SARTORIUS

Simplifying Progress

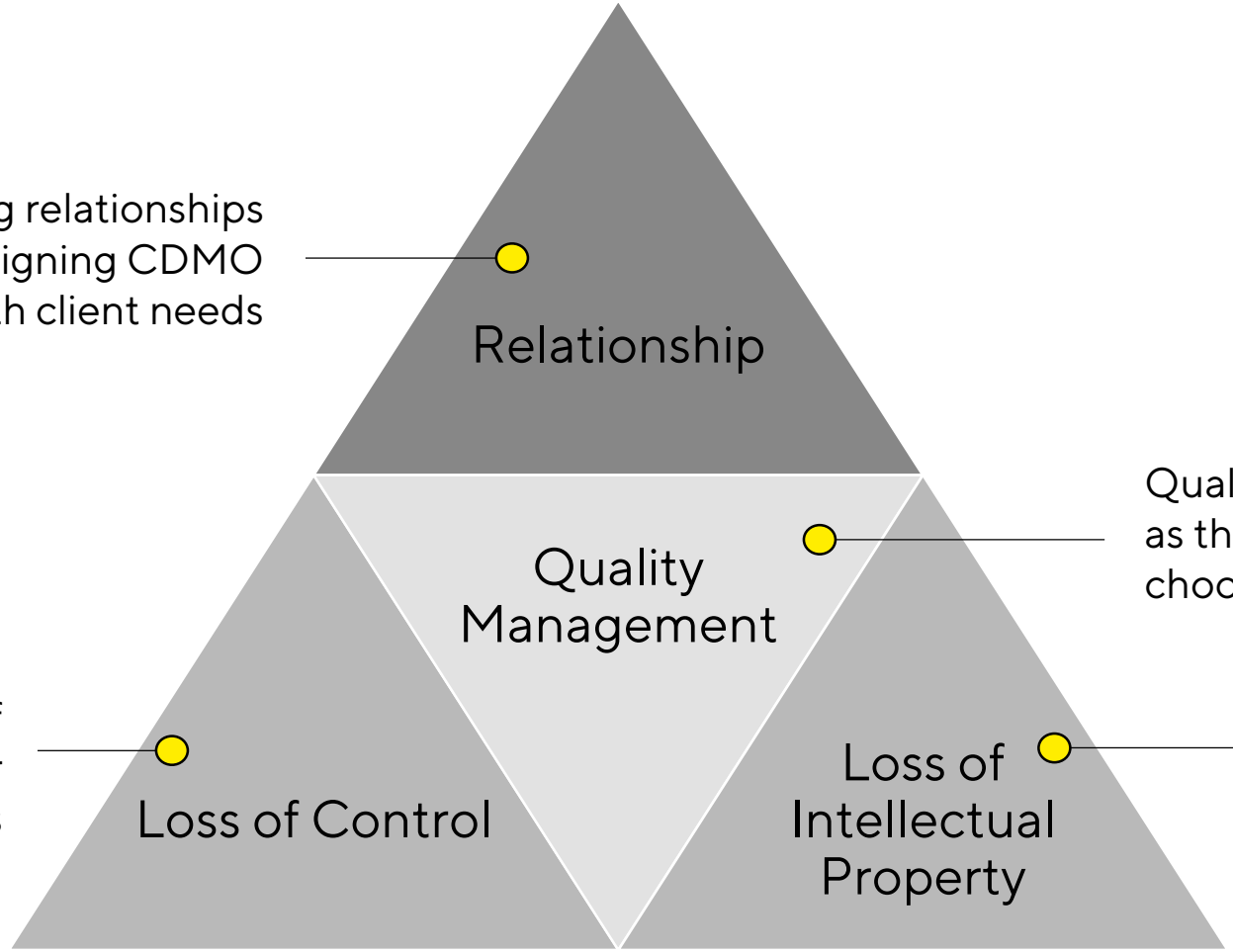
OSIsoft and Sartorius Partner to Help CDMOs Leverage their Data

November 24th, 2020

Agenda

- Introduction: Data integrity: The New CDMO Challenge
- Presentation from OSIsoft
  - Who is OSIsoft?
  - OSIsoft in Life Science Industry
  - How to handle Data Integrity in a Global Ecosystem
  - OSIsoft PI System Implementations at CDMOs
- Faster and More Reliable Operations: A FUJIFILM Diosynth Biotechnologies' Case Study
- Closing: Q&A

If you Remember from our Last Webinar…



Outsourcing relationships benefit from aligning CDMO expertise with client needs

Quality has superseded cost savings as the top criterion when companies choose their CDMO partner.

Clients often stand to lose a significant amount of control and visibility over their processes

Clients are required to divulge considerable amounts of confidential data.

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

New CDMO Challenge: Data Access and Sharing

- Disparate internal and external IT and data management systems
- Data stored in non-electronic systems (e.g. paper records)
- Increased complexity in global supply chains
- Compliance in a new era of regulatory scrutiny (FDA & SEC)
- Process complexity of new therapies

Top Data Related Challenges in the CDMO Industry

Source: Skyland Analytics, The New Challenge: Data Access & Data Sharing (2019)

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So What?

Many large and small CDMOs don’t have data management systems in place

These CDMOs struggle to provide secure, compliant data sharing with their partners

Therefore they have to manually extract, manage, and share their data

Lack of Data Transparency Can Result In….

- **Delay in Business Critical Processes –** tech transfer, IP transfer, regulatory approval,…
- **Operational Inefficiencies –** longer cycle times, lower yields, minimized throughput…
- **Cost to Reputation –** failed audits, extended time-to-market, supply chain shortages…

It’s your data – take control

WHO WE ARE

Pioneers in operational data management for essential industries

40
years

$5B
valuation

21k
sites

140+
countries

2B
data streams

24*
of our first 25 customers are still with us

OSIsoft.

Leading the market in critical operations

Oil & Gas

85%
of the top oil and gas companies

Power & Utilities

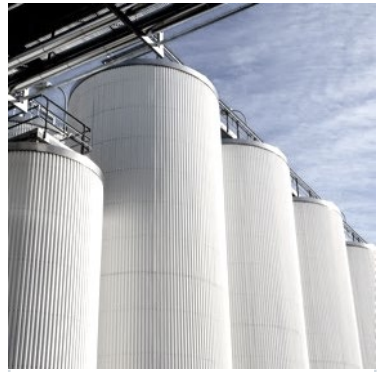
1000+
utilities worldwide

Mining & Metals

25
of the top 25 mining and metal companies

Pharma & Life Sciences

25
of the top 25 pharmaceutical companies



Chemicals

9
of the top 10 chemical companies

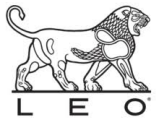
Manufacturing

6
of the World Economic Forum's Factories of the Future

OSIsoft: Proud to support the Pharmaceutical Industry

Frame = EA customer

OSIsoft: Proud to support the Pharmaceutical Industry



Digital Fundament

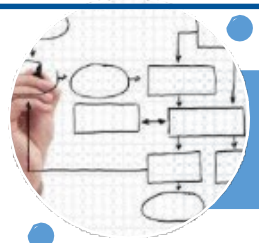
Plug & Produce

Knowledge driven

User Driven
Agile
Transparent
Value driven

Information

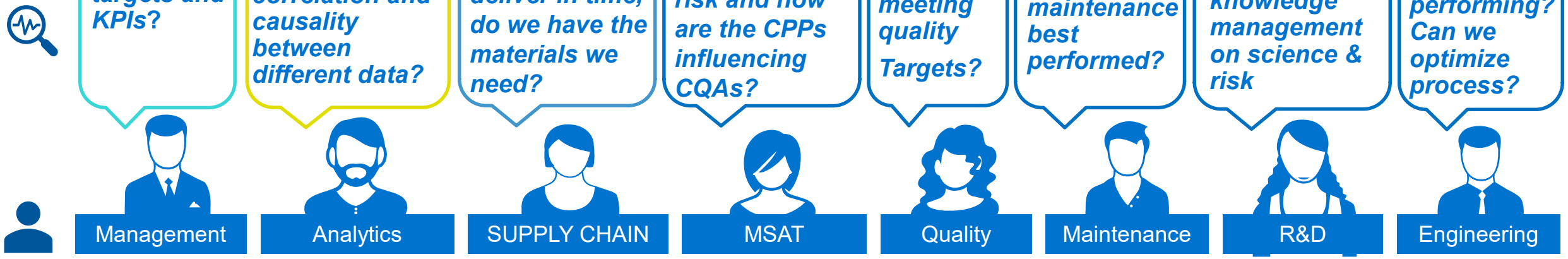
Data centric
- Accesible
- Scalable



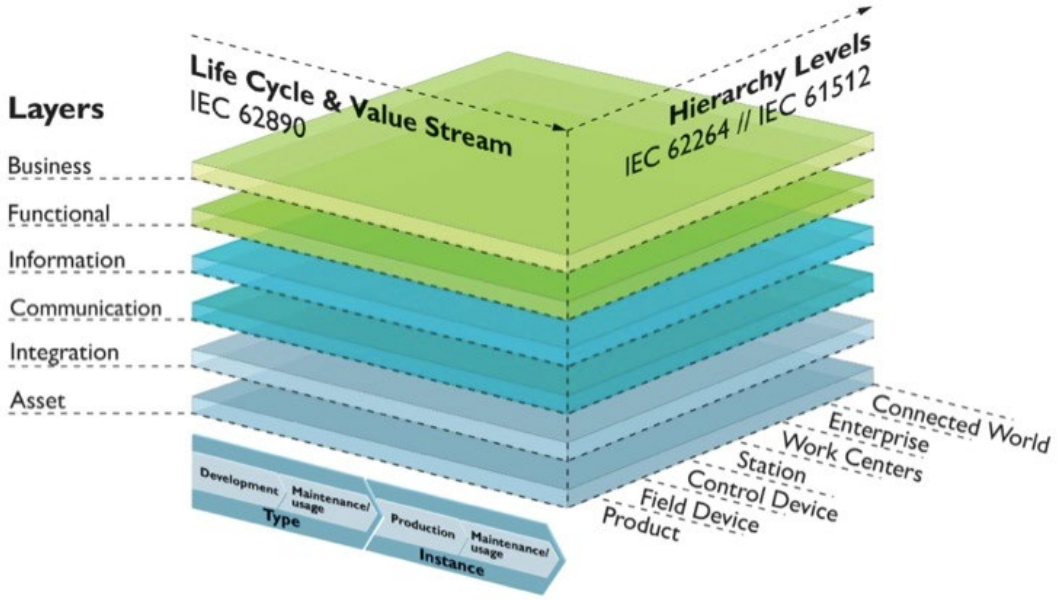
Metadata

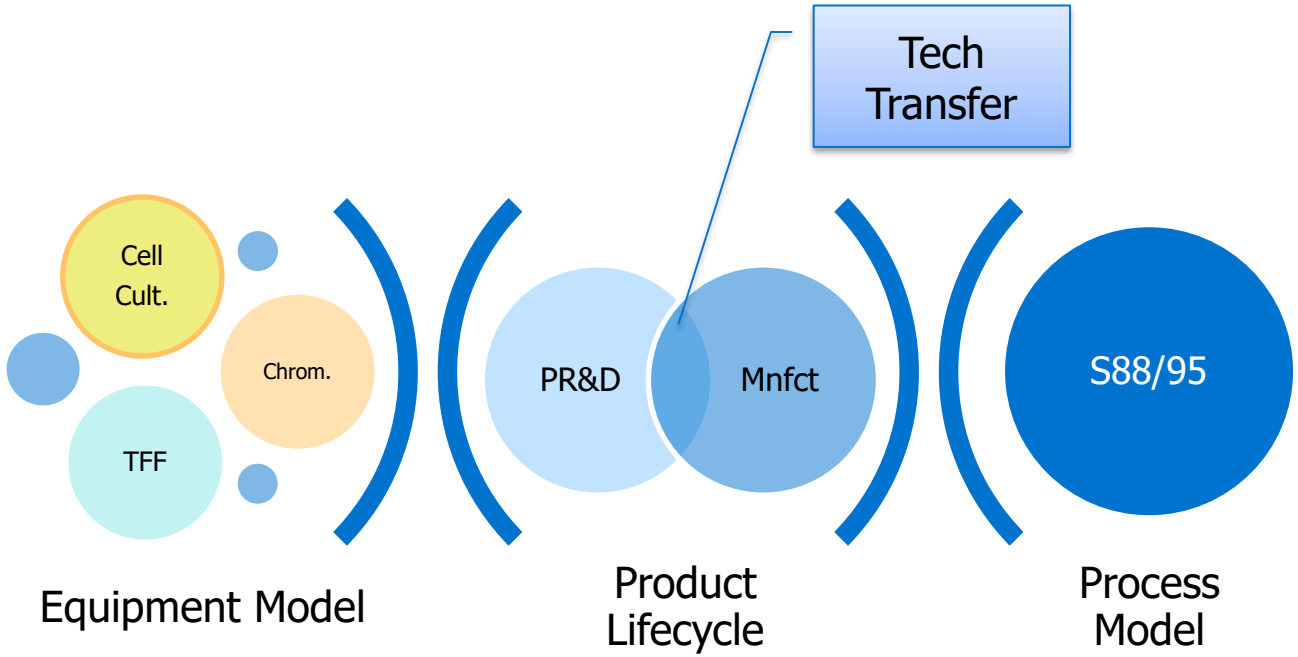
Data

User Driven, who are the drivers?



Three key dimensions

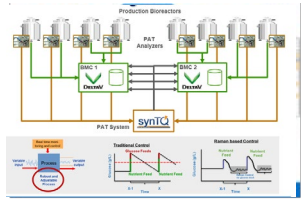




Equipment & Process models builds the Smart Pharma

Fermentation Template


Chrom. Template

Smart Application Template

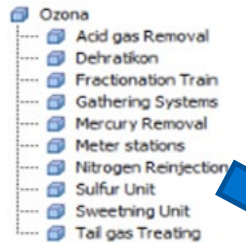
- Metadata
- Sensors
- Time Series
- Equipment data
- Performance curves
- KPI / OEE
- SOP
- Alarms
- Events
- Notifications
- Predictions
- Biomass
- Product
- Metabolites
- Endpoints
- Calibration status
- Etc.

