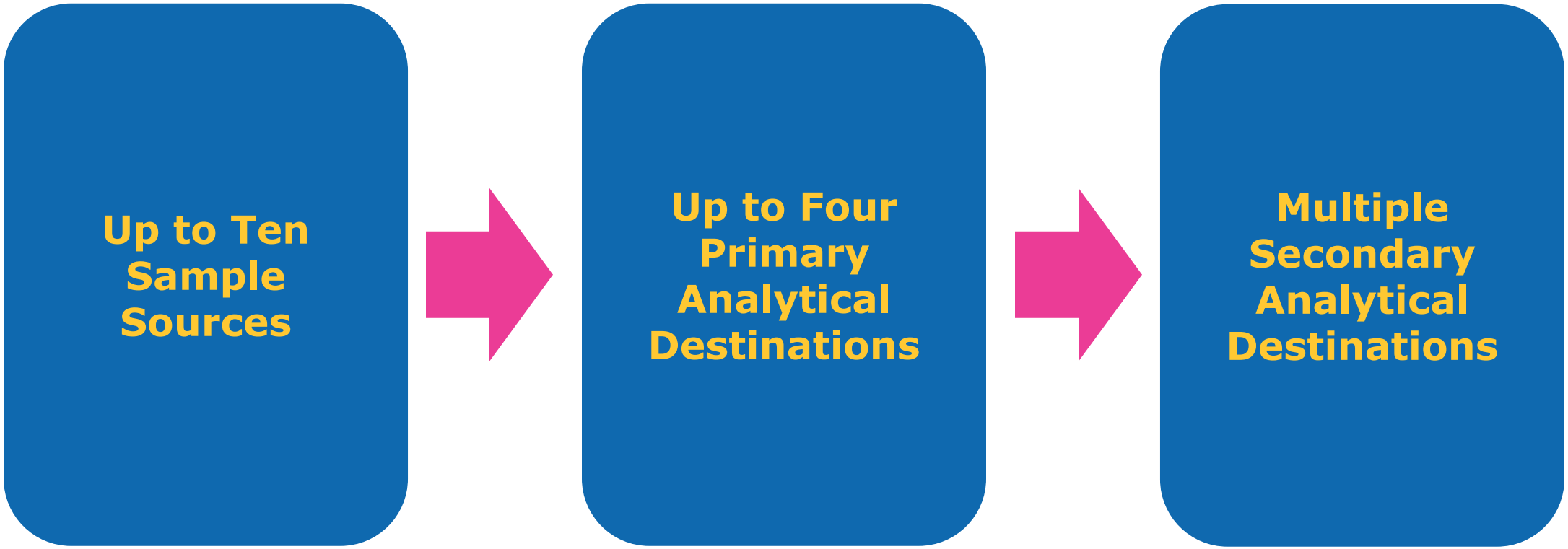
2. Sanitant and inert purge gases that flow through the Sample Pilot pass through 0.2 micron rated filters

3. Sterile source protected by rigorous system interlocks



MAST® Module Configurations

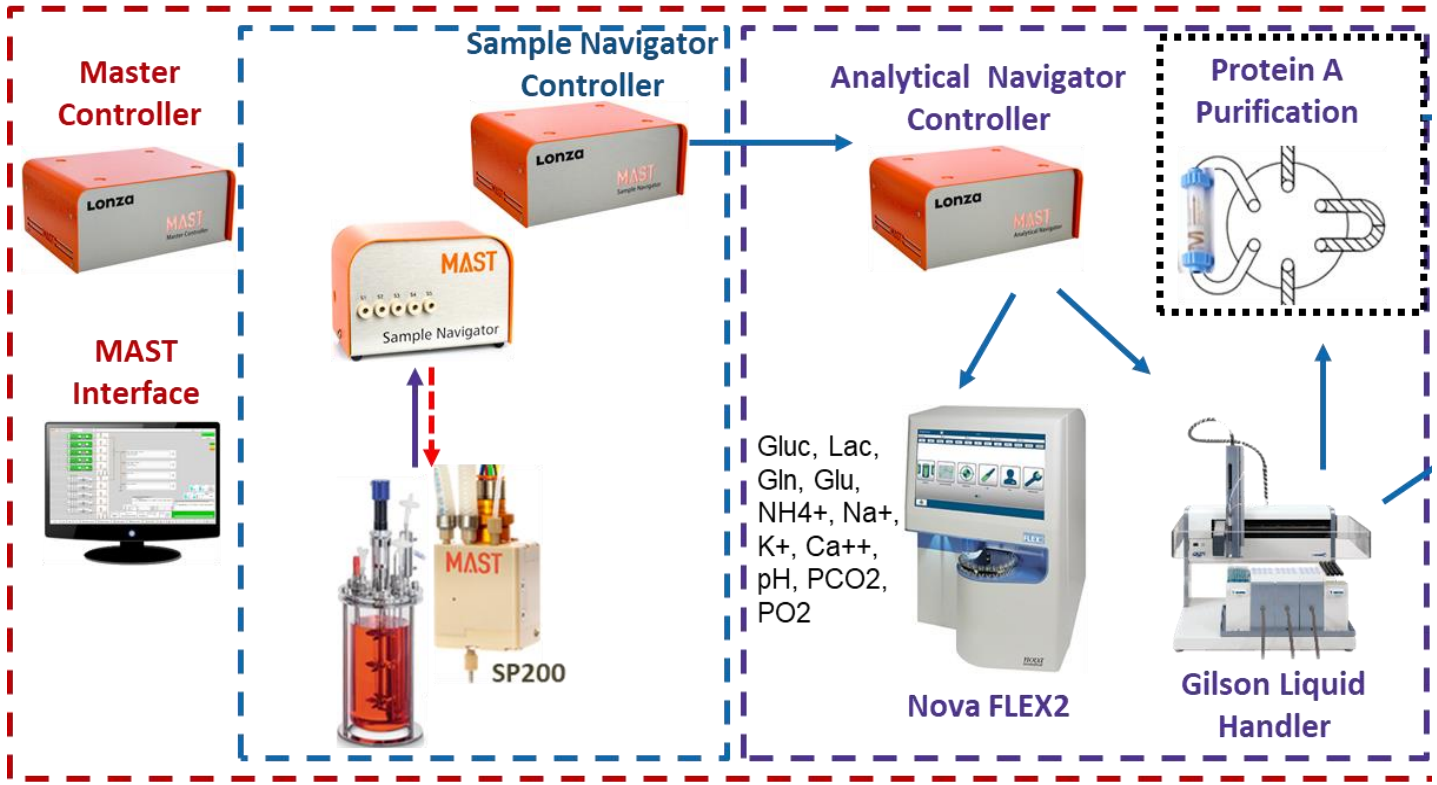
MAST® Offers Streamlined Analytics Through Connectivity to Primary and Secondary Analyzers



MAST® Module Configurations

Example of a MAST® Solution

1. Master Controller
2. MAST® Interface
3. Analytical Navigator Controller (Up to 4)
4. Sample Navigator Controller (5 per controller)
5. Sample Pilot (Depending on how many bioreactor)
6. Filters
    1. Sanitant
    2. Purge
    3. Cleaning solution
7. Cleaning Solutions
    1. Sodium Hydroxide
    2. 70% IPA + 0.5 g/L NaCl



Soon to come:

Cell Removal System & HPLC

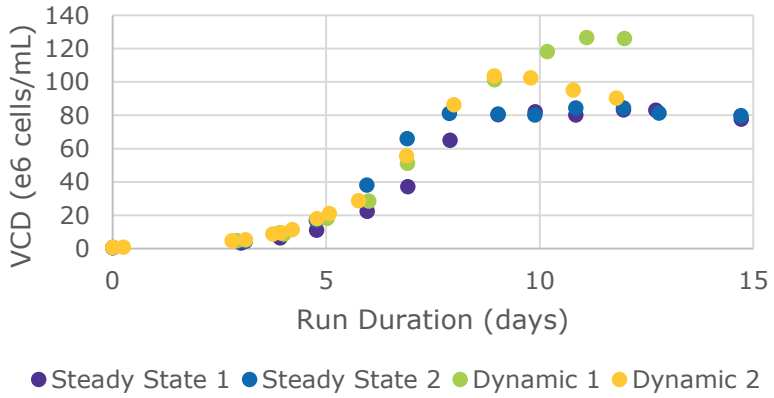
MAST® Provides Increased Data Access While Maintaining Data Accuracy and Reducing the Workload

