

Rapid Development of a Real-Time Multivariate Process Monitoring System

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Agenda

- Process Monitoring at Takeda Lexington Facility Historically
- Development of Process Monitoring System Vision
- Analysis of Takeda Infrastructure
 - What systems configurations will work?
 - What systems required modifications?
- Case Studies
- Online process monitoring system
- Global Initiative Trigger
- Summary

Process Monitoring at Takeda Historically

- Discrete data (i.e. daily cell counts, step yields, etc.)
 - Data fed into software system to trend this information
 - Not done in a timely manner
 - Only examined post batch in most cases if at all
 - Monitoring driven by observed issues - reactive
- Continuous Data
 - No platform software or approach to trending
 - Several different methods employed by individuals
 - Variables examined on a univariate basis
 - Difficult and high resource requirement to compare to historical batches
 - Monitoring also very reactive – examined once an issue was observed.

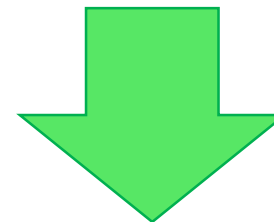
Process Monitoring Vision: Turn our Data into Information

- Data currently available – PI System
- How do we turn it into information?
 - Make monitoring easy
 - Efficient data storage & retrieval
 - Platform process monitoring technique
 - Increased monitoring leads to:
 - Early detection of process perturbations
 - Increased process understanding
 - Both in manufacturing and support groups
 - Reduced manufacturing risk
 - Multivariate process monitoring (SIMCA)

12348 13368.4351 43544.46543 5463.432
1322.134 46546687.4346 463468 986.464
2836465 546.9546 746943 486.1 94 36468
2454.41 468.48 3674683434 98.4 478.489
256.4 4534365135 431 43514 3.5 41 35 43

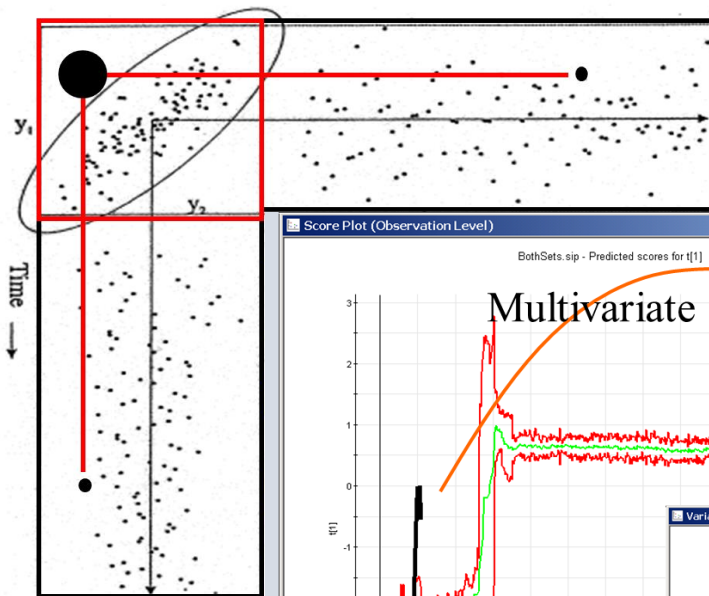


Information



Knowledge

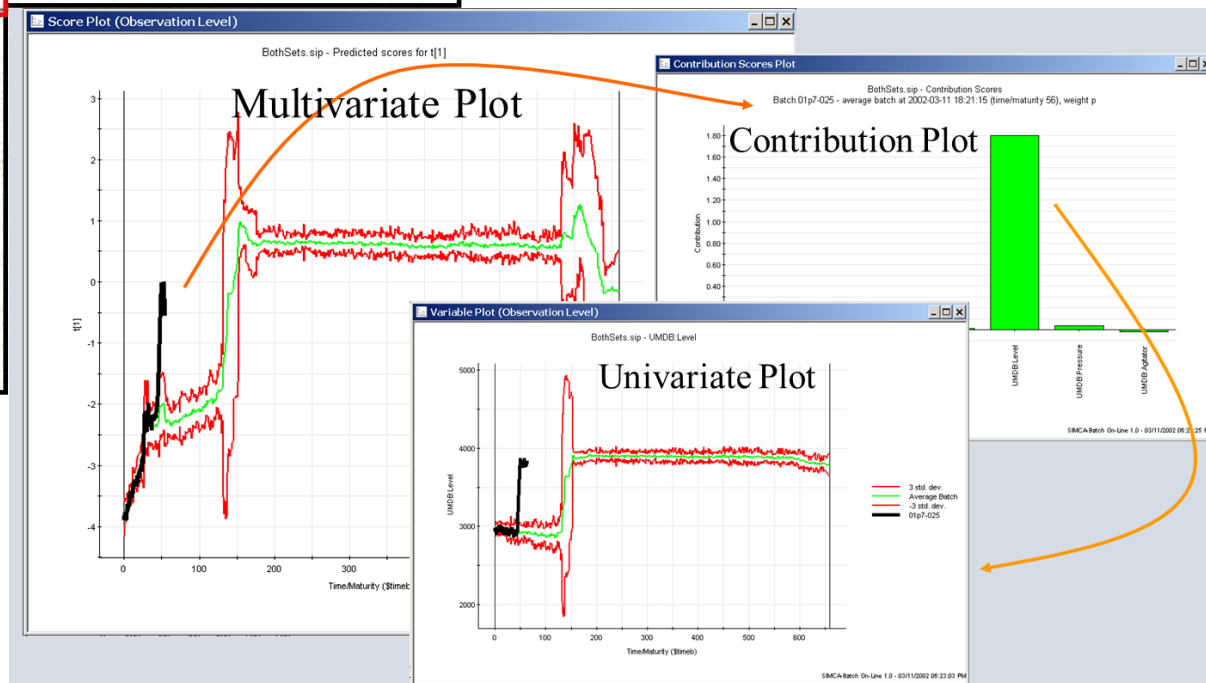
Why Multivariate Process Monitoring?