E.g. Bioreactor Digital Twin

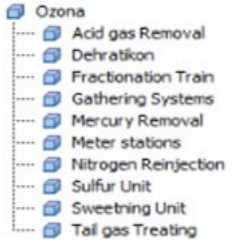
Bio Pharma Plant #1

Pharma Plant #2

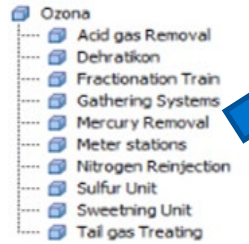
CDMO #1



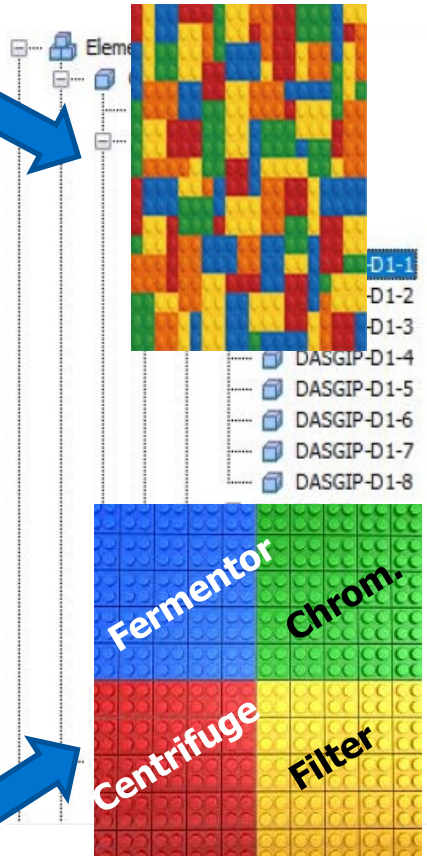
Digital Plant #1



Digital Plant #2

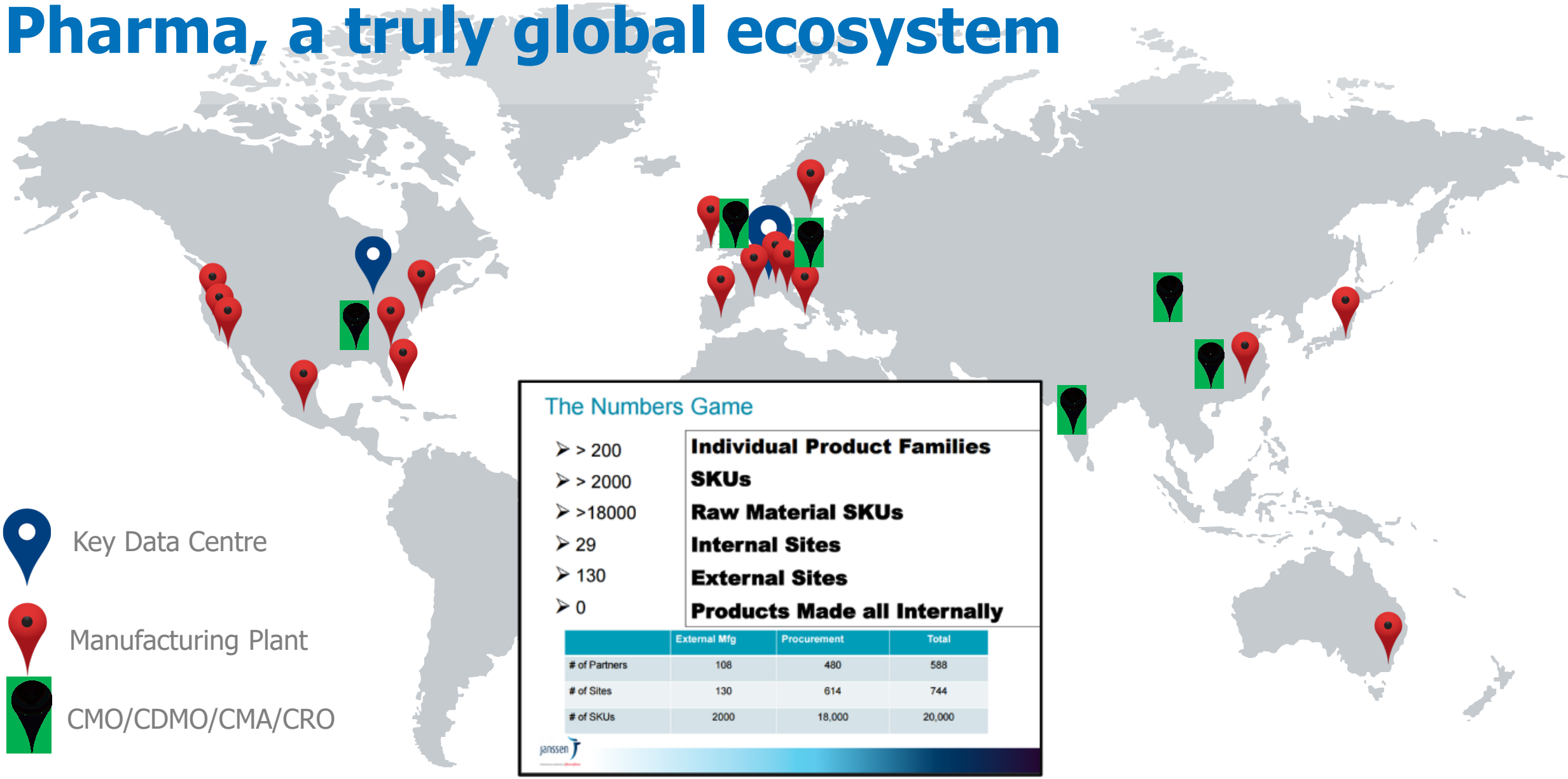


CDMO #1



Digital Enterprise

Pharma, a truly global ecosystem



Key Data Centre

Manufacturing Plant

CMO/CDMO/CMA/CRO

The Numbers Game

> 200	**Individual Product Families**
> 2000	**SKUs**
>18000	**Raw Material SKUs**
29	**Internal Sites**
130	**External Sites**
0	**Products Made all Internally**

	External Mfg	Procurement	Total
# of Partners	108	480	588
# of Sites	130	614	744
# of SKUs	2000	18,000	20,000

janssen

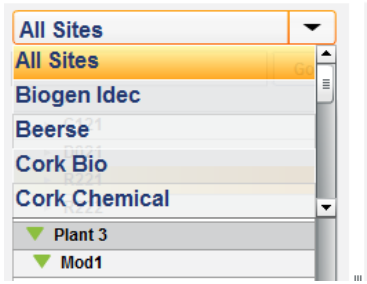
Global Process Maps

Johnson & Johnson

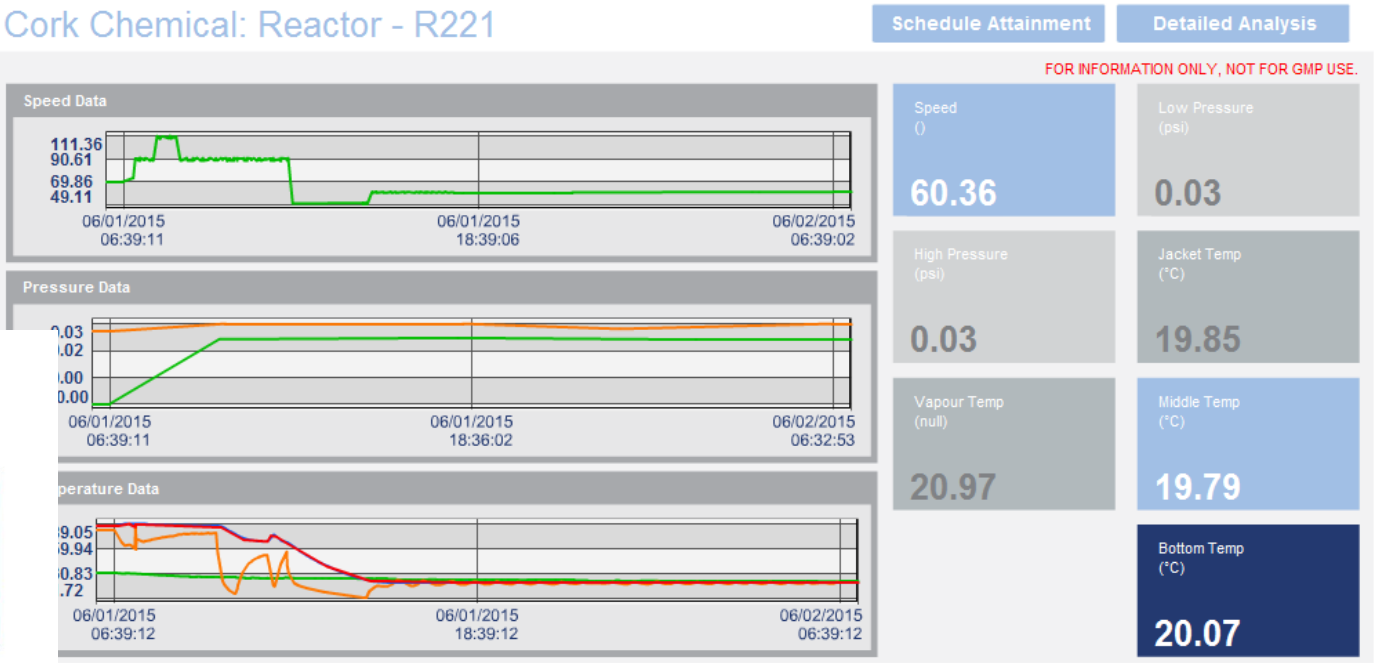
Process Visualisation

SPIRIT

Unit Selection



Cork Chemical: Reactor - R221



Global Interconnected Standard Visualization

Source: P McKenzie Janssen

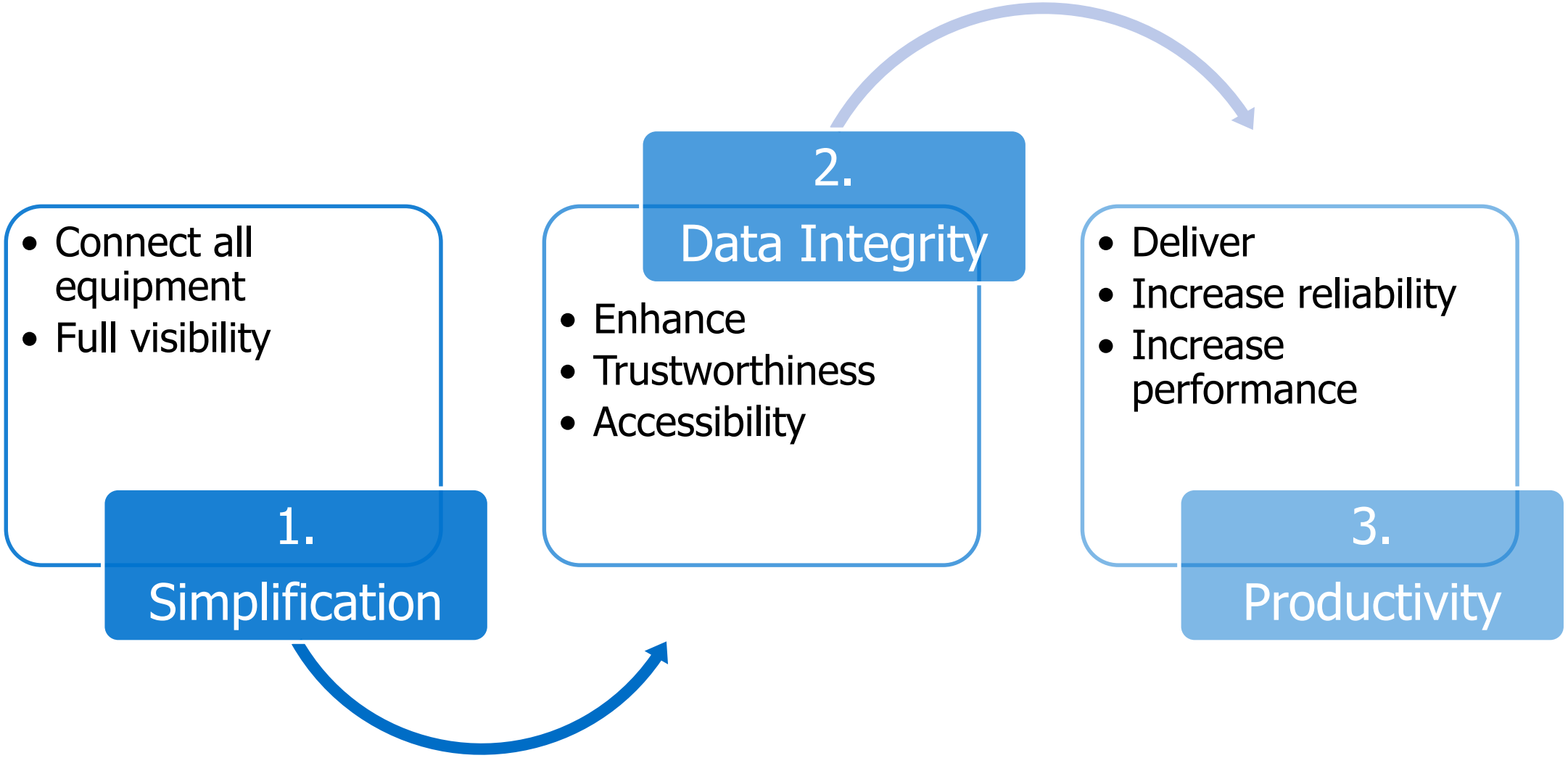
janssen

OSIsoft.

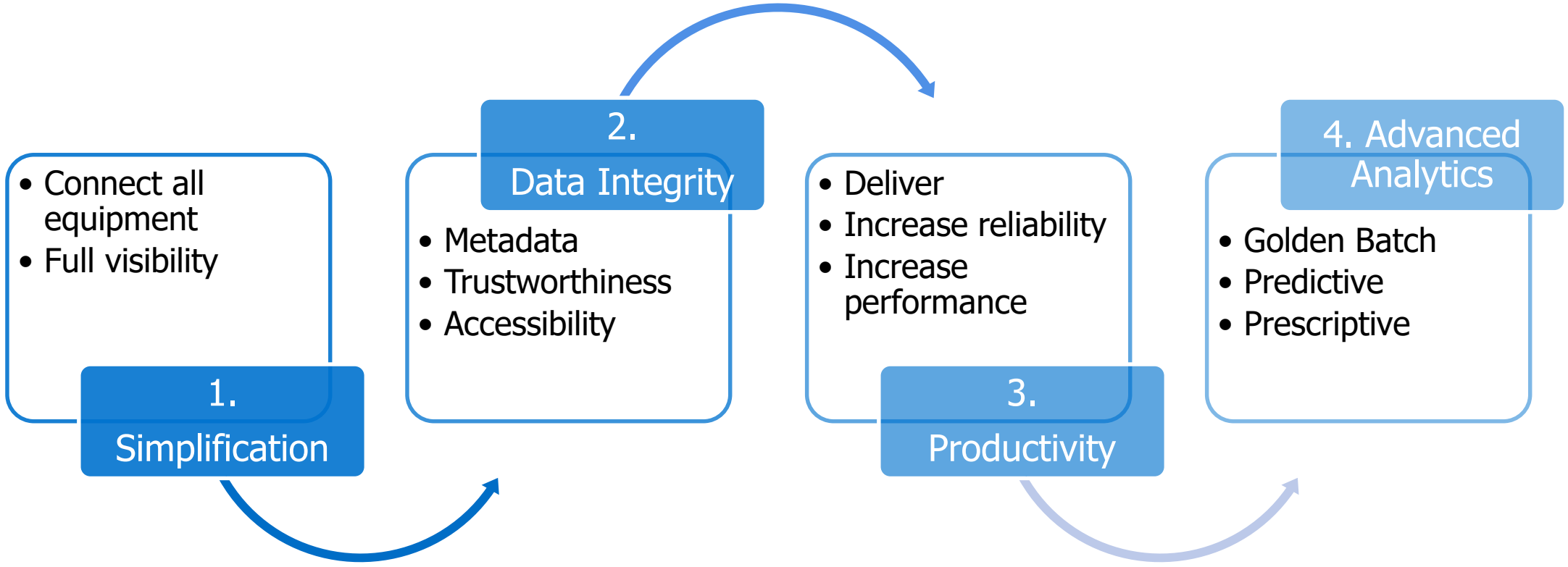
How do we reach there?