Increase frequency of data acquisition…

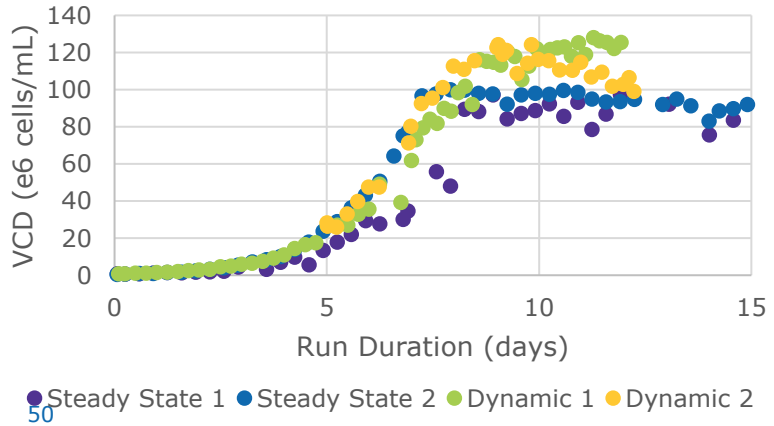
…while maintaining data accuracy…

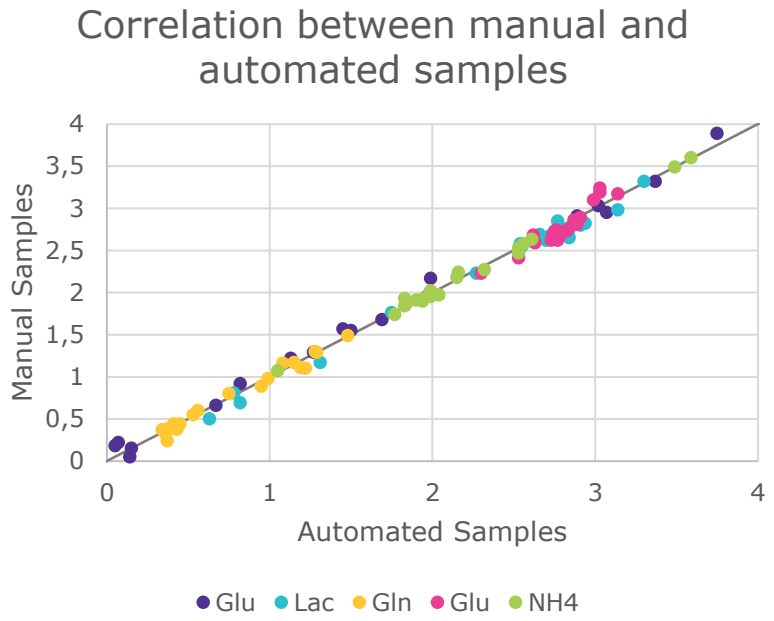
…and reducing workload for scientists!

Manual Data (1 sample/day)



Automated Data (4 samples/day)

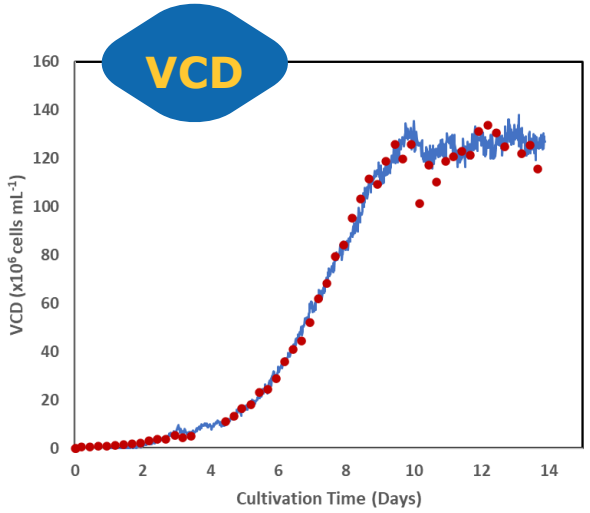


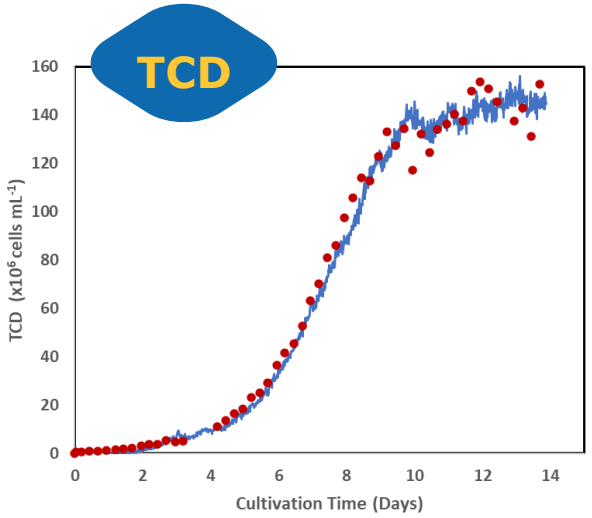


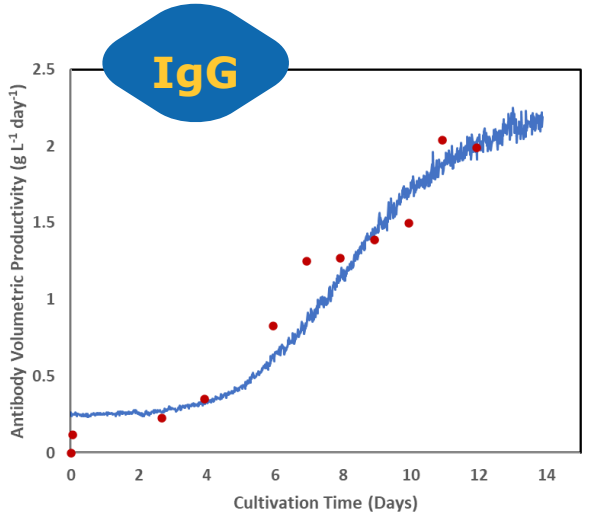
- Data falls close to the y=x line, indicating a good correlation between manually acquired data and automatically acquired data

- ✓ Reduces the number of experiments needed for decision making in process development by providing near real-time process information including product quality attributes
- ✓ Reduces risk of contamination by eliminating operator error during sample draw
- ✓ Saves on labor for sample acquisition, processing, and analysis; including prevention of weekend or off-hours work
- ✓ Can achieve real-time release by analyzing the product as it is produced

MAST® Can Be Used in Combination with Other PAT Tools to Accelerate and Enhance Model Building



