Next Generation Biologics Manufacturing: Delivering the Vision

Presented by
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The driver behind Biogen's Next Generation Manufacturing

Alzheimer's Disease

5.3 million people in the US, and *25 million* world-wide live with Alzheimer's

Alzheimer's is the *6th leading* cause of death in the US

http://alz.org

Aducanumab Phase 1b Results

"*Aducanumab demonstrated an acceptable safety profile and patients treated with aducanumab experienced a dose- and time-dependent, statistically significant reduction of brain amyloid plaque, which is believed to play a key role in the development of the symptoms of Alzheimer's disease. Additionally, a dose-dependent, statistically significant effect of slowing clinical decline was observed in the aducanumab study arms.*"

http://for.tn/1QkEiAQ

Biogen's Next Generation Manufacturing

The Next Generation Manufacturing will be the intersection point and realization of key Biogen initiatives that have been developing over the past several years:

Initiatives

- **3X Technology**
- **Next Generation Automation**
- **Real-time Release**
- **Enhanced Process Control / PAT**
- Integrated work teams
- Repeatability via Bio-Manufacturing Cell
- **Through-put analysis**
- Sustainability

Guiding Principles

- Process / Process equipment is the critical path – Not support equipment
- **Real time data** availability that enables product impact decisions to be made on the floor
- The NGM facility should **produce drug substance (DS) at 1/5 the cost** of our other facilities
- Ensure **repeatability, dependability** for delivering to our patients (*Bio-Manufacturing Cell Concept*)
- Ensure site atmosphere is an enjoyable place to work – lockers, natural light in process area, collaboration space on the floor, lab space on the floor
- **Minimize Manpower for material flow**

Biogen's Next-Generation Facility

- Under construction in Solothurn, Switzerland
- Start of production in 2019
- Bio-Manufacturing Cells (BMC)
  - Initial: 2 BMCs, ~10 Metric Tons
  - Expandable to 35 Metric Tons
- 3X platform – up to 15 g/L CC titer
- 55,000 m^2 in Phase 1
- Integrated Execution Systems

Reaching 1 Million Patients by 2020

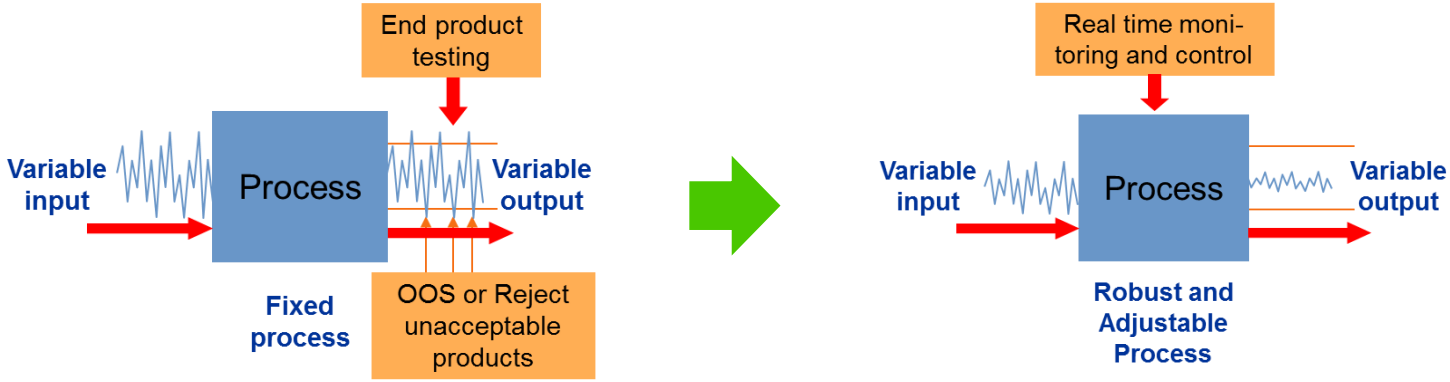
"Act as if a million patients are counting on us to perform today. Because they are!"