Remember it is about the business strategy

From standalone to integrated operation

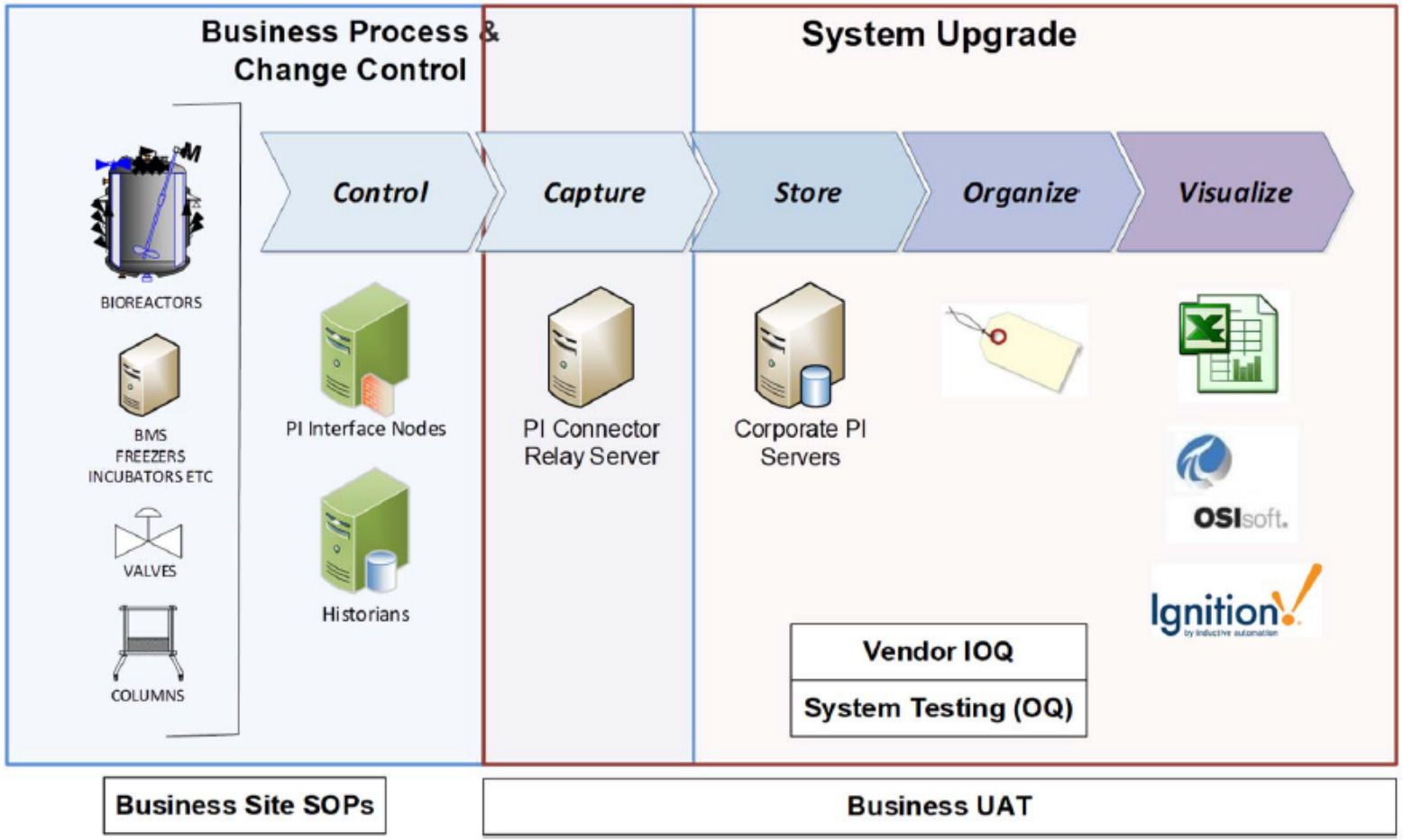


From standalone to integrated operation



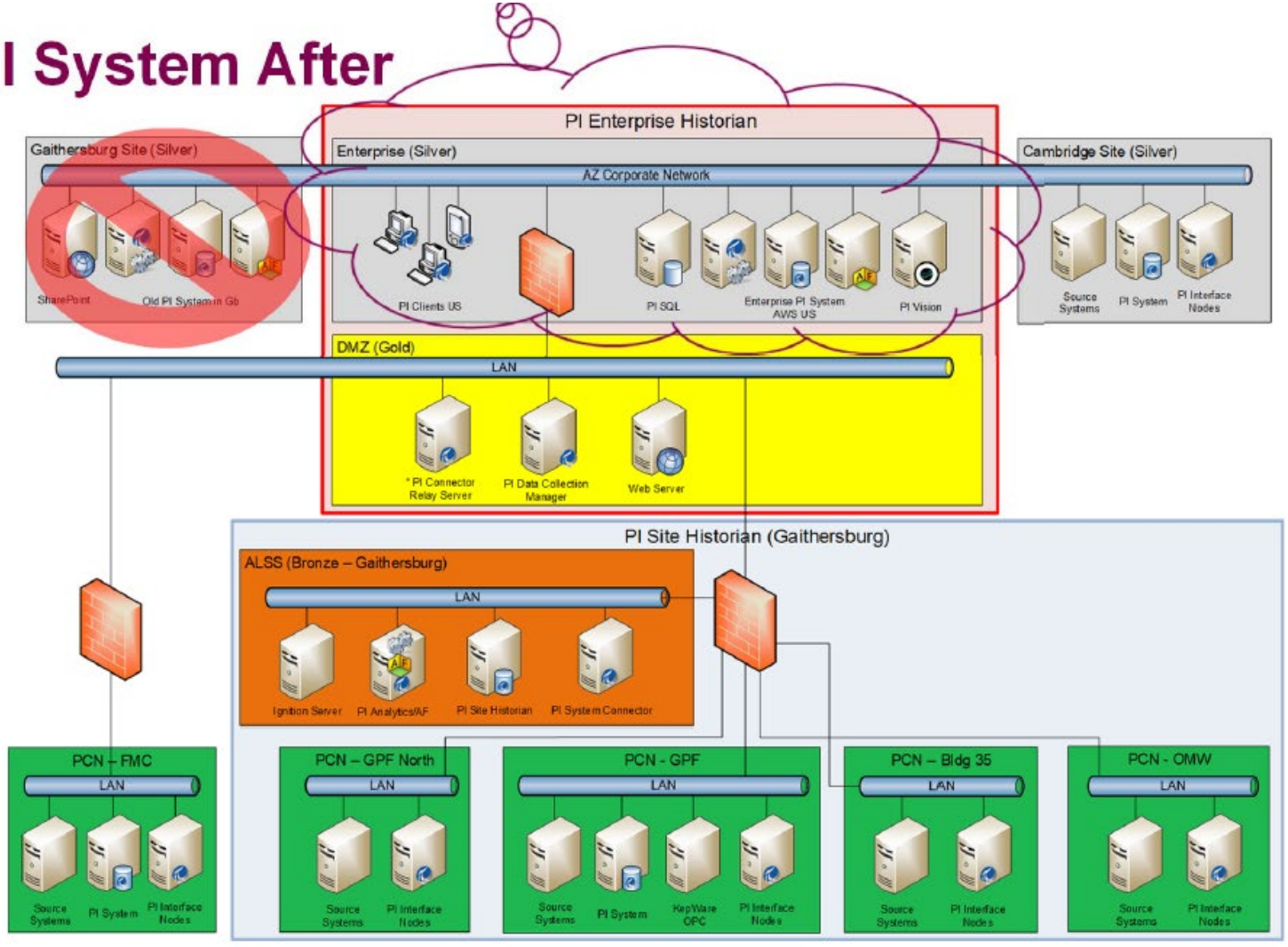
1. Simplification

PI Enterprise Validation Approach



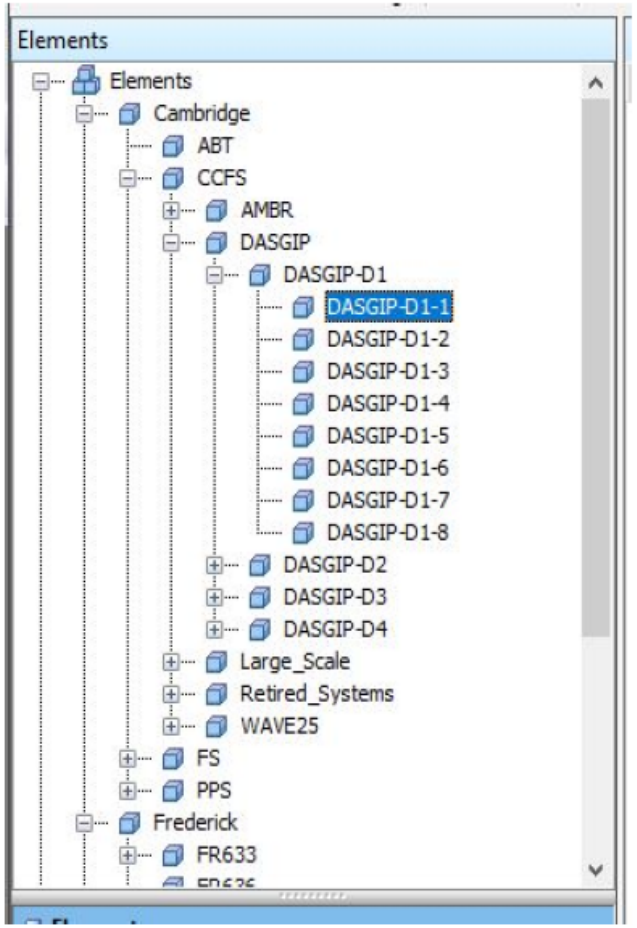
- Focus on the Enterprise Historian NOT the Site

OSI PI System After



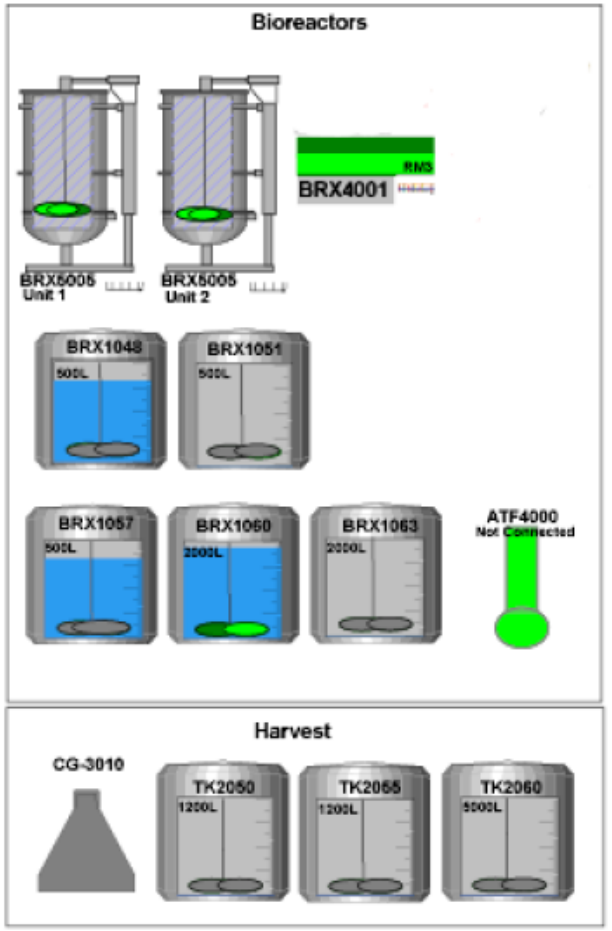
Customer Value – Tags & Assets

- Deployment of new assets with templates
- Standardized navigation for assets allowing users to quickly find instruments and data of interest
- Ability to integrate process data with other asset context
- Alignment with AZ standards for tag naming and architecture



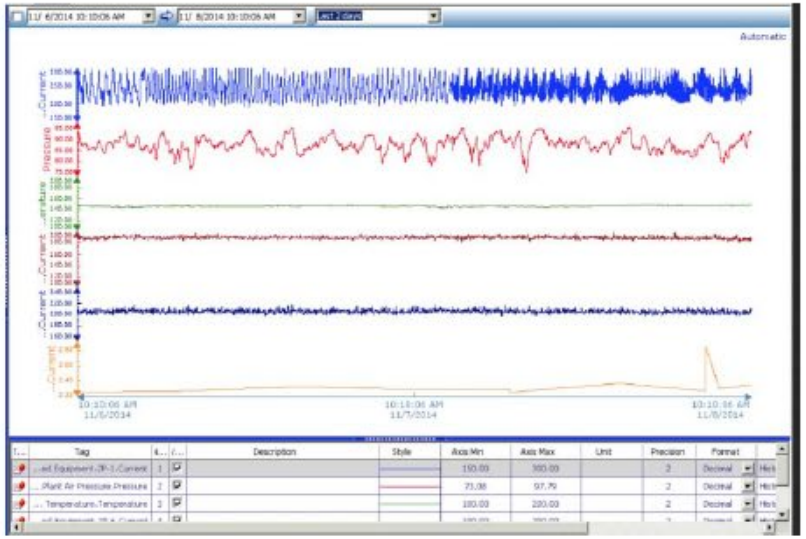
Customer Value – User Interface

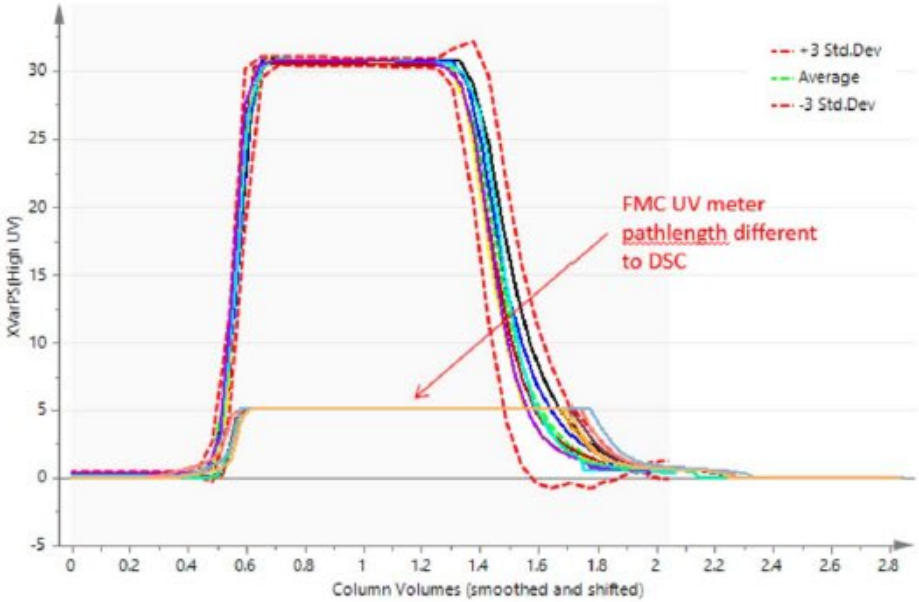
- An enhanced, web-based, user experience
- Increased application stability
- Ad hoc report creation without needing local PC installs, reducing overhead for our support teams and our users
- Improved reporting for GMP equipment
- No interruptions to critical processes in our R&D labs and for pilot plant operations