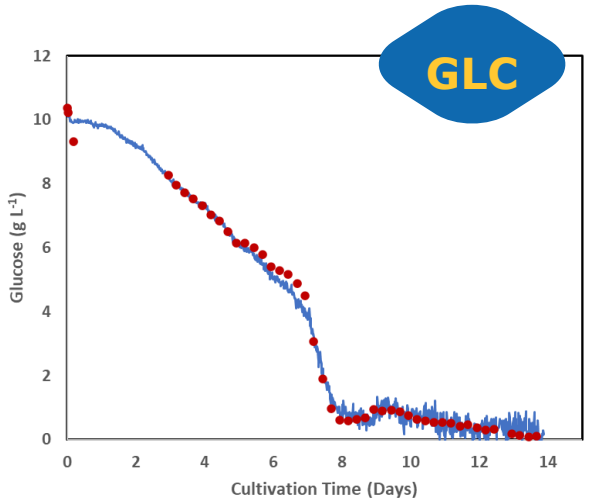


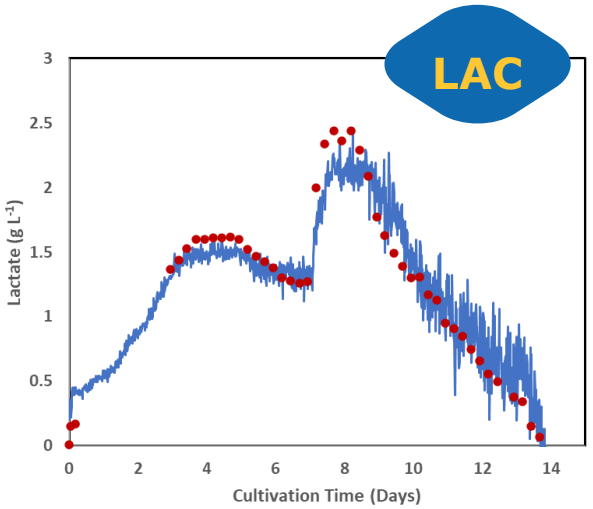


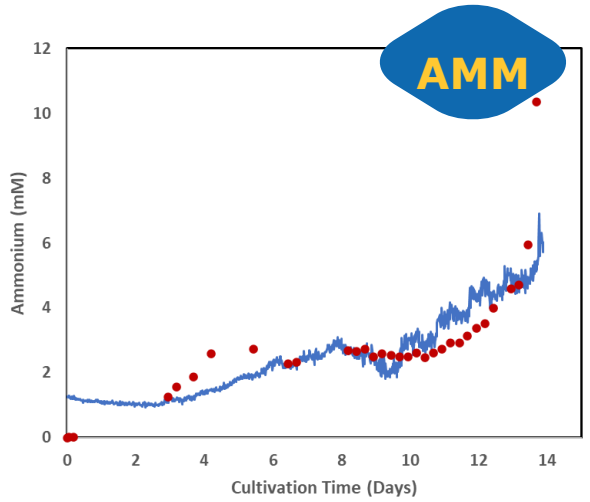
N Dynamic perfusion culture

In-line sensor

On-line sensor



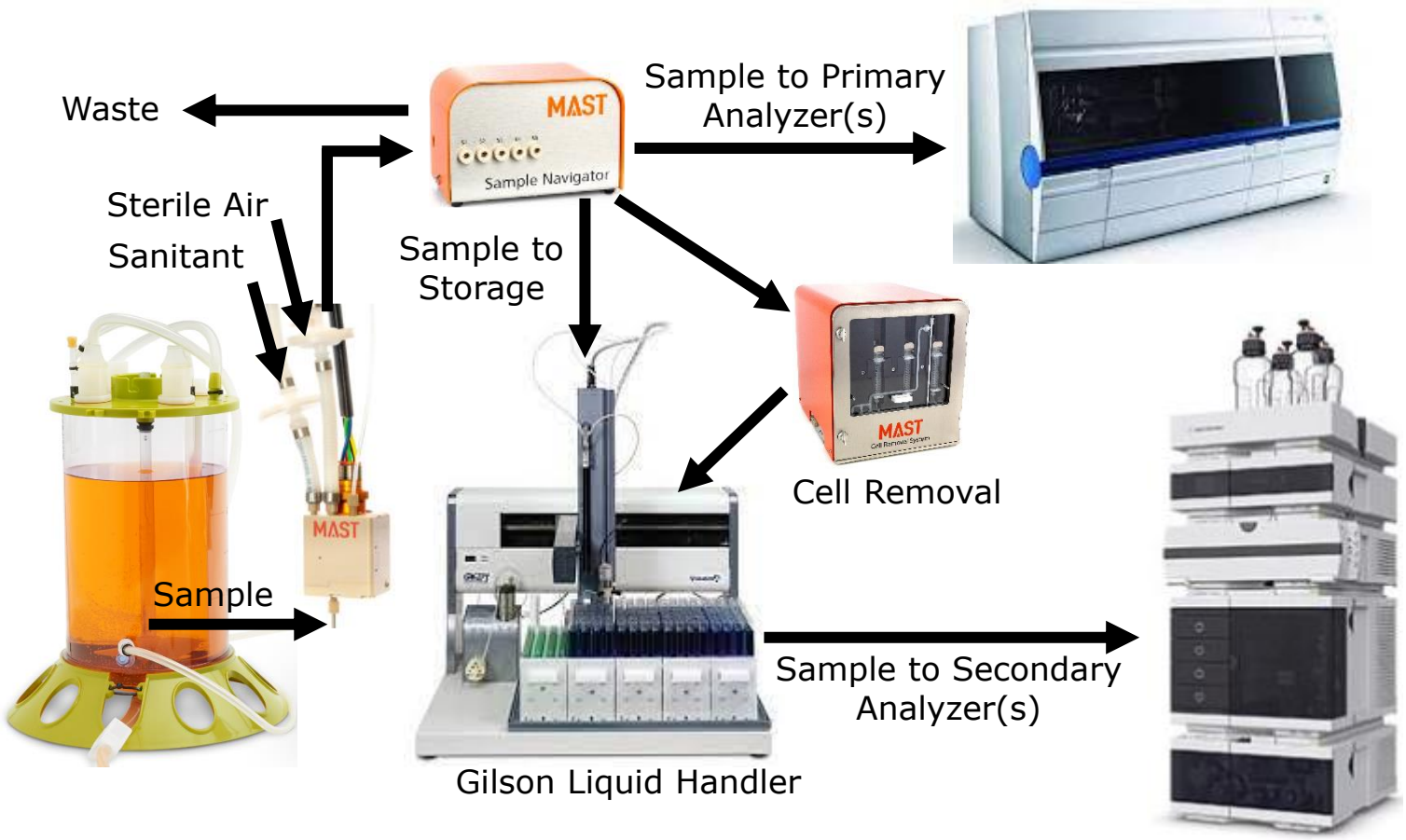




MAST® Addresses Your Automated Sampling Needs

Sterility	**Robust sterility protection** confirmed by extensive MAST® customer experience.
Accuracy	Exceptional data accuracy**– strong correlation between manual and automated samples.**
Analytics	Compatible with **several common analyzers** (Nova, Cedex, HPLC, etc.)
Ease-of-use	Flexware setup is quick and easy, maintenance is manageable, and software and sample scheduling are **simple to learn**.
GMP-readiness	Diaphragm pump enables **fast sample delivery** up to 80 ft across a production facility, initiating analysis within seconds. Software has option for 21 CFR part 11 compliance.
Flexibility	Modular system provides **tailored fit for each facility** and connectivity to any vessel type. Minimum sample volumes of ~10 mL enable use across scales and 20-30 min sample rate allows for frequent data acquisition.
Sample Processing	System can connect to a Gilson® liquid handler for sample **storage, dilutions, and processing.** Cell removal system enables **cell separation**.

MAST® is an integrated system for the automation of sampling and sample management



MAST® Integrations:

- Gilson liquid handler
- Nova BioProfile FLEX & FLEX2
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- Waters Acquity Systems via Empower
- ThermoFisher LC Integration via Chromeleon
- Agilent LC Integration via ChemStation
- Cary 60 UV/Vis Analyzer

Raman PAT Platform

ProCellics™ Raman Analyzer with Bio4C™ PAT Raman Software

Name, date
Short version

Millipore®

Preparation, Separation, Filtration & Monitoring Products

Raman PAT Platform

A global solution for real-time monitoring of bioprocesses

Hardware

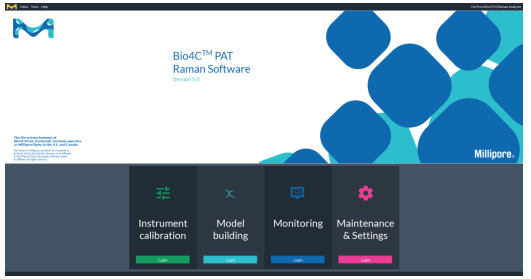
ProCellics™ Raman Analyzer

Single Channel (1 probe)

Multi-Channel (4 probes)

software

Bio4C™ PAT Raman Software



Chemometric Model Building support & Training

OPC Connect support

services

A valuable service offer

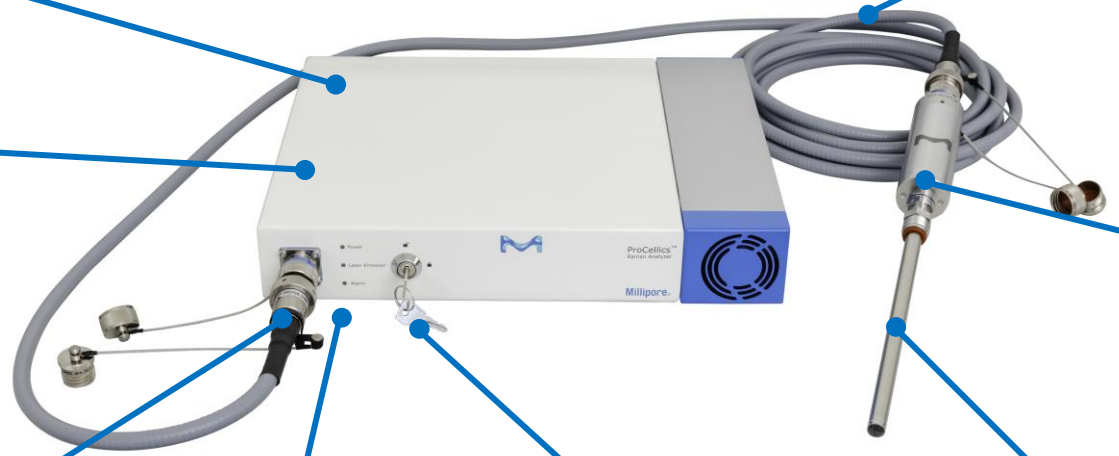
- Preliminary study
- System Rental package (1month)
- Ad-hoc supports
- IQOQ
- Service Plan
- Spare Parts

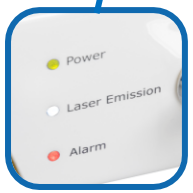
ProCellics™ Raman Analyzer

A compact and easy-to-implement hardware

High ingress protection:
The analyzer is IP65 enclosed preventing ingress of dust and water jets from any angle.

Space-saving:
Small, compact footprint





Interlock systems – Warning lights – Laser key control

User safety: The safety laser management system protects personnel from accidental exposure to possible laser hazards.

Adaptable:
Six meters of optical cable between the analyzer and the probe allows for flexibility in placement and ease of use.

Easy implementation:
The probe head and tube can be easily assembled and disassembled.
The port adaptor is compatible with standards ports of single-use bags and bioreactors (P13.5); three lengths of tubing are available.

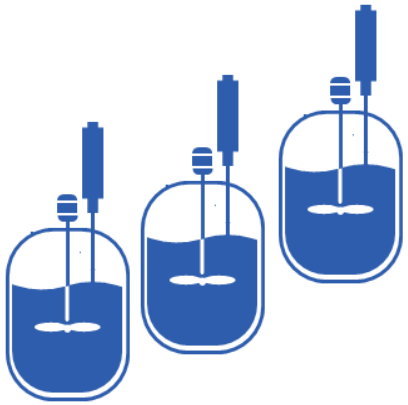
CIP/SIP compatibility:
The stainless-steel immersion tube is compatible with CIP/SIP and autoclave sterilization.