Every day *and* ***every batch*** *counts!*

Limitations in legacy manufacturing
Output of manufacturing process per unit time
Requirement to wait for testing and to react to process variation
Manual transfer of information between systems, waiting for batch release

Driving the process via Reliable and Consistent Control

Strategic Intent: Well understood and controlled process to drive Robustness & Consistency, Improved Efficiency, and Real-time Quality



Legacy Bio Manufacturing Process

Next Generation Manufacturing

Enhancing Controls to reduce variability and improve performance

Raw Material Control

- Achieve prospective Raw Material control through Raw Material screening and genealogy
- Minimize internal Raw Material testing using Rapid ID and electronic data exchange.

Process Control

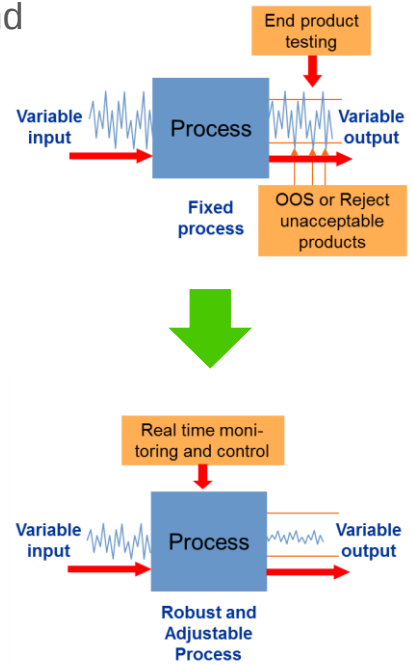
- Bioreactor controlled through inline instruments, sampling for process control eliminated
- Adaptive process control levers developed (e.g. HMW FF control)
- Plant floor and lab execution by recipe (S88)

Quality Control

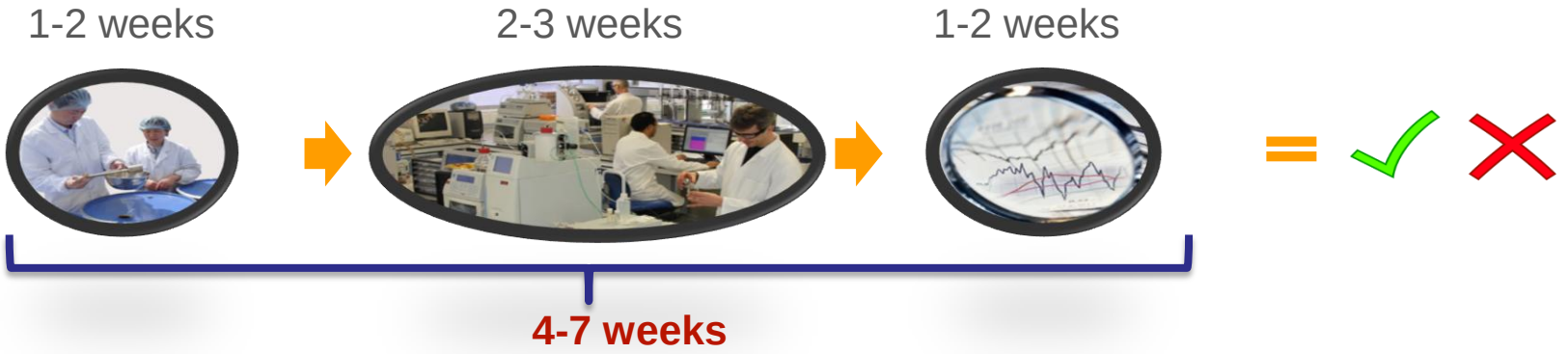
- “Right time release” to ensure testing is not rate limiting
- Testing completed as early in the process as possible