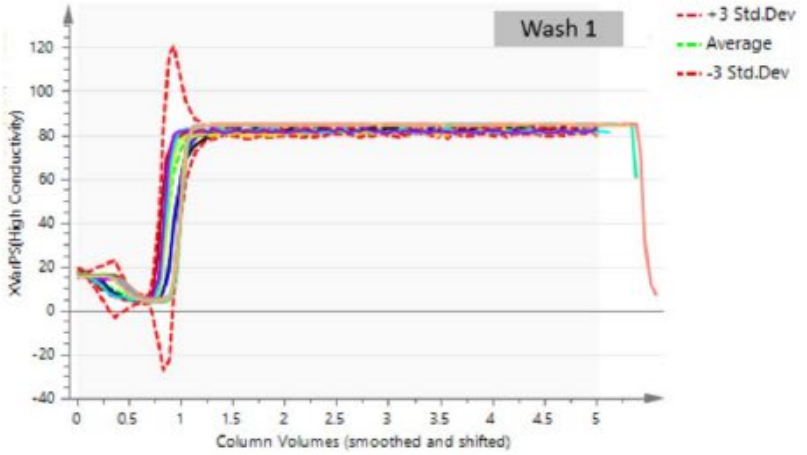


Customer Value – Future

- AWS cloud supports better collaboration across sites
- Capability to determine “Golden Batch”
- Ability to use mobile devices







2. Data Integrity

Validation of a global data mart

GlaxoSmithKline Vaccines

Creating a global PI Solutions Store to Ease Site Deployment and Increase Compliance

CHALLENGE

Align and accelerate OSIsoft PI deployment in parallel on several manufacturing sites

- Several sites implementation to manage in parallel
- Minimize the local efforts for implementation & qualification

SOLUTION

Global qualification approach of OSIsoft tools with pre-qualified and documented modules

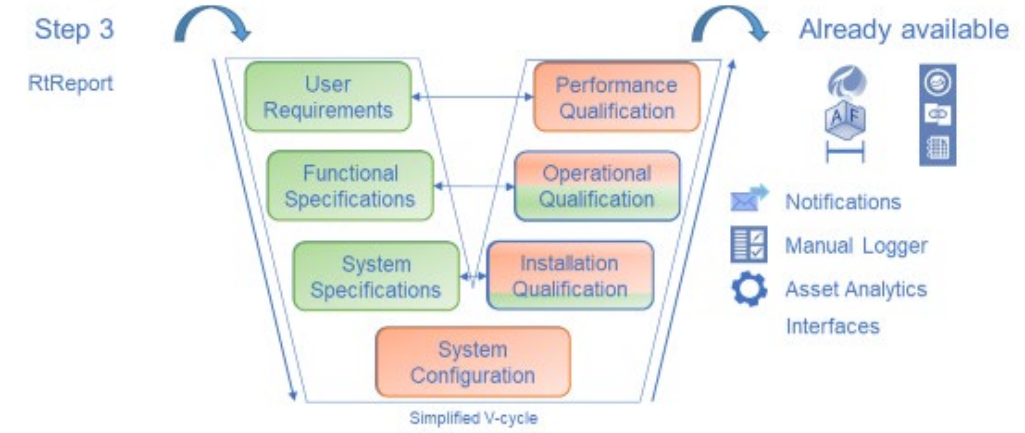
- Strong partnership with OSIsoft (EA) and PAS integrator
- Involvement of local sites in the budget estimate and scope definition

RESULTS

60% reduction of local qualification effort

- Similar approach for other systems: ROI after 5 instances implementation
- Expected to quickly increase the solutions available thanks to the collaborative approach

The infrastructure qualification approach



Solutions

Facilities

- **Maintenance 4.0** — CBM & Predictive
- **Alarms Analytics** — Equipment & PCS
- **EMS Analytics** — Room analytics / HVAC Qualification
- **Deviation Investigation** — Pi-DataLink, Pi-Vision & RT-Reports
- **Energy Analytics**

Equipments (Std objects)

- **Autoclaves**
- **Fermentors**
- **Filling Line**
- **Visual Inspection**

Shared:

- **Reporting** (GMP or not)
- **Digital Dashboard** — Realtime data display
- **Process Analytics**
- **Machine Learning** — OEE, Analytics ...

Data Integrity

Before - Paper

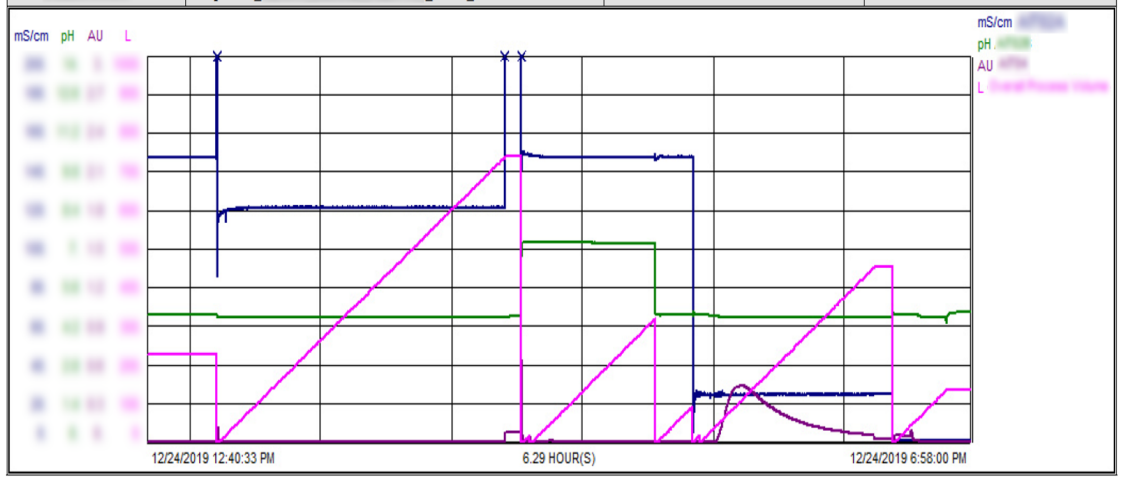
After - RbE

RtReport
PI Historian BiOMARIN

RtReport Template: Chromatography Review-By-Exception **Rev:** 1.0	**Unit ID:**
Batch ID:	**Recipe:** PR_ _PART_2
Start Time: 24Dec19 12:40:33 | **End Time:** 24Dec19 18:58:00	**Exceptions Effective Date:**
No Exceptions	

Overall Recipe Trend -

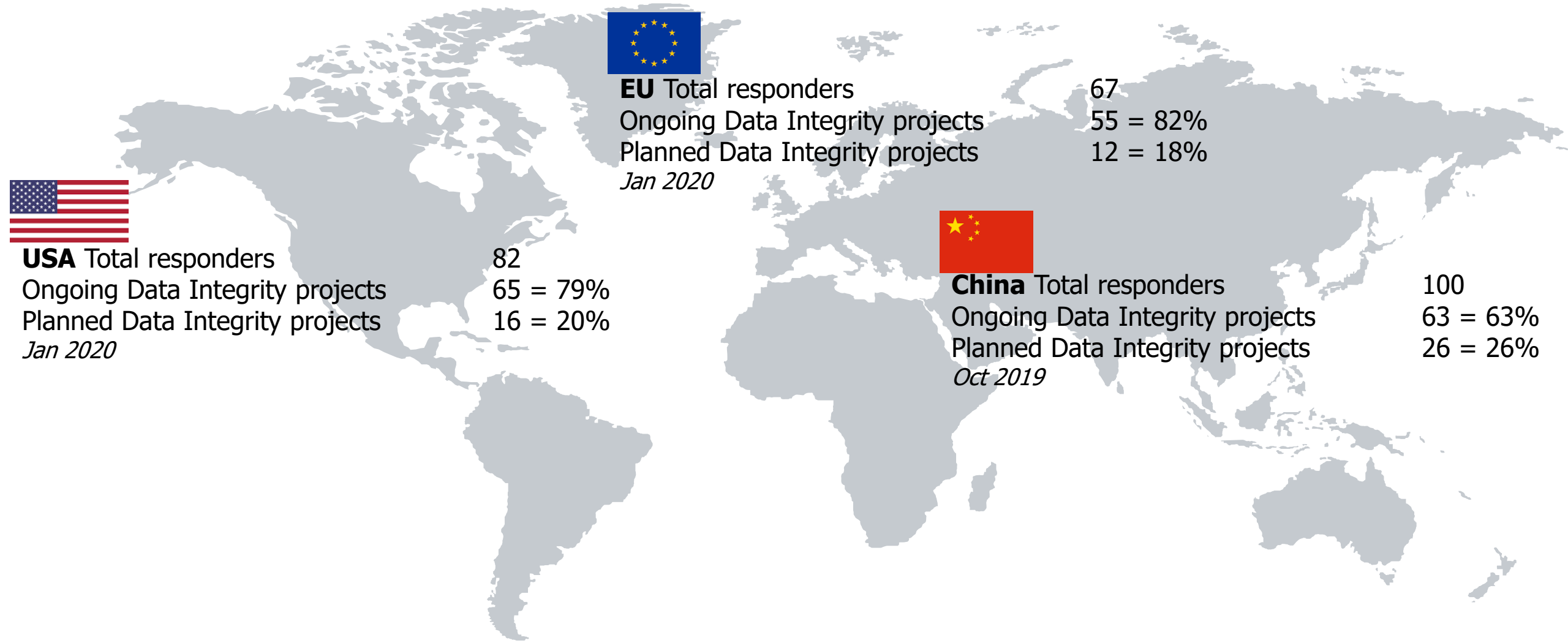
User:	**Recipe:** PR_ _PART_2	**Start Time:** 24Dec19 12:40:33	**End Time:** 24Dec19 18:58:00



Equipment Interventions
No Equipment Interventions

Process Parameter Exception Review
No Process Parameter Exceptions

Data Integrity – a global snapshot



EU Total responders 67
Ongoing Data Integrity projects 55 = 82%
Planned Data Integrity projects 12 = 18%
Jan 2020

USA Total responders 82
Ongoing Data Integrity projects 65 = 79%
Planned Data Integrity projects 16 = 20%
Jan 2020

China Total responders 100
Ongoing Data Integrity projects 63 = 63%
Planned Data Integrity projects 26 = 26%
Oct 2019

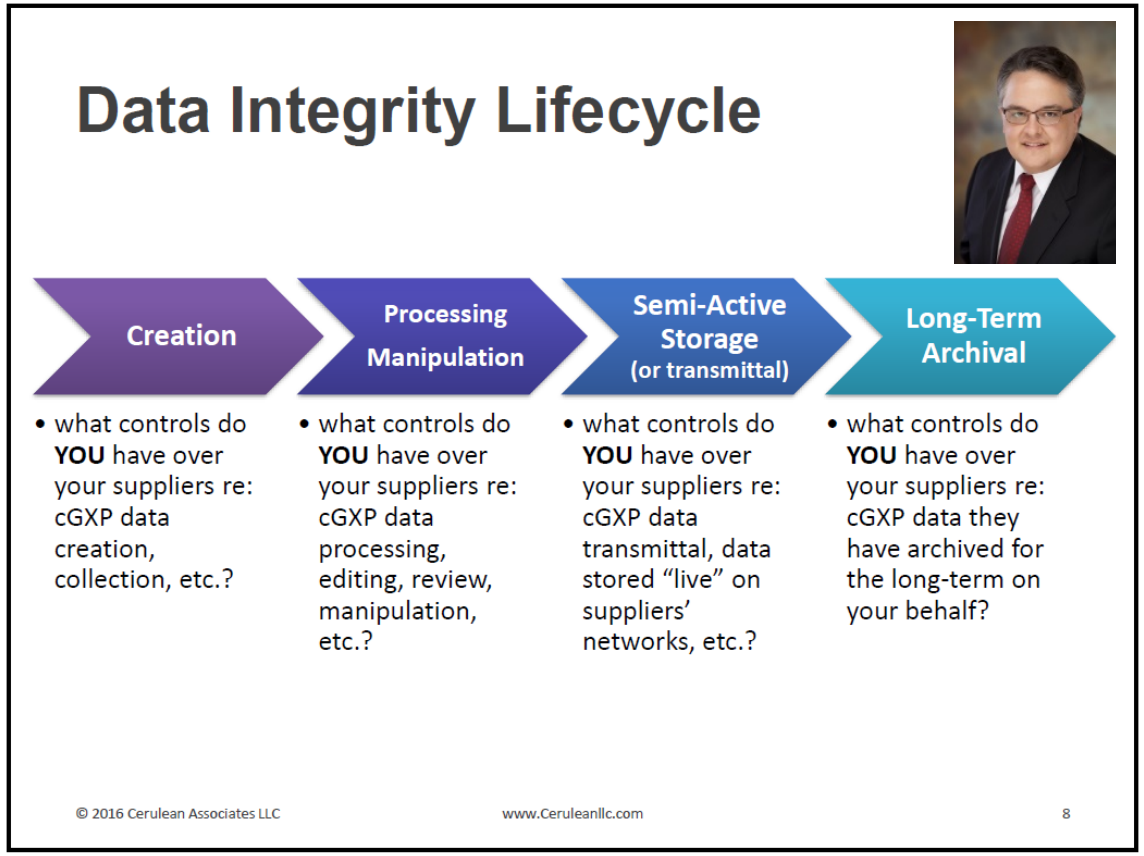
Data Integrity and Contract Organizations (CMO/CDMO)

Carmelo Rosa, Director of FDA OMPQ's

"*Data integrity issues have always existed!*"

Drug makers should not look to contract manufacturers to reduce their responsibility for data accuracy and reliability, Some biopharma companies regard contract testing and production operations as one way to alleviate their involvement in inspections and dealings with regulatory authorities.