Raman for Bioprocess Monitoring

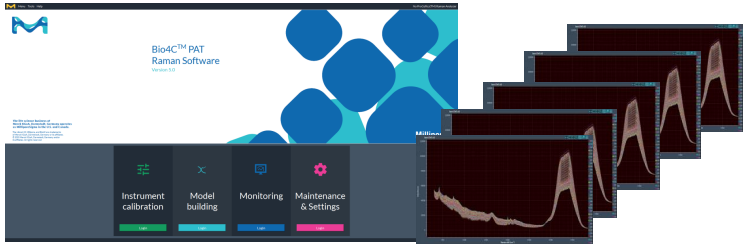
Chemometric modeling: Raman spectra and offline mathematical link

Multivariate calibration

Monitoring

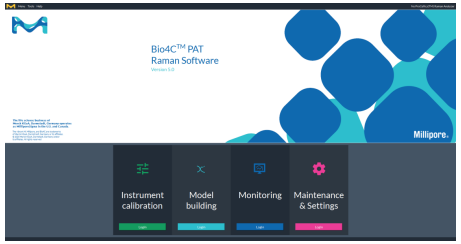


Raman Analyzers



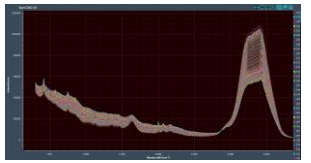
Raman spectra captured by Bio4C™ PAT Raman Software

Chemometric model building in Bio4C™ Chemometric expert

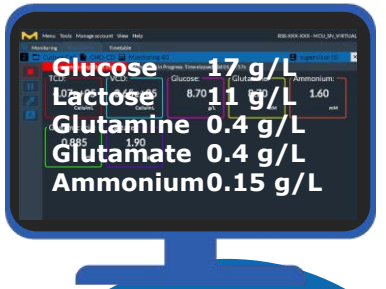


Seamless model export to Bio4C™ PAT Raman Software

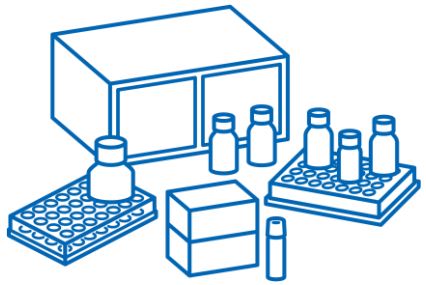
Raman spectra capture live



Chemometric models



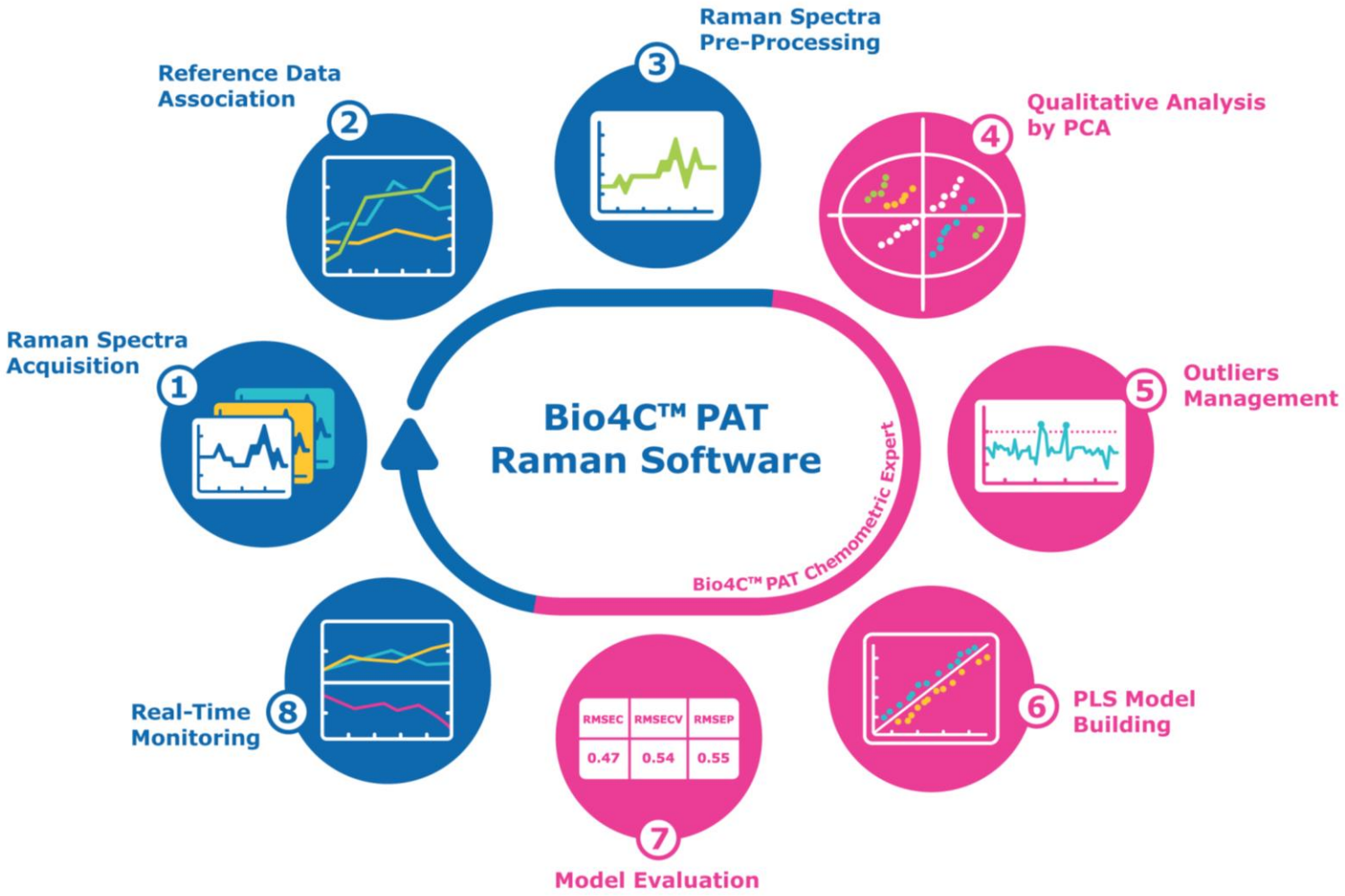
Real-time monitoring



Quantitation sample TN
Quantitation sample T4
Quantitation sample T3
Quantitation sample T2
Quantitation sample T1

Bio4C™ PAT Raman Software 5.0

End-to-end functionalities for spectral acquisition, reference data association, spectral pre-processing, chemometric model building, and real time monitoring

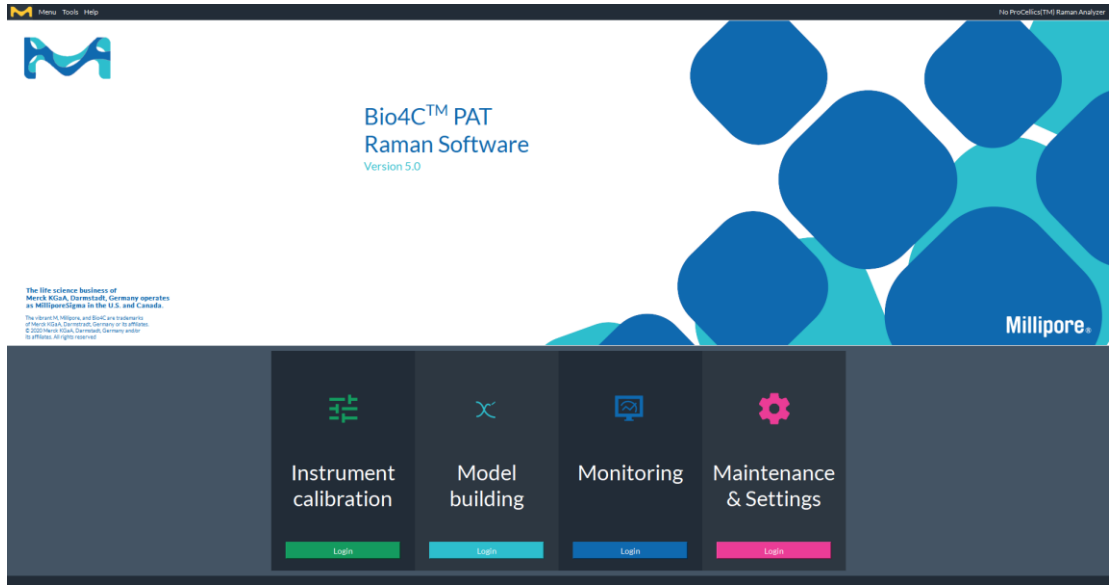


Bio4C™ PAT Raman Software 5.0

ProCellics™ Raman Analyzer, collect calibration datasets, build models and monitor

Easy-to-Use Modules

- **Instrument Calibration** – Enables calibration verification & re-calibration to ensure the best quality spectral acquisition
- **Model Building** – Interface to collect Raman spectra and off-line reference data and optimize spectral acquisition with smart preprocessing tools and build chemometric models
- **Monitoring** – Provides the capability to monitor and display process parameters and quality attributes in real-time
- **Maintenance and Settings** - Enables user management and houses all software settings