Models

- Models for PQ prediction and consistency assessment wherever feasible
- Model capabilities grow and evolve as additional experience is gained
- Leverage established ASTM guidance and previous BIIB experience for model implementation and LCM



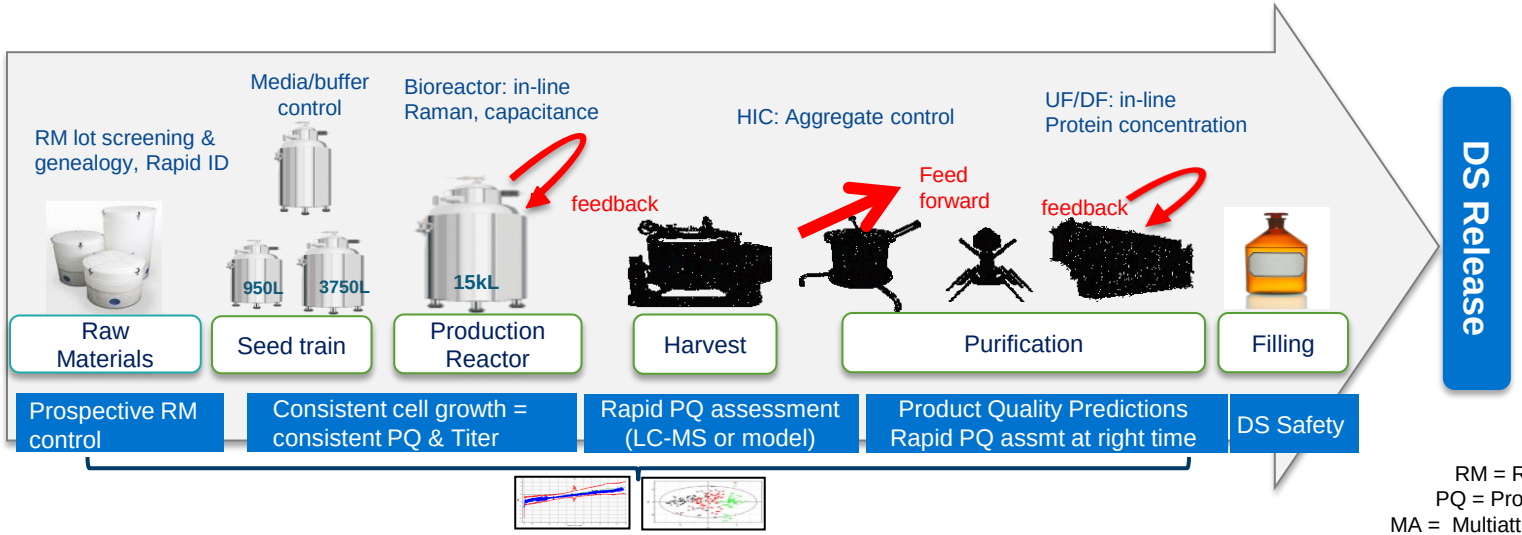
Direct Dispense:
Raw Material Lead Time Reduction



- **Reduces Inventory that must be carried to cover the 4-7 weeks lead time for QC testing.**
- **Facilitates "Just in Time" inventory reducing operational costs of inventory**

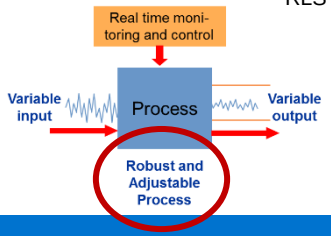
Electronic Data + Real-time analysis
Reduces Lead Time to ***1 DAY***

Delivering a Robust and Adjustable Process with Advanced Process Controls



Multivariate analysis for process monitoring and disposition decisions
Predictive model for product quality and/or feed forward control

RM = Raw material
PQ = Product Quality
MA = Multiattribute assay
DS = Drug substance
RLS = release



Foundation:

- Extensive understanding of raw materials, process, and product characterization
- A fully-integrated control system

Next Generation Drug Substance CofA

Current State		
Category	**What**	**Where**
General	pH	QC Lab
	Osmolality	
	Color (visual)	
	Turbidity (visual)	
Quantity	Protein Conc by RI	
Identity	ICIEF & Binding Assay	
Purity/Impurities	UPLC-SEC	
	Non-Reducing CE-SDS	
	Imaging Capillary IEF	
Biological Activity	Binding Assays	
Safety	Bioburden (plates)	
	Endotoxin (turbidimetric)	
	In-Vitro Adventitious Virus	

Future State		
Category	**What**	**Where**
General	Inline pH	In-line
	Inline Conductivity	
	Color by HunterLab	At-line
	Turbidity Meter	
Quantity	Protein Conc by SoloVPE	
Identity	Dot Blot ID	
Purity/Impurities	UPLC SEC	
Safety	Endotoxin by EndoSafe	
Purity/Impurities	LC/MS Peptide Map	High Tech Lab
Biological Activity	Binding w/ Automation	
Safety	Bioburden by GrowthDirect	
	NGS for Adventitious Virus	

Self-sufficient **right-time testing** and **exceptions-based review** for instant disposition

Next Generation Manufacturing depends on Next Generation Execution Systems

Aducanumab requires delivering high quality products at a higher volume than we have ever done before

NGM delivers the technology to meet this challenge but require business systems that are not rate limiting

	Limitation		Resolution
✓	Output of manufacturing process per unit time	→	3X Platform: Higher titer, faster upstream and downstream processing
✓	Requirement to wait for testing and to react to process variation	→	APC: Results on the manufacturing floor, real time adaptation, CofA by time DS is frozen
○	Manual transfer of information between systems, waiting for batch release	→	BES: All data electronic and shared real time, release by exception with integrated systems

***Takeaway**: Realizing the full benefits of the new 3X/APC platform is not possible without integrated business execution systems*

Next Generation Manufacturing is driving the evolution of the Biogen Execution Systems

Current State:

- Manufacturing relies on paper records and manual activities
- Records are reviewed in their entirety for batch release
- Test data and supporting documentation transcribed

Future State:

- Integrated systems make information available real time
- Batches are released by exception
- Transcription of data is eliminated
- Reduction in time required and error

1. Eliminate Manual Activities
2. System to System Interfaces
3. Data Rich Environment

The BES Integrated Solution

ERP and Warehouse Management

ORACLE swisslog

Document Management

myCIMS

Production Scheduling

OMPARTNERS

TrackWise

Quality Event Management

SYNCADE

Smart Operations Management Suite

Asset Management

infor

LABWARE

Enterprise Laboratory Platform

lims eln

Integrated Recipe

Statistica

UMETRICS

OSIsoft.

synTQ

DELTAV

Batch and Process Events
Operator Entered Data
Process Parameters
Diagnostic Parameters
Environmental Conditions

Manufacturing Processes

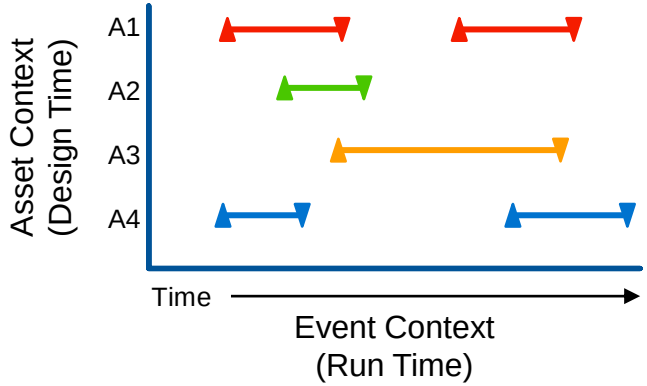
Building a strong foundation with Common Context

CHALLENGE

Inconsistent context across systems and work processes make it ***extremely difficult*** **to use data** easily and effectively.