Data Integrity issues are a Global problem



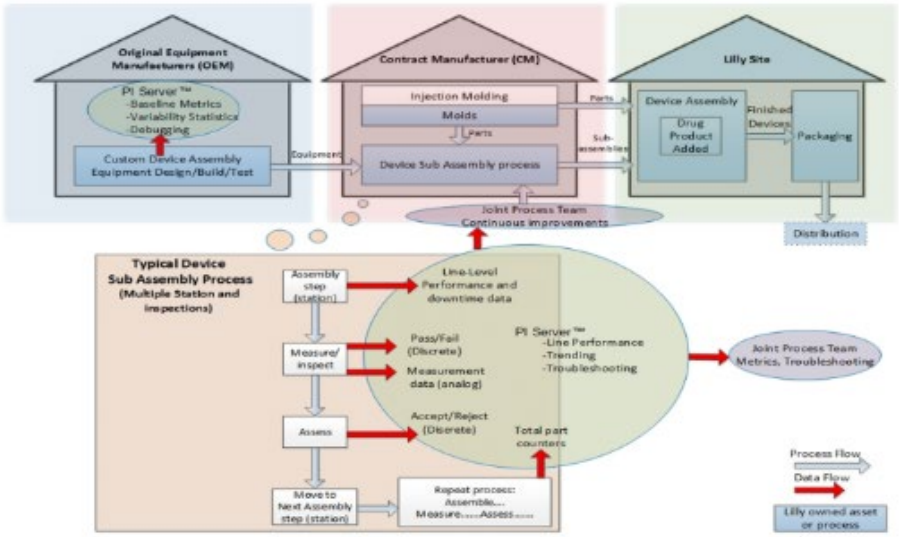
Source: **John Avellanet – CMO Conference www.ceruleanllc.com**

"Every gram we produce is valuable, however the data behind every gram is more valuable" **SVP Lonza**

3. Productivity

Supply chain management and CMO

OEM to CMO to Lilly – Supply Chain



Real-time visualization of the process data in a format that's easy to understand from the CMO.

总结和概览

WuXi Biologics
Global Solution Provider

无锡药明生物技术股份有限公司

PI系统作为智能应用平台用于监控、分析和优化工厂的设备和工艺，提高批次工艺的稳定性，并将逐步应用于全球生产基地。

As an intelligent application platform, the PI system is used to monitor, analyze and optimize plant equipment and processes, improve the stability of batch processes, and will gradually be applied to global production bases.

刘松 自控与信息管理部 执行主任 - Liu Song Executive Director of Automation and Information Management Department

业务挑战

Continuous process data cannot provide batch analysis

The traditional preventive equipment maintenance program cannot reflect the actual operating status of the equipment, and it is easy to cause production losses when the equipment fails

There is no reference case for the construction of process system equipment and equipment model

解决方案

Build batch management of cell culture & purification and liquid preparation system

Use PI's AF and EF to generate event and operation records of equipment in the dosing system

Real-time monitoring of the operating conditions of the equipment in the operating cycle and early warning (including more than **6000** valves, **3000** gaskets, more than **100** pumps and agitators)

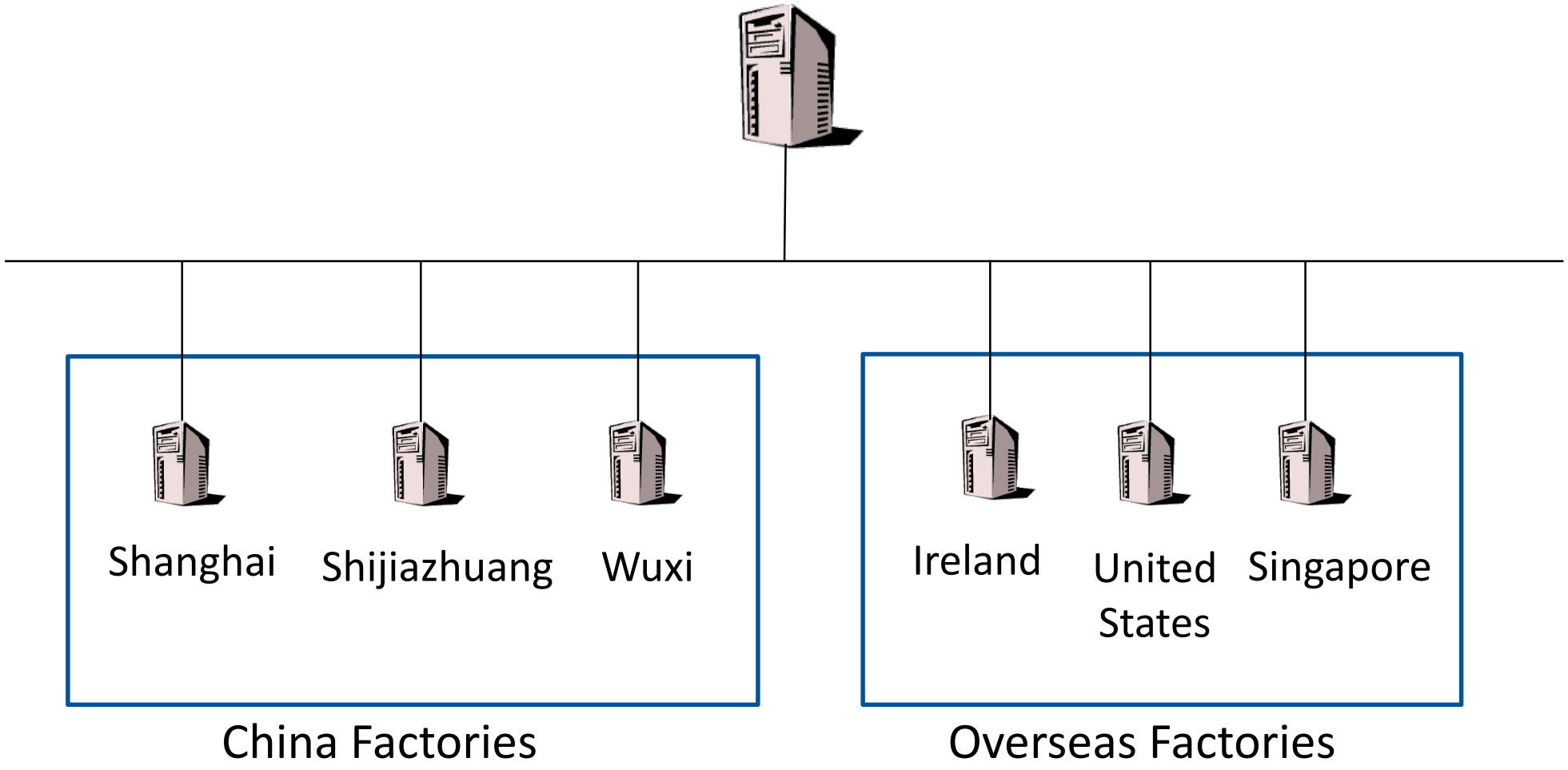
客户成效

Process batch management can better provide process monitoring and deviation warning

Monitor the health factor of equipment in real time and guide equipment maintenance based on early warning to reduce the cost of equipment maintenance

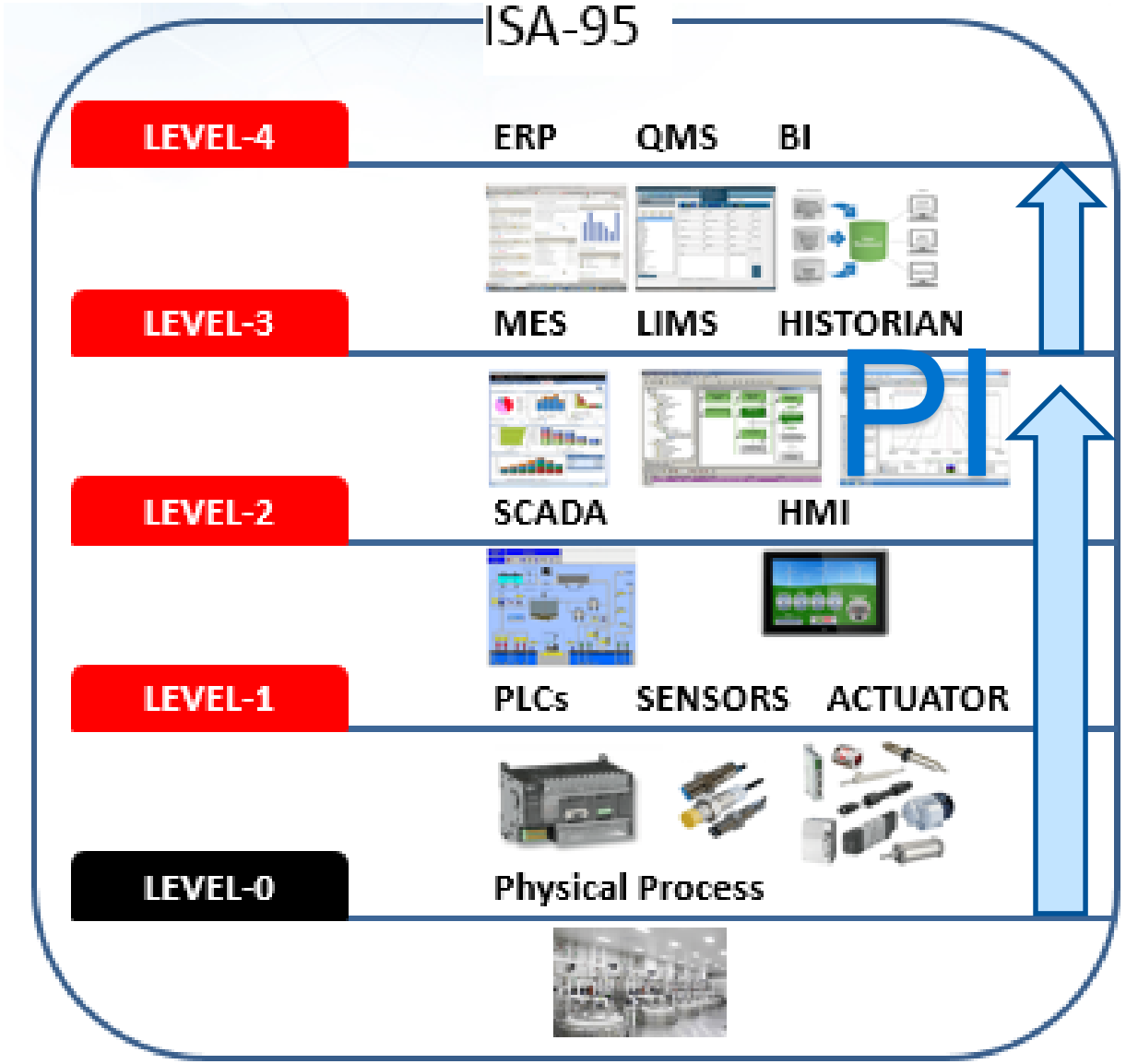
Transform preventive maintenance based on equipment usage to predictive maintenance based on equipment status

PI System
Global Architecture Diagram



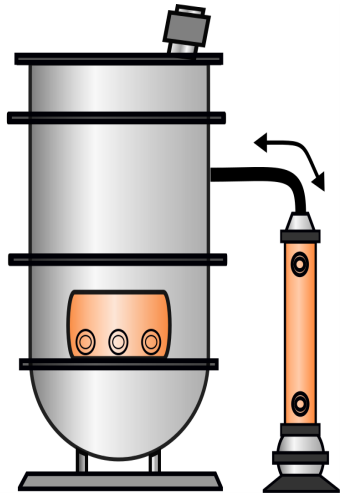
PI 系统策略

- PI system is more than a historian, PI system is more than a reporting tool.
- A production data platform, provide data access, digital management and analysis
- GMP or Non-GMP ?