Bio4C™ PAT Raman Software 5.0
Benefits

Adaptable

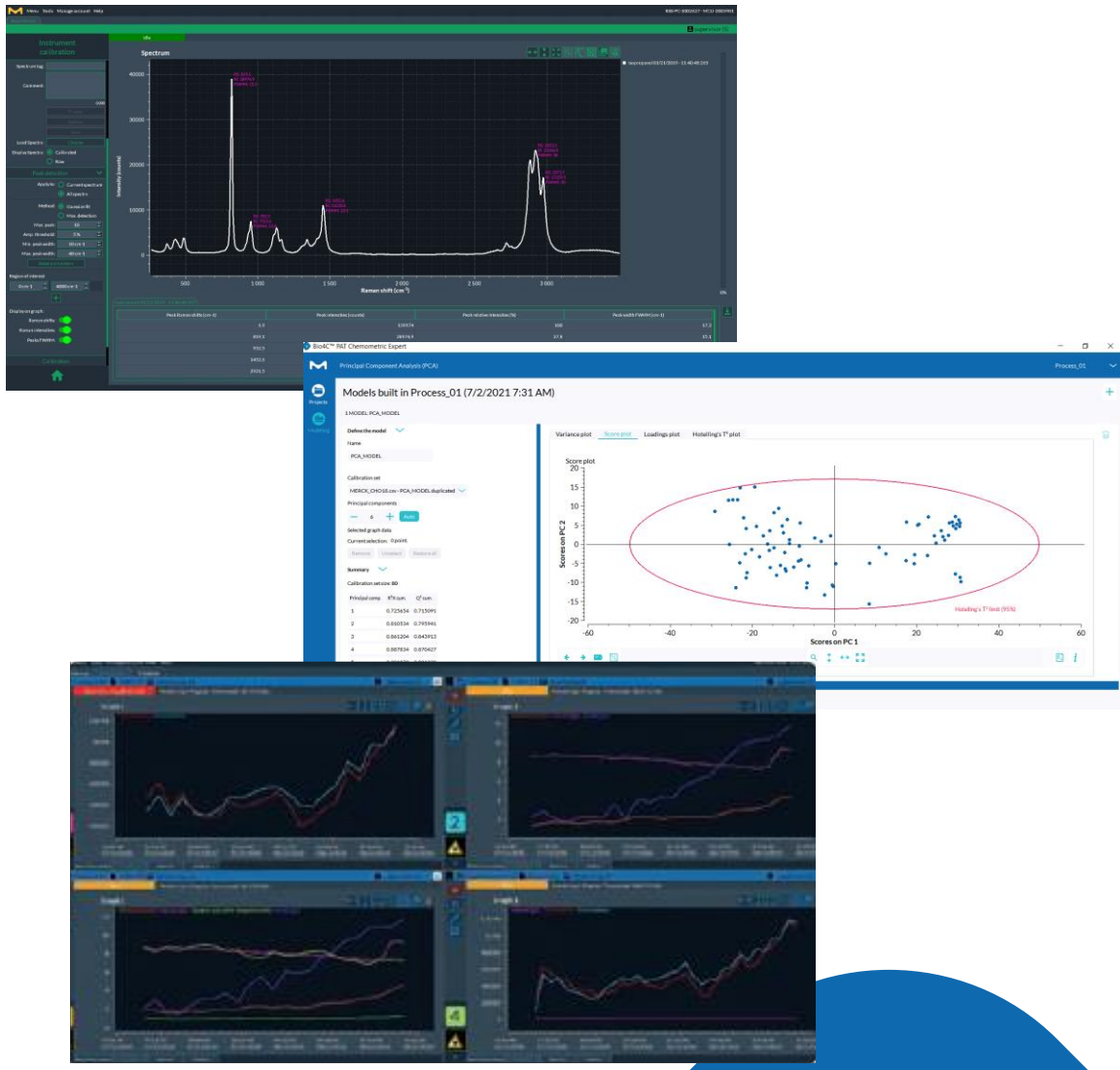
- Automatically detects the Multi-Channel Unit and adjusts the interface accordingly
- Several batches can run in parallel with different attributes
- Facilitates 21 CFR Part 11 compliance

Open Data Communication

- Remote communication through TCP/IP
- Easy to configure Open Platform Communications (OPC-UA)
- Easy data export and import for chemometric model building

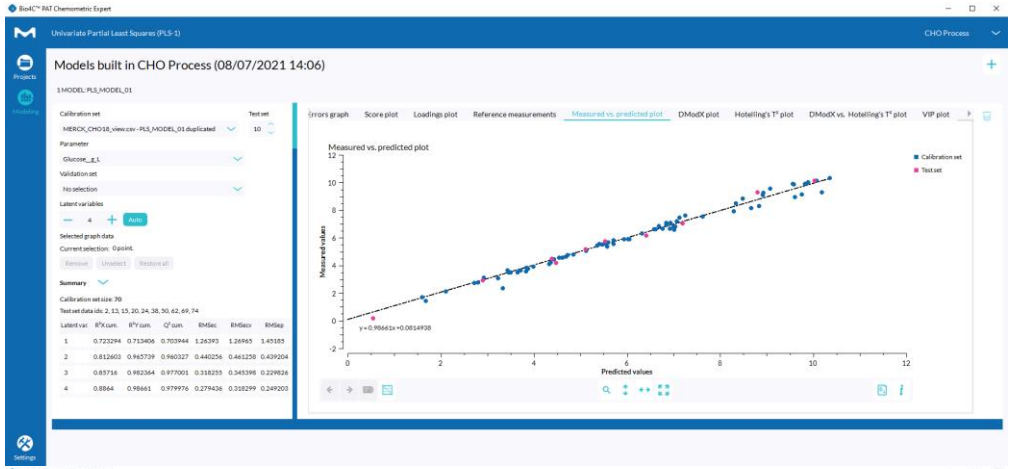
Consistent Model Building and Real-time Monitoring

- Easy and robust data management
- Provides capability to associate off-line data with spectra
- Clear methodology to set acquisition parameters, pre-process spectra and associate models with processes



Bio4C™ PAT Chemometric Expert
Benefits

- Provides state-of-the-art chemometric model building capabilities for process monitoring and process batch anomalies analysis
- Provides seamless integration with Bio4C™ PAT Raman Software
- Provides flexibility to select chemometric models based on statistical errors such as Root Mean Squared Error of Calibration (RMSEC), Root Mean Squared Error of Cross Validation (RMSECV) and Root Mean Squared Error of Prediction (RMSEP)



Bio4C™ PAT Raman Software Versions

	Bio4C™ PAT Raman Software 4.0	Bio4C™ PAT Raman Software 5.0
Key Modules		
• **Instrument Calibration**	√	√
• **Spectral collection, offline association and optimization**	√	√
• **Monitoring**	√	√
• **Maintenance and Settings**	√	√
• **Chemometric Module for Model building**	×*	√
Support Process Development	√	√
Support GMP Operations	×	√
• **Facilitates 21CFR part11 compliance**	√	√
• **Facilitates Data Integrity requirements**	×	√
• **Facilitates category5 GAMP5 recommendations**	×	√
Chemometric Model Building Support	√	√
Timely Updates and Upgrades	√	√

*Supported through SIMCA-Q software

Please note that Merck will no longer support earlier software versions (v2.0 or v3.0)

Bridging Study

To evaluate the performance (Model error assessment) between SIMCA and Bio4C™ PAT Chemometric Expert for our established customers

Bridging Study Process (1 week)

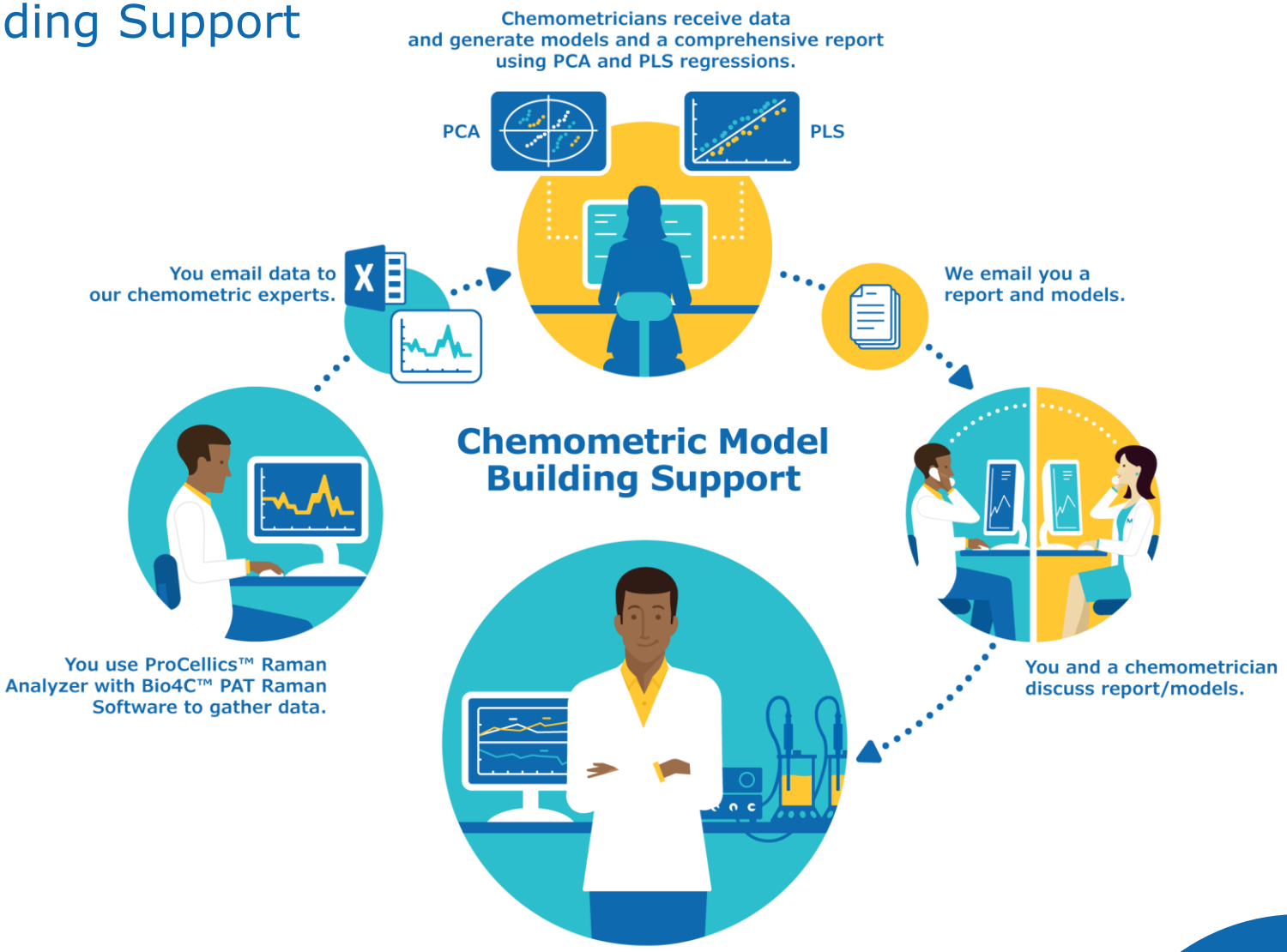
- Collect spectral dataset referenced with offline measurements
- Built chemometric model using Bio4C™ PAT Chemometric Expert on the collected dataset for 3 metabolites (with varied error ranges)
- Compare and analyze RMSE between model built by SIMCA vs. Bio4C™ PAT Chemometric Expert
- Consolidate the results and present it to the customer