It is ***challenging and time consuming*** to introduce context post-execution with a risk of inconsistent results

Breaking down this barrier unlocks tremendous value from the data!



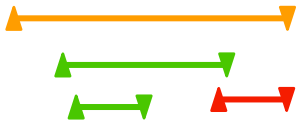
Single and complete source of Context
… from multiple systems ...
linked in PI EF

Different contexts to support business needs

Batch Execution

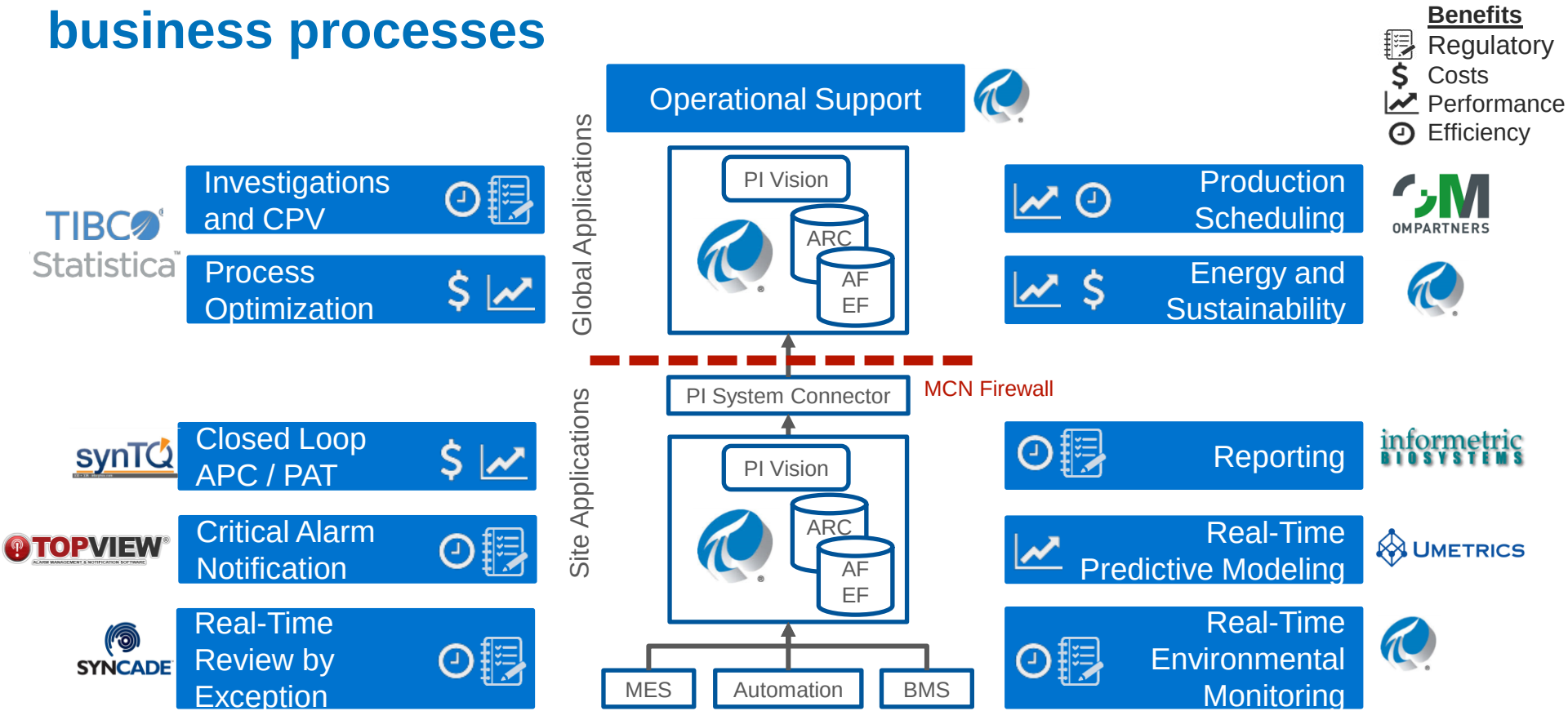
Equipment Utilization