生物制药工艺: 本质上基于批次过程

Biopharmaceutical process: essentially based on a batch process



Seeding 接种

Seeding N-1 细胞扩增

Production 细胞培养

Harvest 收获

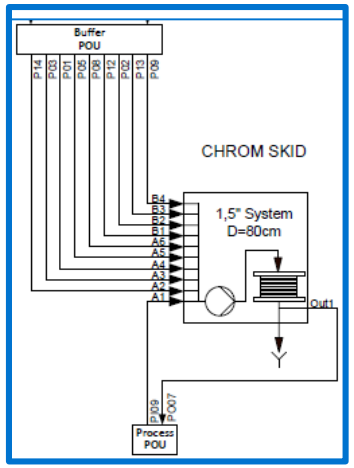
Purification 1 纯化一

Purification 2 纯化二

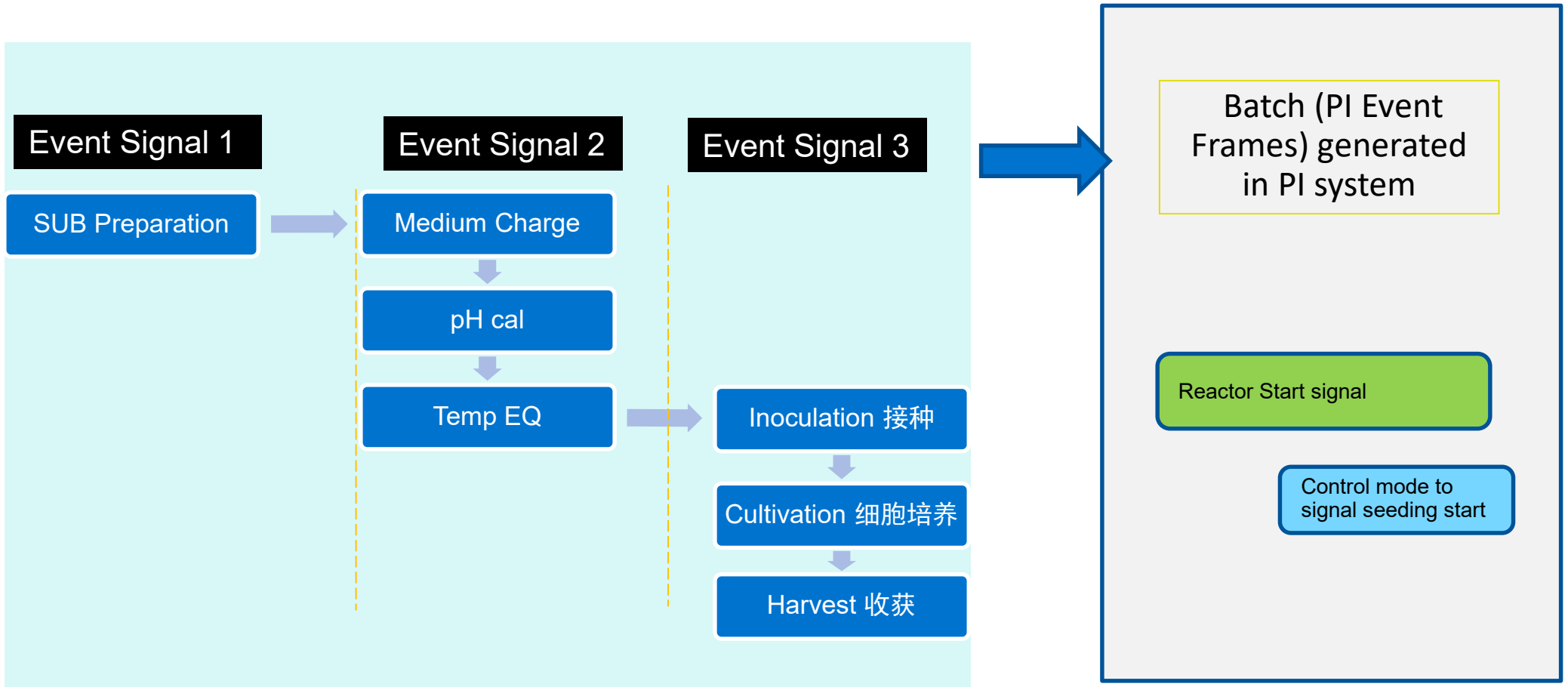
Purification 3 纯化三

Bulk filling 分装

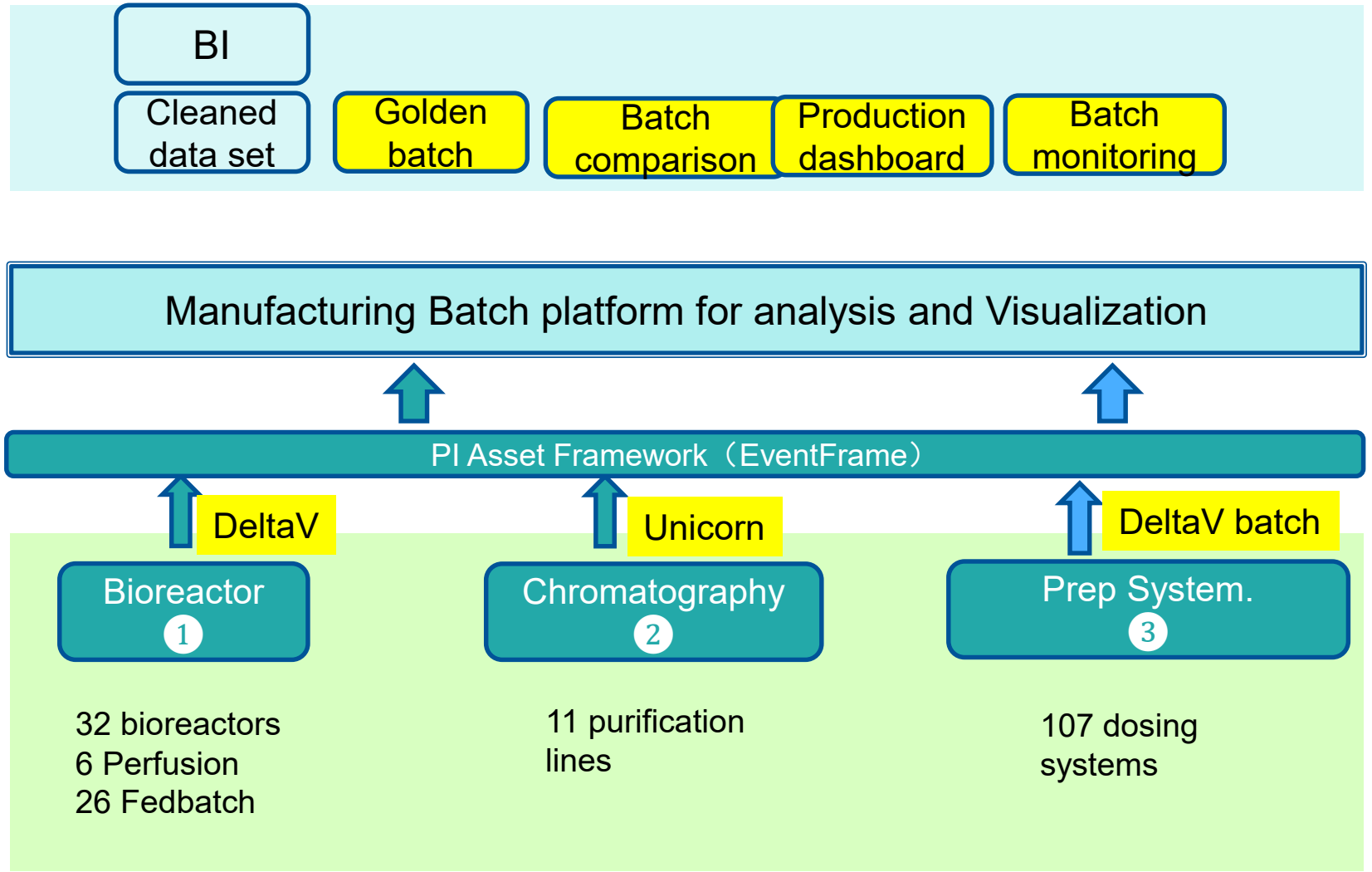
Drug Substance 原液



细胞培养流程的批次化 - Batch cell culture process

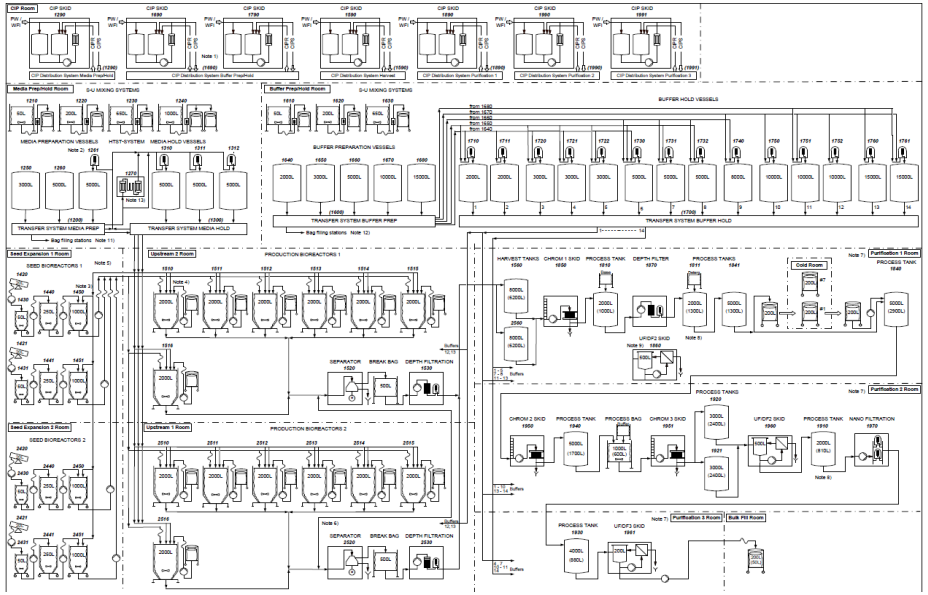


生物制药批次信息数据平台 - Biopharmaceutical batch information data platform



SMART MAINTENANCE

- Traditional: Preventive Maintenance (PM) & Repair
  - PM as defined by GMP SOP, impacting production slot & cost
  - Repair when there is malfunctioning, leading to product loss
- Smart Maintenance: Predictive Maintenance based on utilization and status
  - Early prediction/detection of component failure
  - Reduce deviations caused by malfunctioning between PMs
  - Reduce loss of production slots and cost for maintenance



Super Skids for Biologics Manufacturing

- Vessel Systems
- CIP/ SIP Operations
- Auto valves
- Gasket connections
- PM at fixed time interval

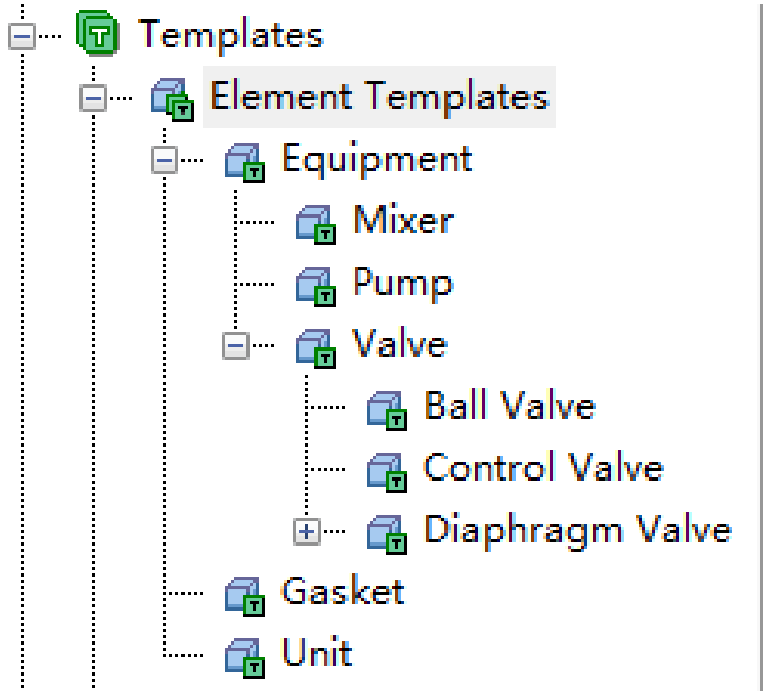
>200 CIP/SIP operations
>6000 automatic valves
>4000 gasket connections

Smart Maintenance System

Five steps to build smart data application

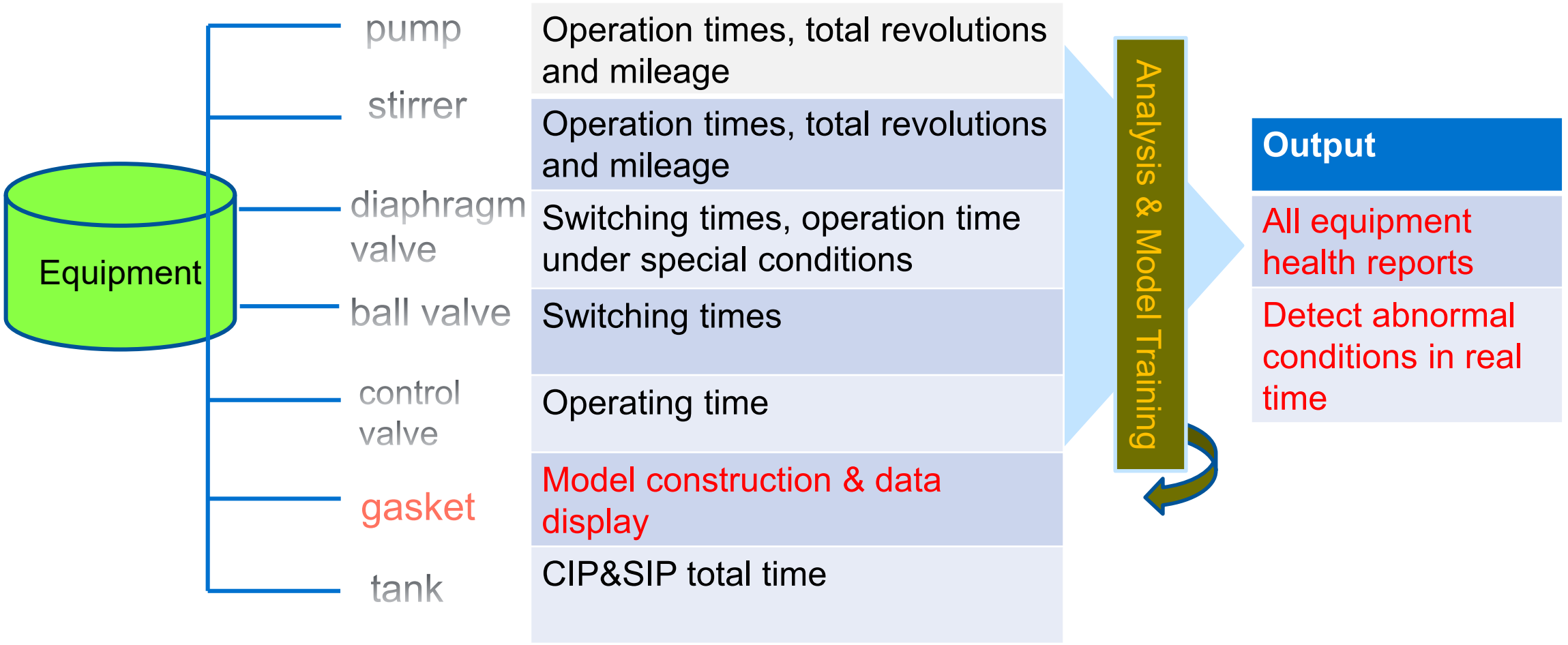
- PI System as the infrastructure
- PI AF is used to structure the plant's equipment assets
- The usage of each equipment component can be tracked according to different operating conditions

Equipment model built by PI AF



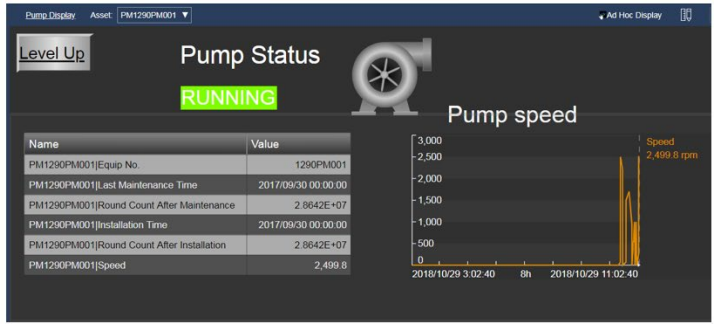
Smart Maintenance System

Based on the operating status of the equipment in the operating cycle



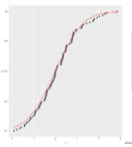
Smart Maintenance Dashboard

- When was it installed?
- When was its last maintenance?
- Round Count – “the mileage”
- Operation counts – “Stop/go”
- Speed profile



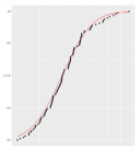
- ❖ Alert is generated when CHI exceeds set limit, calling for maintenance
- ❖ Alert is listed up based on its criticality
- ❖ Alert disappears when maintenance is performed
- ❖ The system now is in test bed for real world data

- Operation Count
- Round Count – “mileage”

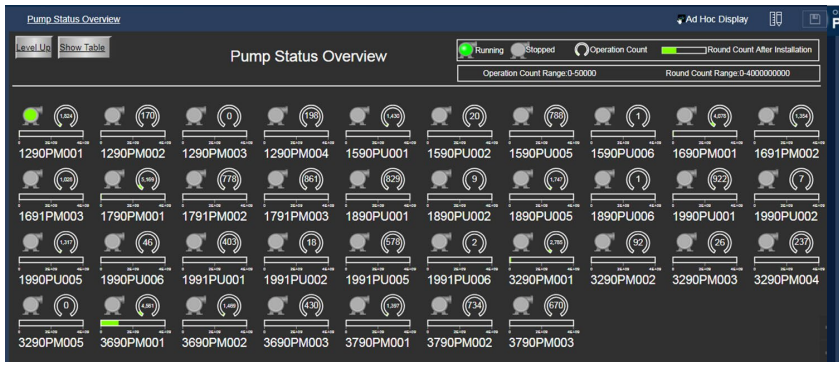


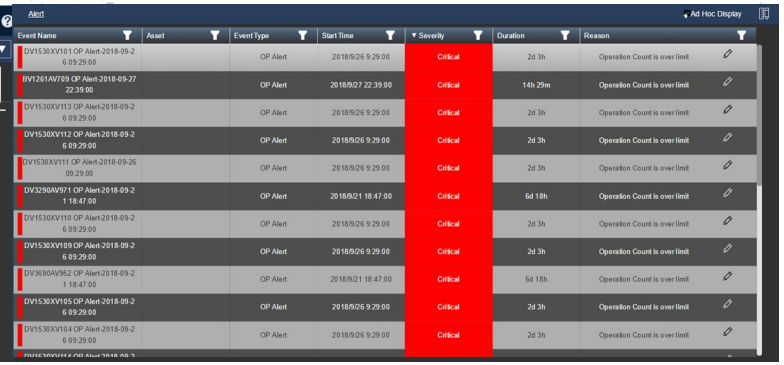
Aggregated Component Health Index (CHI)

- Operation Count
- High Temp Exposure Time



Aggregated Component Health Index (CHI)





Achieved

- Batch process data platform to realize real-time data analysis and deviation warning
- Smart maintenance system, monitor the health coefficient of key components of liquid dispensing system in real time and guide equipment maintenance based on early warning
- Asset structures and data models can be seamlessly applied to global factories

Next step…

- Aiming at the current smart maintenance system, to introduce AI tools (machine learning, model training) such as SIMCA, R and MATLAB
- Model trial and data verification to optimize the maintenance process
- Promote Wuxi's PI System to global production bases

The largest user community for operations data in Life Sciences?