Raman PAT Platform
Services & support offering

We are here anytime you need us

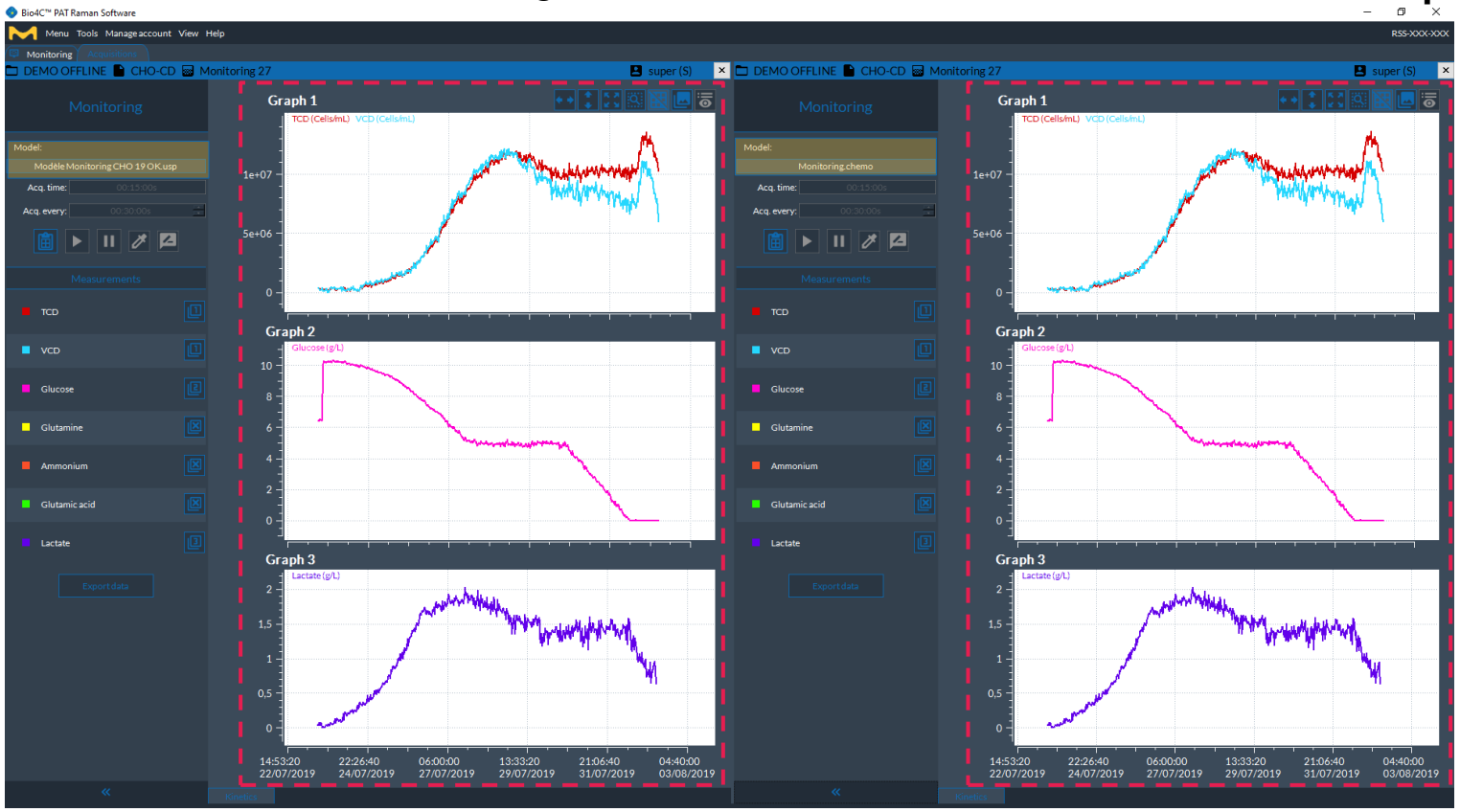
Bio4C™ PAT Raman Software

Chemometrics Model Building Support



Value modelling for Bio4C™ PAT Chemometric Expert vs Simca® solution

SIMCA ® **Bio4C™ PAT Chemometric Expert**



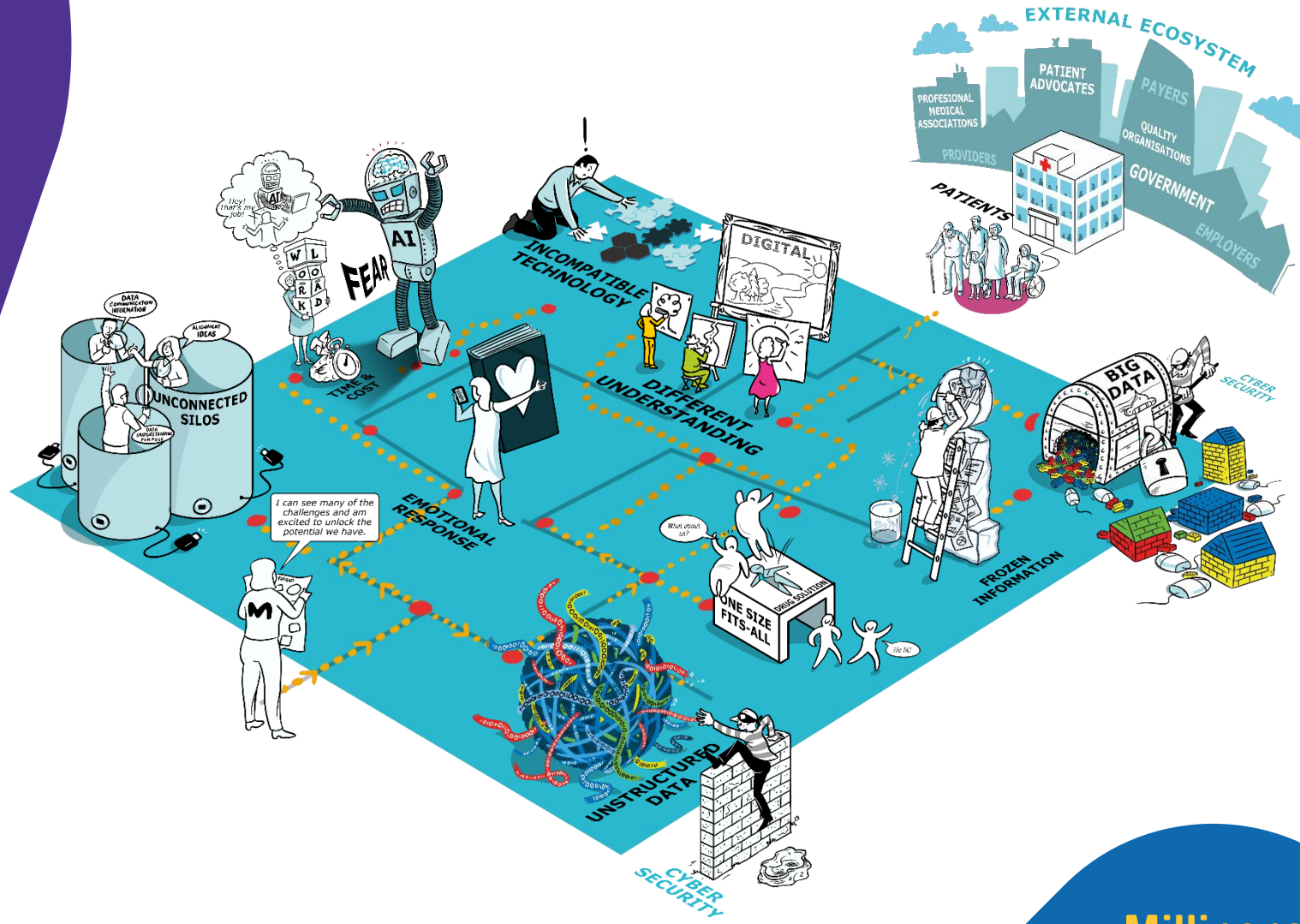
Relative errors between both monitoring

Culture parameters	Relative errors (%)
TCD	0,00006
VCD	0,00008
Glucose	0,00003
Lactate	0,00029