Resource Consumption



* WAGES = Water, Air, Gases, Electricity, Steam

Capturing a single version of truth enables critical business processes

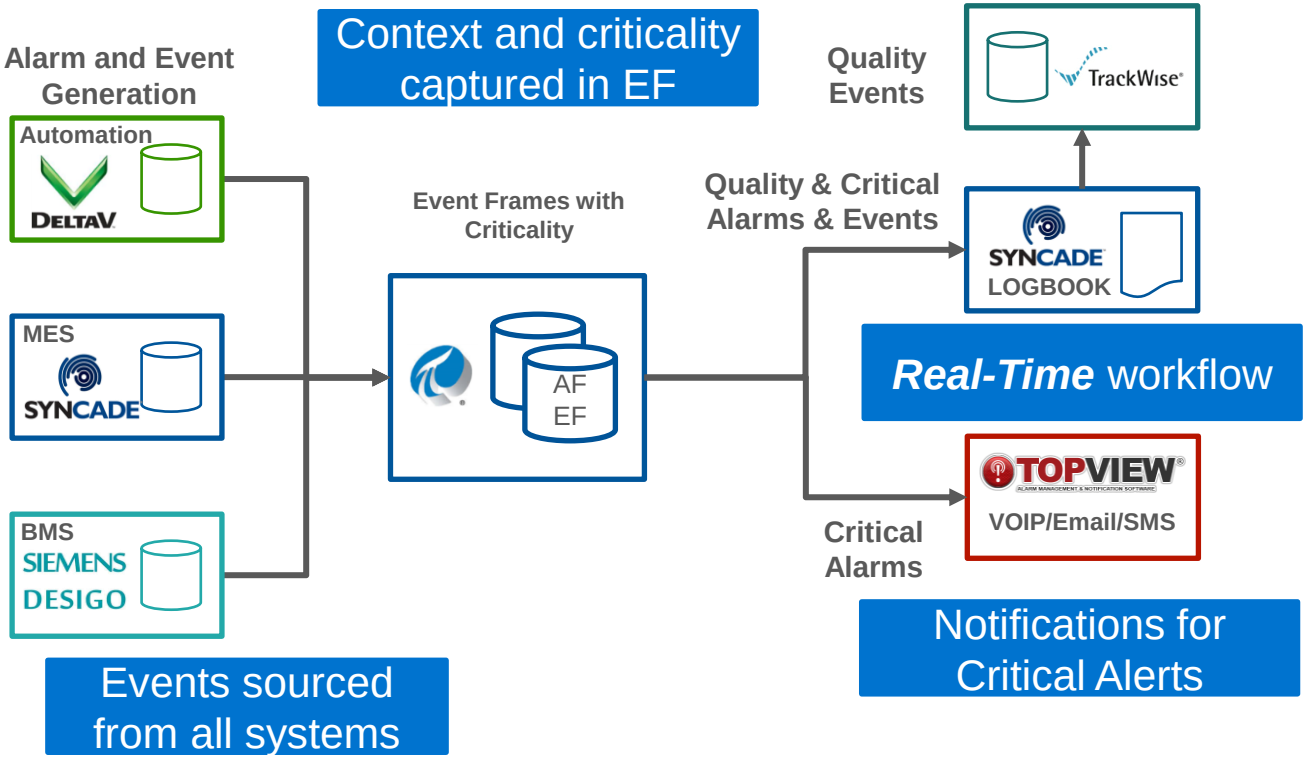


Real-Time Review By Exception reduce time to release batches

CHALLENGE

Current regulations require that we actively **review** computerized **audit trails** to detect abnormal execution of the manufacturing process **prior to product release**.