850+ members, 250+ organizations

www.pisquare.osisoft.com/groups/life-sciences

Steering Commitee

- Biogen
- Lilly
- Genentech
- Roche
- Regeneron
- BioMarin
- DRL
- Novo Nordisk

Faster and More Reliable Operations: A FUJIFILM Diosynth Biotechnologies' Case Study

Challenge

Being able to review and verify process performance is a key step in biopharmaceutical manufacturing. However, traditional chromatography review, like visually reviewing elution peaks, was a **time-consuming, error prone, and paper-intensive** process.

Solution

Paring Sartorius Data Analytics tools with OSIsoft PI technology FUJIFILM Diosynth Biotechnologies developed a new digital chromatogram dashboard for **enhanced chromatography review.**

Benefits

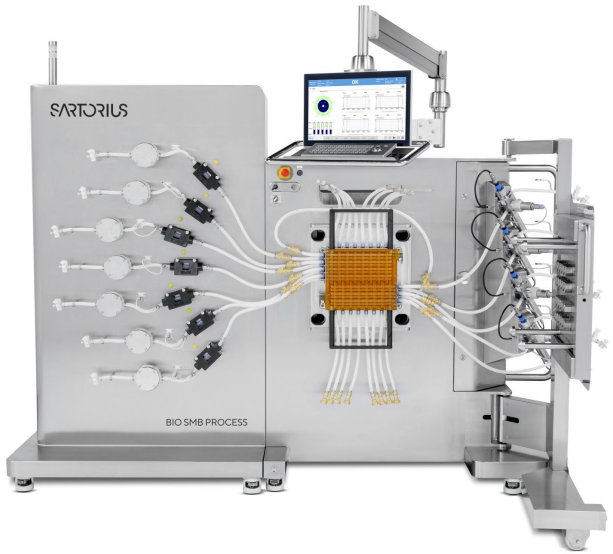
Shorter review times, resource expenditure **optimized** tenfold, paper footprint **reduced** by ~10,000 sheets/year, **on demand data** accessibility, and **increased partner trust** and collaboration opportunities.

Using Data Analytics to Overcome Chromatography Review Challenges

Traditional chromatography process monitoring, like visually reviewing elution peaks, is time consuming, error-prone, and not fit for continuous bioprocessing.

Multivariate data analytics tools like SIMCA® and SIMCA®-online enhance chromatography monitoring and review by detecting small deviations in peak shapes before traditional methods can.

- Monitor process consistency
- Identify process failures and other trends before they become problematic
- Easily detect and correct column, cycle, or batch deviations
- Expedite chromatography release process - bringing you one step closer to RTRT



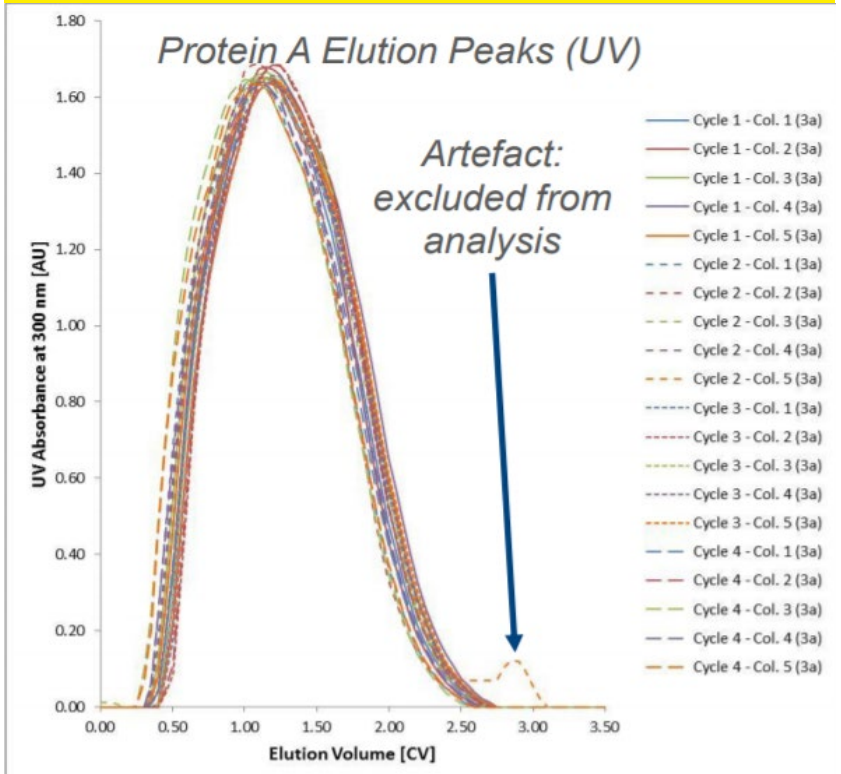
BIOSMB Process 80/350

Single-Use Continuous Chromatography Systems For Perfusion and Batch Bioreactor-based Processes

Identify Column-to-Column Variations

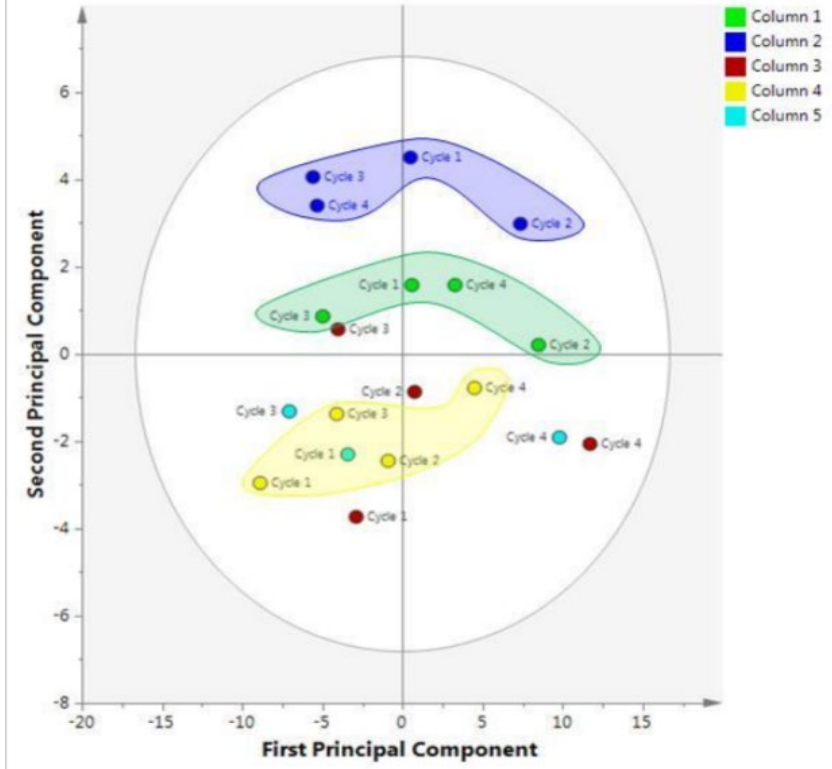
Boehringer Ingelheim

Traditional Univariate Analysis



Significant Variations Difficult to Detect

Multivariate Analysis



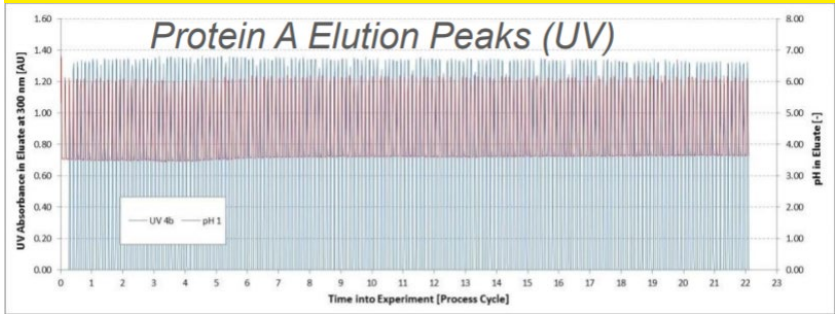
Column-to-column variations Easy to Detect

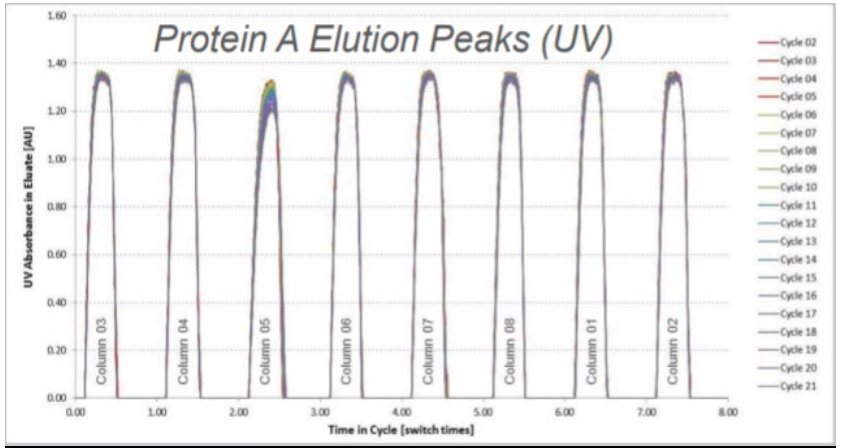
Source: Capturing the Value of Continuous Chromatography, Umetrics User Meeting 2015, Pall Life Sciences, Marc Bisschops
Data Generated at Boehringer Ingelheim Fremont, CA

SARTORIUS

Identify Column Malfunctioning

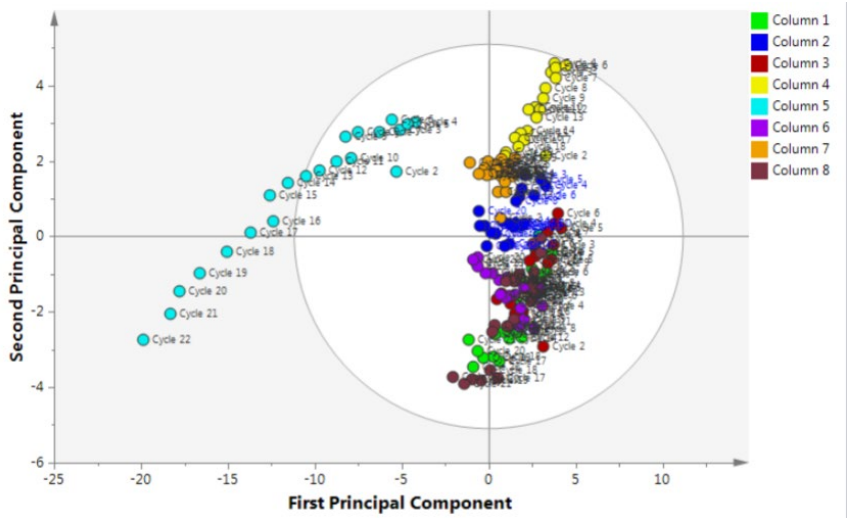
Traditional Univariate Analysis





Cycle-to-cycle overlay shows some effect in column 5

Multivariate Analysis



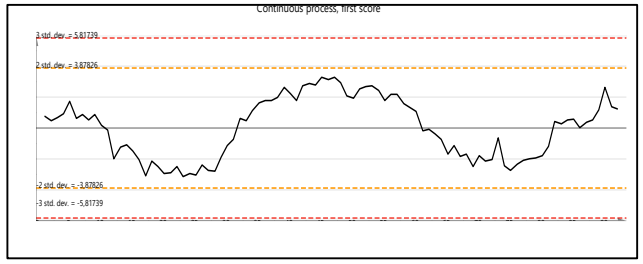
Performance decay in column 5 clearly indicate. Investigation revealed inadequate cleaning conditions.

Source: Capturing the Value of Continuous Chromatography, Umetrics User Meeting 2015, Pall Life Sciences, Marc Bisschops
Data Generated at Sanofi-Aventis Hoechst, Germany

Implementing Model Based Batch Review

1. Model Building: Trained Model Builder Collects Historical Data (IPC, Analytical, Raw Material) and Builds Model with SIMCA®

4. Monitor Incoming Batches: SIMCA®-online applies MVDA in real-time for monitoring new batches



t[1] = x1*Temperature + x2*Pressure + x3*Speed + x4*pH + ...