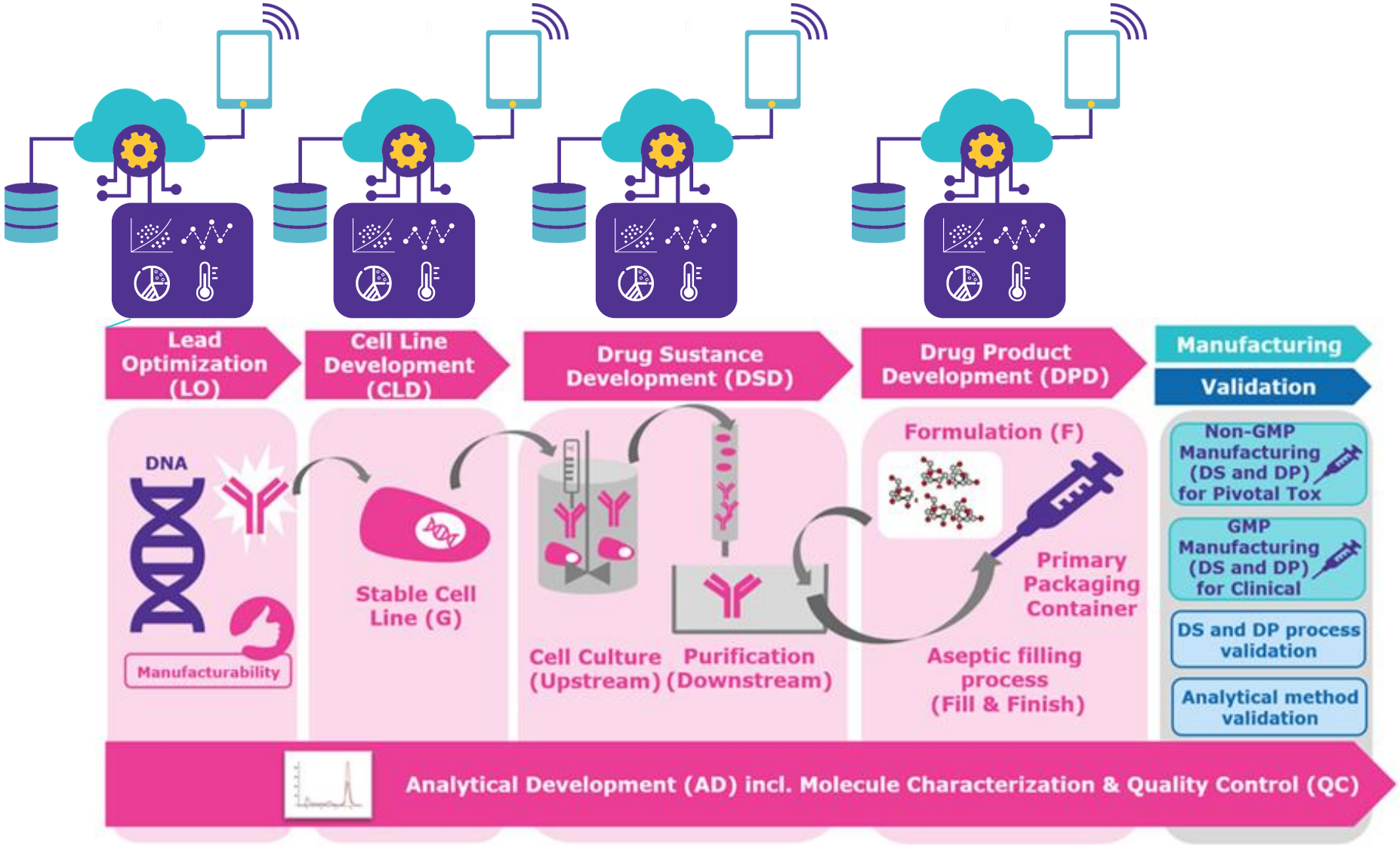
09

current state of industry

Siloed work on digital solutions to answer individual business questions **without scaling** & unlocking the full potential of our data assets

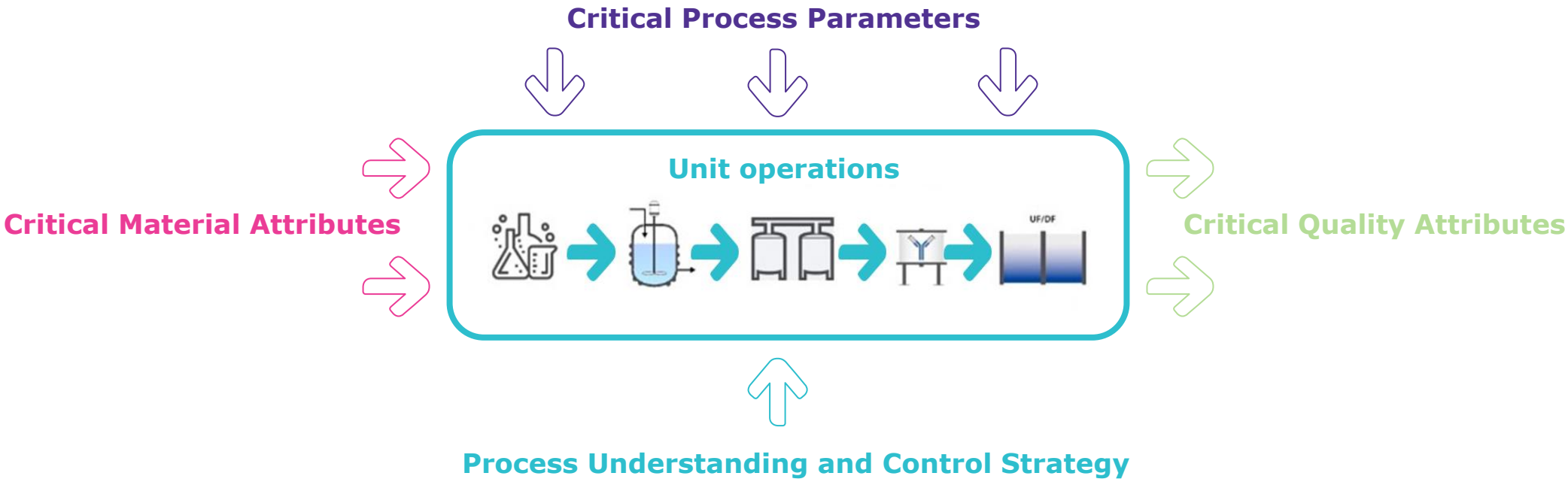


Ever-Increasing Data Along the Drug Development Life Cycle



Defining the right process control strategy

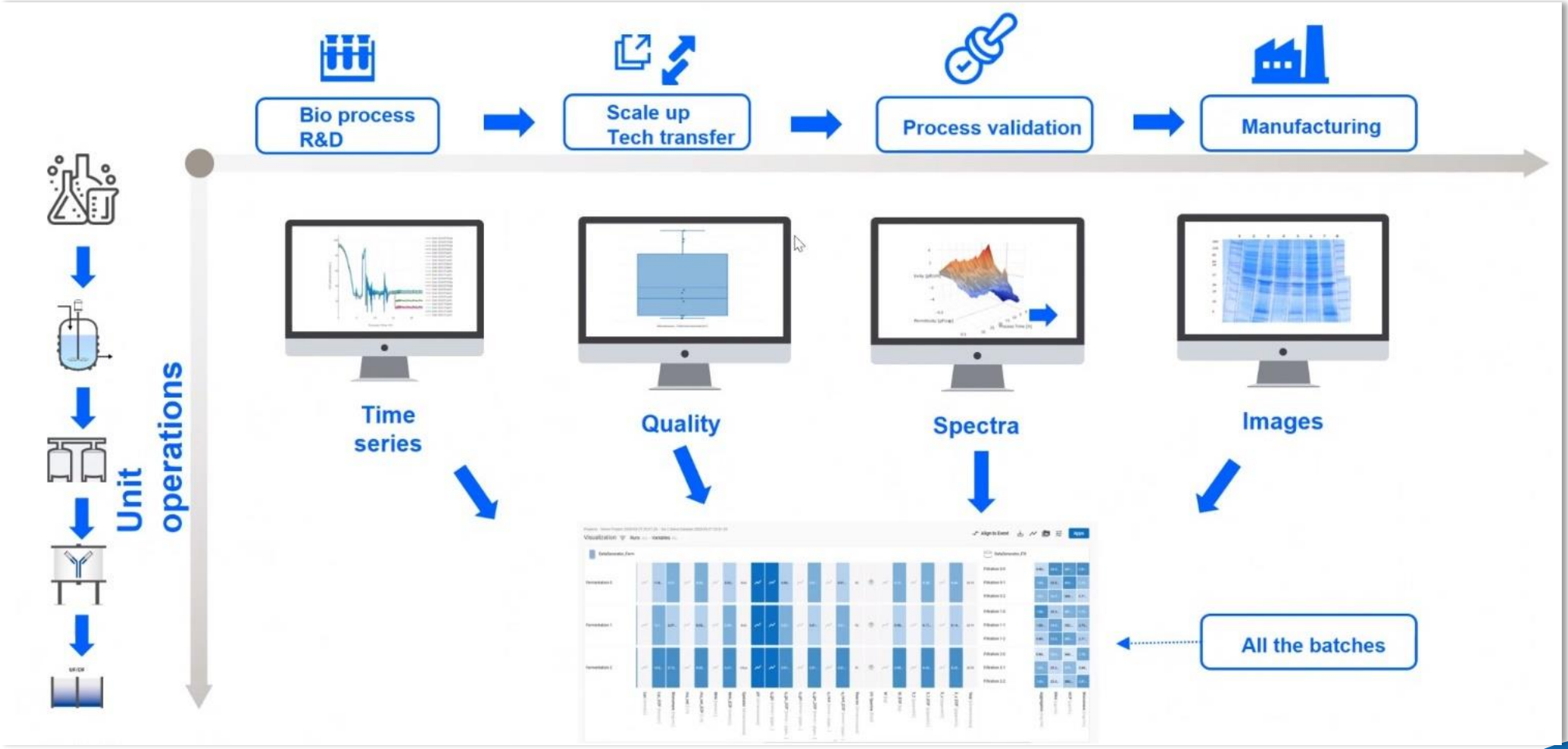
The impact and multidimensional interdependency of manufacturing parameters