Computerized systems generate a significant amount of logs and ***only a small percentage*** of the entries are ***pertinent*** (”*needle in a haystack*”), making ***manual review time consuming and error prone.***

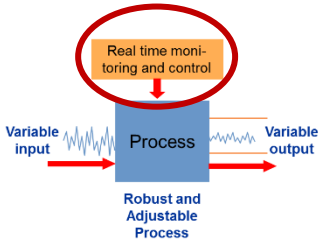


Enabling Real-Time predictive modeling and advanced process control

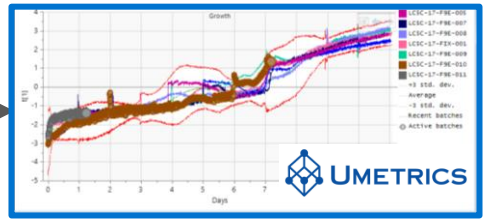
CHALLENGE

Biologics manufacturing processes are **inherently variable**, causing yield and quality issues.

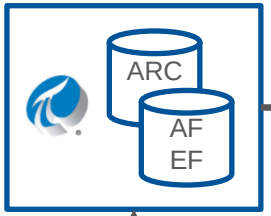
Multi-Variate Predictive models can drive improved control but are **challenging** to generate **without the correct data to train** the model and the **correct context to launch** the model, and robust real-time data to provide timely effect.



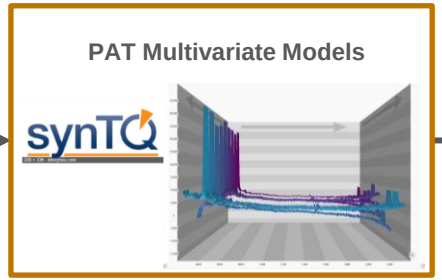
Multi-Variate Predictive Models and Analytics running in Real-Time with data and context from OSI PI



Real-Time performance prediction

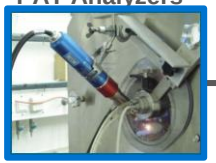


PAT Multivariate Models



Closed Loop PAT based Control

PAT Analyzers



Predicted CPPs And Control Actions

Automation

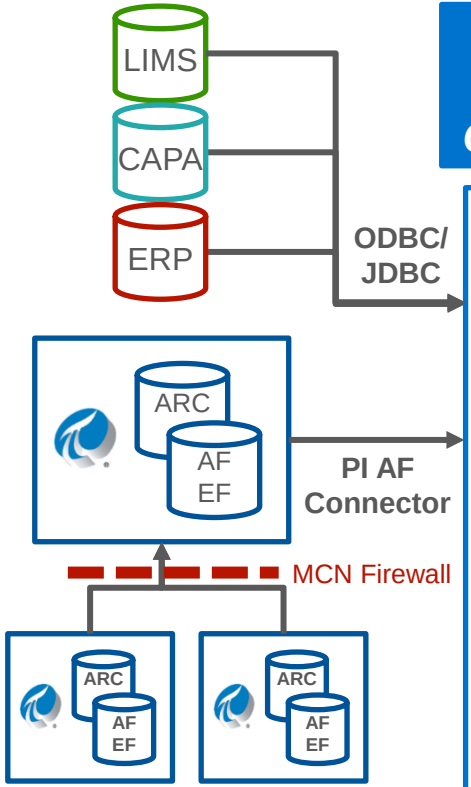
Driving continuous improvement via Process Trending, Optimization and Quality Event Support

CHALLENGE

There are **many sources of data** generated across the Enterprise from the manufacturing process.

Effective analysis **requires consistent context** and the ability to easily locate and join data

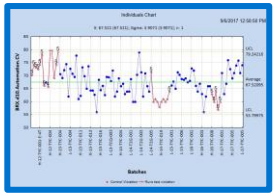
A **tremendous amount of data is necessary to optimize the process** via statistical and machine learning techniques.