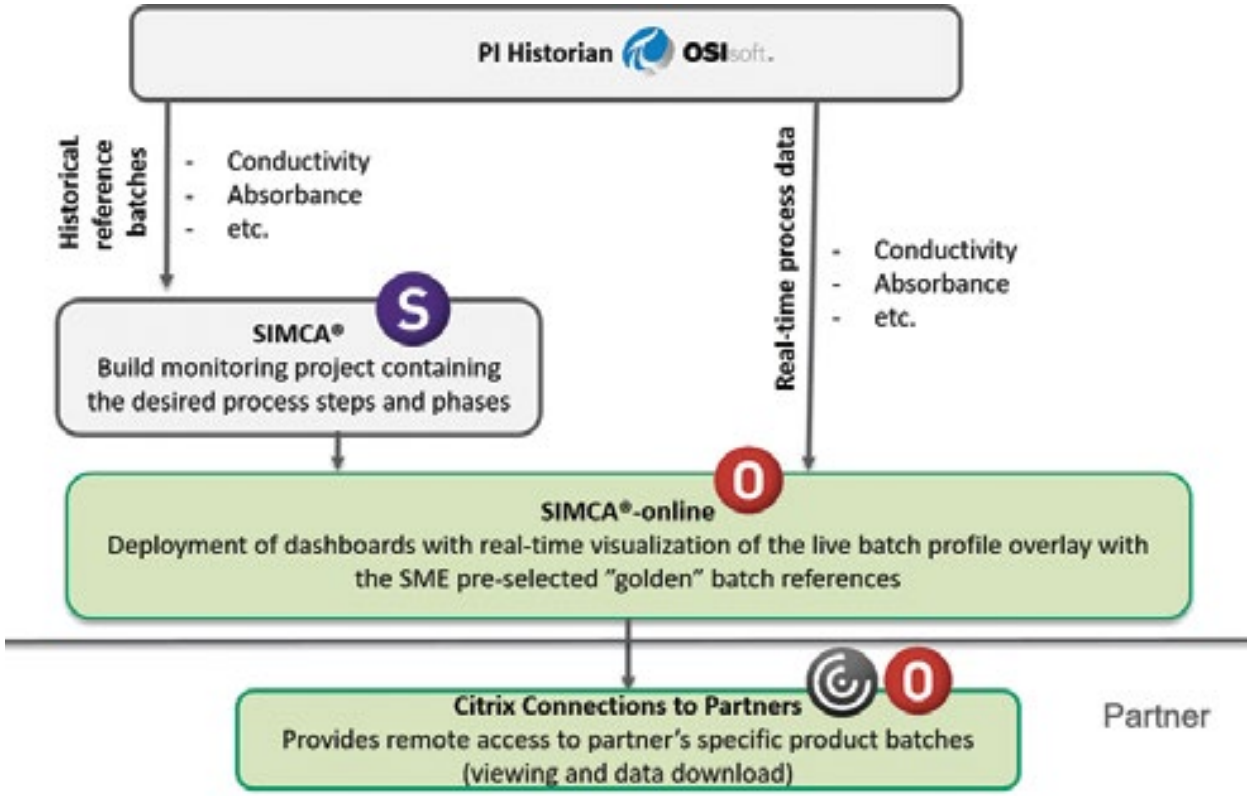
2. MVDA Compression: Large datasets compressed into smaller latent variables allows for a simpler representation

5. Real-time Quality Assurance: Trends are viewed live on plant floor or from control room

3. Connecting Data Sources: In order to enable real-time monitoring the model is connected to the original data sources

6. Immediate Risk Mitigation: alarms highlight process deviations and allowing for fault faster reaction

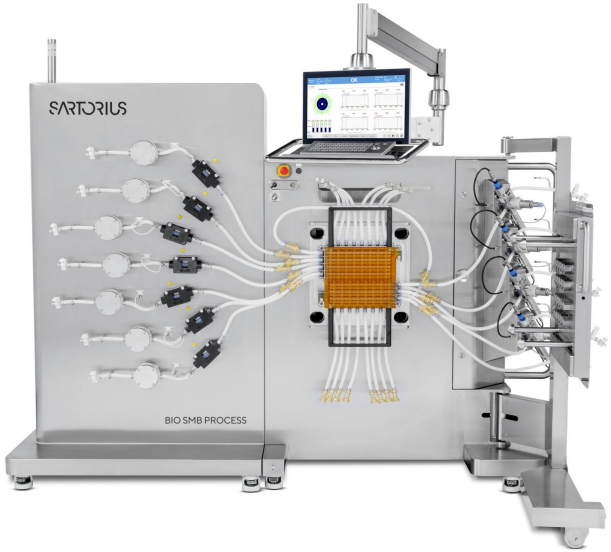
System Set-up: A FUJIFILM Diosynth Biotechnologies' Case Study



- Historical data stored in the OSI PI system were used as reference batches and to build the digital chromatogram project
- During production, data ingested from the manufacturing SCADA system to OSI PI system were transmitted to SIMCA®-online through a SimAPI at real-time frequency
- The visualization dashboard were then made available to operators, quality assurance personnel reviews, and the partner

Improving Partner Data Visibility

CDMO Process



Real-time Process Window and Data Download

Partner

Benefits Realized: A FUJIFILM Diosynth Biotechnologies' Case Study

- **Shorter** review times → Accelerated Delivery
- Resource expenditure **optimized** tenfold → COGs Optimization
- Paper footprint **reduced** by ~10,000 sheets/year → Positive Environmental Impact
- **On demand** data accessibility → Improved Process Traceability
- **Increased** partner trust and collaboration opportunities → Increased Reliability

CDMOs are Putting a Greater Importance on Data and Data Analytics

"Data integrity deficiencies are cited in **65% of *all* FDA warning letters"**[1]

Consequently this has put pressure on CDMOs to implement data management systems that provide **transparency, preserve customer confidentiality,** and meet **regulatory guidelines**

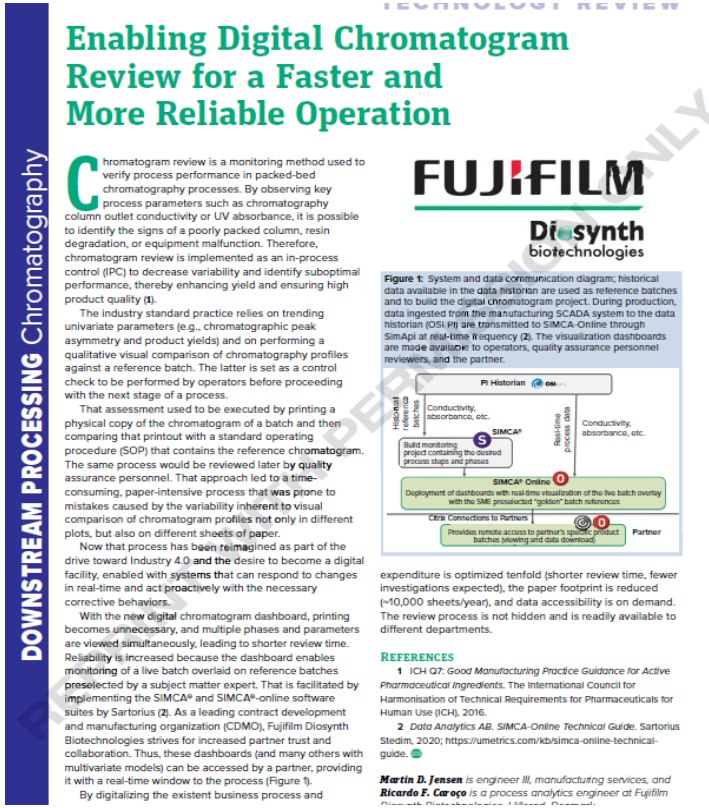
CDMOs have realized the **additional value opportunity** that comes with adopting data management systems along with data analytics tools and have transformed these new technologies into **service offerings**

1: "An Analysis Of FDA FY2017 Drug GMP Warning Letters", B. Unger, Unger Consulting, Pharmaceutical Online (2018)

Acknowledgements and References

Thanks to **Martin D. Jensen** and **Ricardo F. Caroço** from FUJIFILM Diosynth Biotechnologies in Hillerød, Denmark

Enabling Digital Chromatogram Review for a Faster and More Reliable Operation, M. Jensen, R. Caroço , *Bioprocess International,* Industry Innovators, pg. 30, 2020-2021



DOWNSTREAM PROCESSING Chromatography

Enabling Digital Chromatogram Review for a Faster and More Reliable Operation

Chromatogram review is a monitoring method used to verify process performance in packed-bed chromatography processes. By observing key process parameters such as chromatography column outlet conductivity or UV absorbance, it is possible to identify the signs of a poorly packed column, resin degradation, or equipment malfunction. Therefore, chromatogram review is implemented as an in-process control (IPC) to decrease variability and identify suboptimal performance, thereby enhancing yield and ensuring high product quality (1).

The industry standard practice relies on trending univariate parameters (e.g., chromatographic peak asymmetry and product yields) and on performing a qualitative visual comparison of chromatography profiles against a reference batch. The latter is set as a control check to be performed by operators before proceeding with the next stage of a process.

That assessment used to be executed by printing a physical copy of the chromatogram of a batch and then comparing that printout with a standard operating procedure (SOP) that contains the reference chromatogram. The same process would be reviewed later by quality assurance personnel. That approach led to a time-consuming, paper-intensive process that was prone to mistakes caused by the variability inherent to visual comparison of chromatogram profiles not only in different plots, but also on different sheets of paper.

Now that process has been reimagined as part of the drive toward Industry 4.0 and the desire to become a digital facility, enabled with systems that can respond to changes in real-time and act proactively with the necessary corrective behaviors.

With the new digital chromatogram dashboard, printing becomes unnecessary, and multiple phases and parameters are viewed simultaneously, leading to shorter review time. Reliability is increased because the dashboard enables monitoring of a live batch overlaid on reference batches preselected by a subject matter expert. That is facilitated by implementing the SIMCA® and SIMCA®-online software suites by Sartorius (2). As a leading contract development and manufacturing organization (CDMO), Fujifilm Diosynth Biotechnologies strives for increased partner trust and collaboration. Thus, these dashboards (and many others with multivariate models) can be accessed by a partner, providing it with a real-time window to the process (Figure 1).

By digitalizing the existent business process and

FUJIFILM Diosynth biotechnologies

Figure 1: System and data communication diagram; historical data available in the data historian are used as reference batches and to build the digital chromatogram project. During production, data ingested from the manufacturing SCADA system to the data historian (OSI-PI) are transmitted to SIMCA-Online through SimApi at real-time frequency (2). The visualization dashboards are made available to operators, quality assurance personnel reviewers, and the partner.

expenditure is optimized tenfold (shorter review time, fewer investigations expected), the paper footprint is reduced (~10,000 sheets/year), and data accessibility is on demand. The review process is not hidden and is readily available to different departments.

REFERENCES

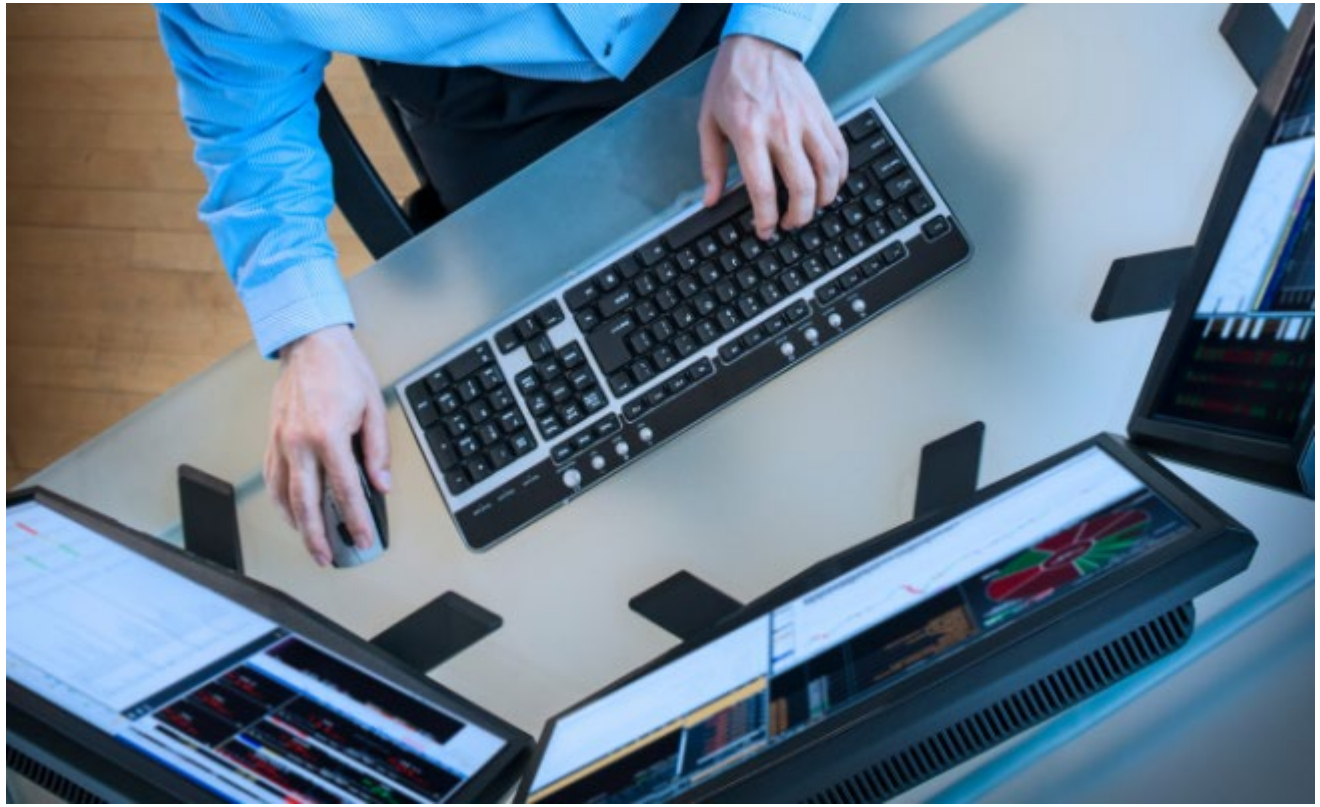
1 ICH Q7: *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2016.

2 *Data Analytics AB. SIMCA-Online Technical Guide*. Sartorius Stedim, 2020; https://umetrics.com/kb/simca-online-technical-guide.

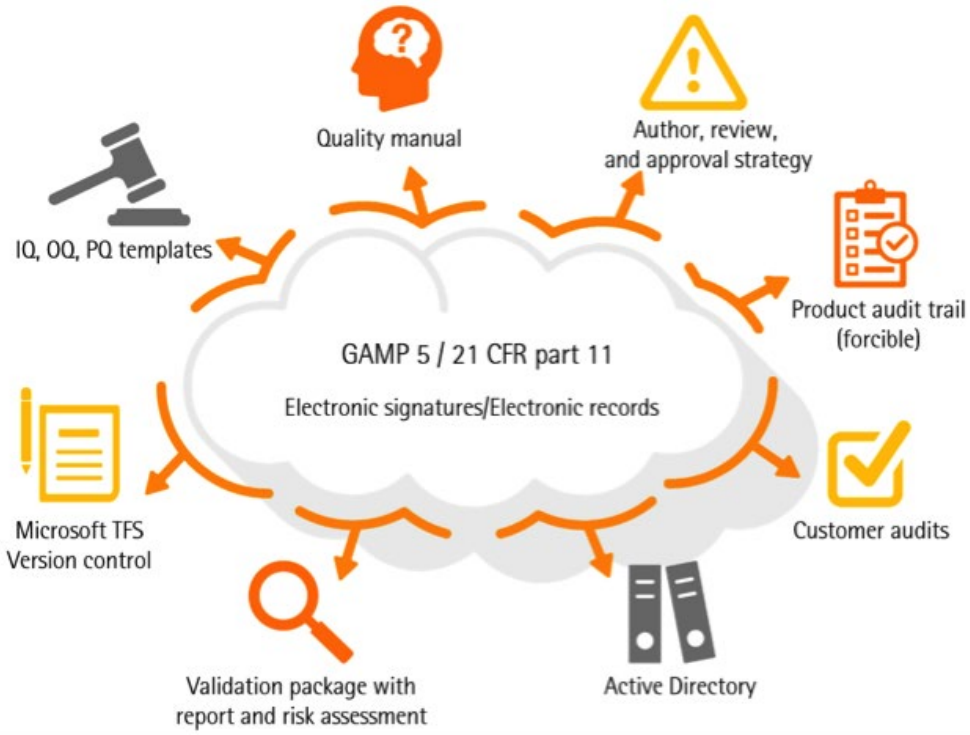
Martin D. Jensen *is engineer III, manufacturing services, and* ***Ricardo F. Caroço*** *is a process analytics engineer at Fujifilm*

Enabling Digital Chromatogram Review and More Reliable Operation

Interested in Reading More about Data Integrity?



How to ensure data integrity and compliance of your data analytics systems, Erik Renberg (2018)



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