Source: ©Körber-Pas-X Savvy

The holistic understanding of manufacturing processes

Data are be available from multiple dimensions in different formats



Source: ©Körber-Pas-X Savvy

From MANUfacturing to SMARTfacturing

The Next Generation Manufacturing Excellence

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From MANUfacturing to SMARTfacturing

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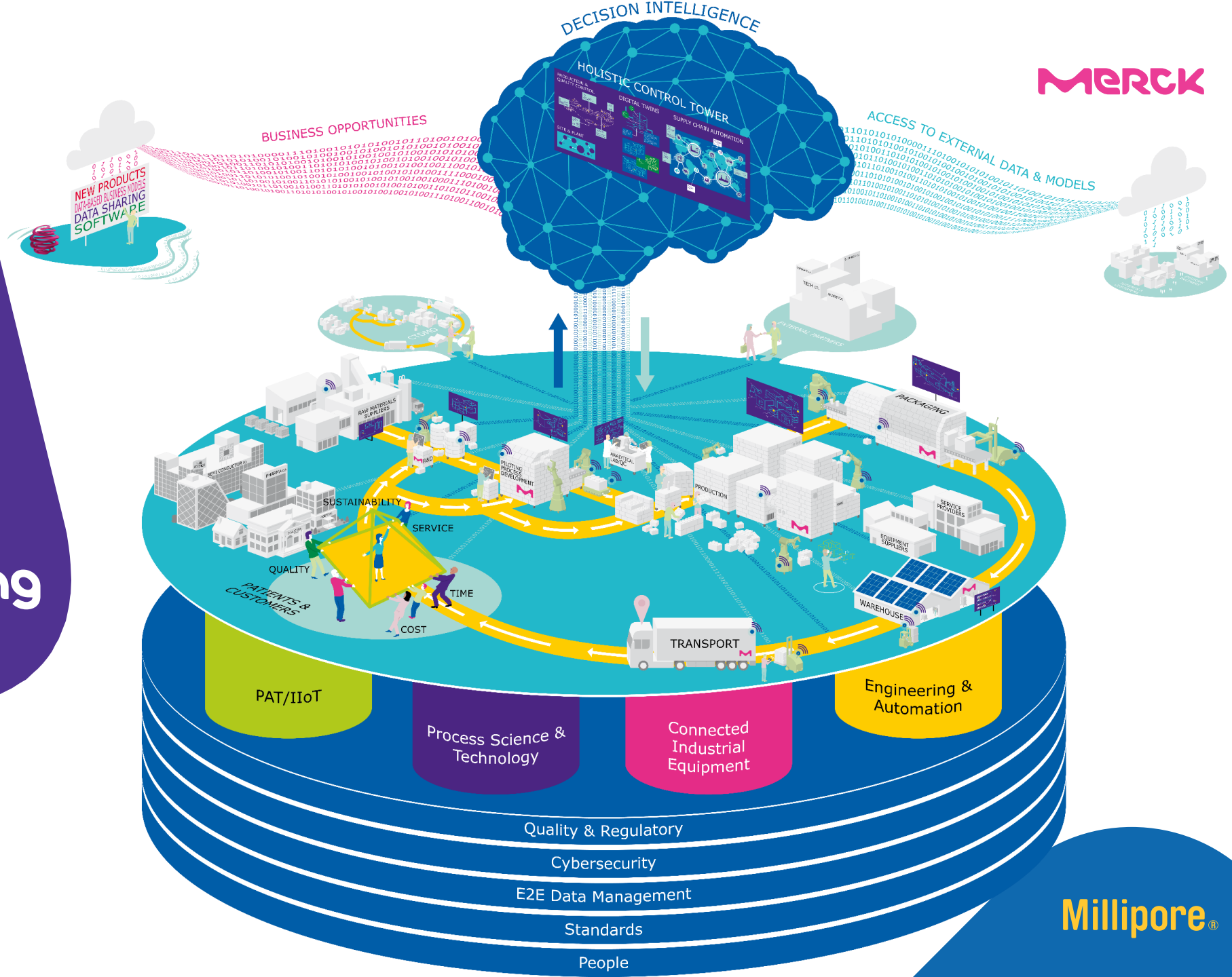
Envisioning our future with smartfacturing



To realize the benefits, potential data and digital solutions can be implemented across all SMARTfacturing building blocks

Production Planning and Scheduling

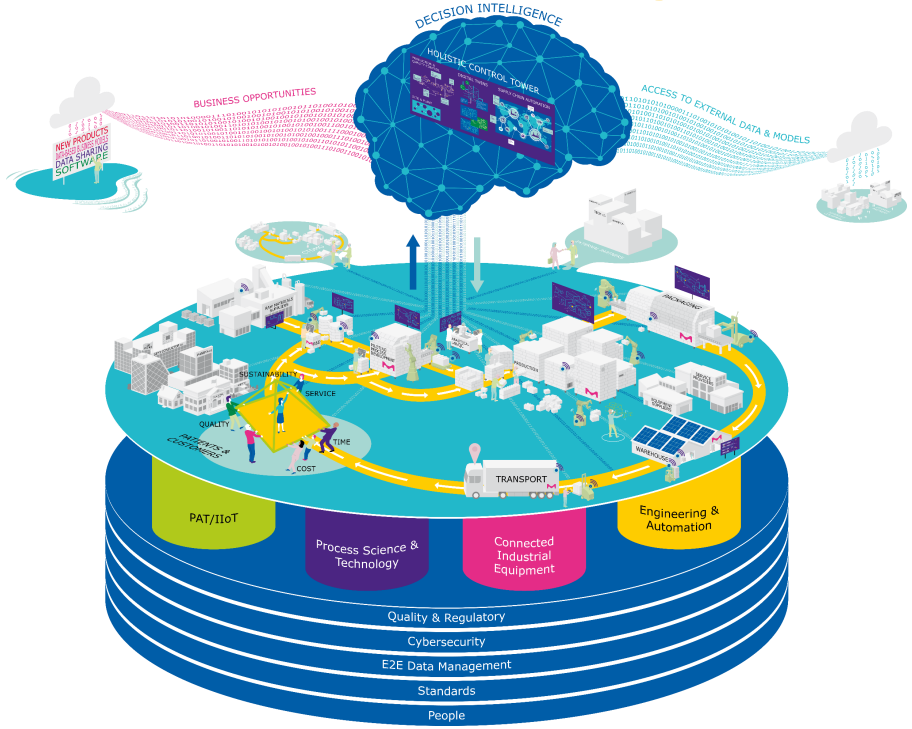
Automated S&OP process, real-time synchronization of supply chain and production, advanced planning/ scheduling

Materials & Inventory Management

Track and trace, data-driven inventory management and optimization, additive manufacturing, digital utilities

Production

Continuous manufacturing, 3D printing, industrial robots, automated guided vehicles, additive manufacturing



Manufacturing Network Operation

Analytics, dynamic routing, real-time supply chain optimization/risk mgmt., next best action/ predictions, advanced process control, connected lab

3rd Party Manufacturing & Service

Automated sourcing agents, supplier rooms, shared cloud platforms, control tower

Performance Mgmt. & Business Intelligence

Real-time KPIs, advanced production and asset utilization based on digital twins, advanced process control, EBR, digital utilities

Manufacturing Engineering

Virtual simulation and experimentation, AI/ML-based routing & job scheduling, additive manufacturing

Manufacturing Reliability & Maintenance

Predictive / remote maintenance, virtually guided maintenance, analytics, additive manufacturing, robotics and automation, workforce enablement

Environment, Health & Safety (EHS)

Waste management optimization and smart energy consumption, workforce enablement, digital utilities, digital EHS

Quality

Automated quality in-line testing, digital quality management, robotics and automation, workforce enablement, EBR

Skills, culture & behaviors

Thank you!

Any Questions?

THANK YOU