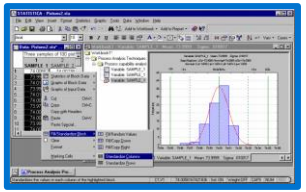
Common Manufacturing ***Context*** from PI EF

Analytics and Models fed from ***all data sources***

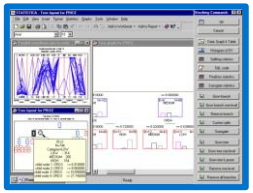
TIBCO Statistica™



Process trending and Continued Process Validation (CPV)



Investigation Support Root Cause, ANOVA



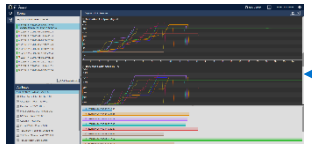
Advanced Analytics for process optimization (ML, MV)

Enterprise access and templates to achieve global operational support, system integration, reports, and KPI's

CHALLENGE

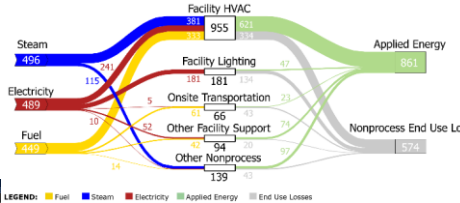
Security requirements protecting the manufacturing systems **creates a barrier to accessing** and leveraging **data** widely beyond the shop floor.

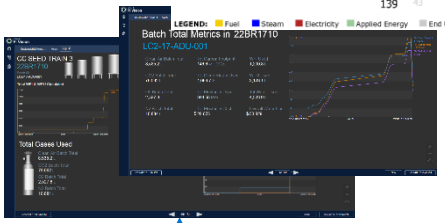
Developing **common analytics** and KPIs **across the enterprise** is hindered by inconsistent data and details, making it hard to compare across sites



Graphics, Ad-Hoc Trending, and Data Link Access

Energy





Easier access to data for users and enterprise applications

Enterprise Historian

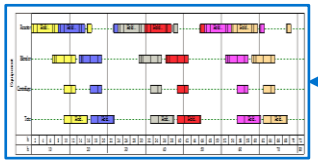
PI Vision

ARC

AF

EF

Consistent global analytics & KPIs



Real-Time Data for Production Scheduling

MCN Firewall

ARC

AF

EF

ARC

AF

EF

Local Site Historians

Infometric InfoBatch Reporting

Next Generation Manufacturing

Deliver meaningful therapies for 1,000,000 patients with Alzheimer's Disease by 2020 at 1/5 the cost of traditional Biologics Manufacturing.

Biogen

BUSINESS CHALLENGES

- Improve the manufacturing process output per unit time
- Reduce the wait time for testing and need to react to process variation
- Eliminate manual transfer of information between systems, Slowing batch release

SOLUTION

- Deploy our 3X Process Technology, Advanced Controls, and PAT
- Deliver smart, integrated systems and with efficient work processes.
- Deliver a data-rich environment

RESULTS AND BENEFITS

- 50% reduction in time waiting for test results
- 70% reduction in batch exceptions
- 78% reduction in batch review time
- A high performing, robust and adjustable process

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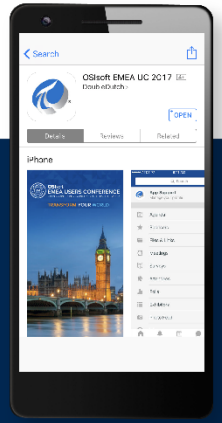
Questions

Please wait for the **microphone** before asking your questions

State your **name & company**

Please remember to…

Complete the Online Survey for this session



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감사합니다

Danke

谢谢

Merci

Gracias

Thank You

ありがとう

Спасибо

Obrigado