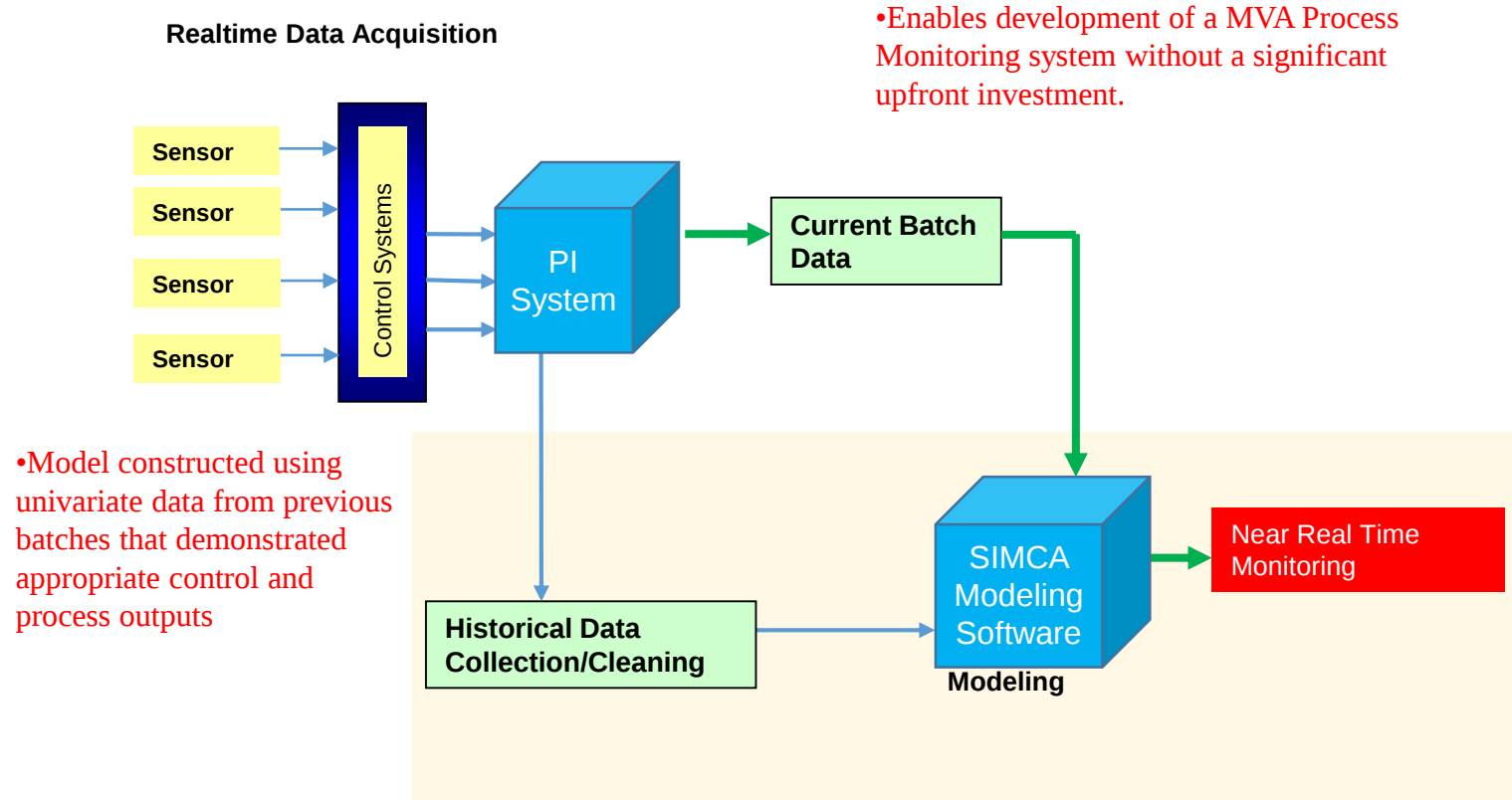
- The two variables are correlated
- The information is found in the correlation pattern, but is undetectable in the individual signals

SIMCA:

- Illustrates abnormal data and allows you to drill down to the univariate data.

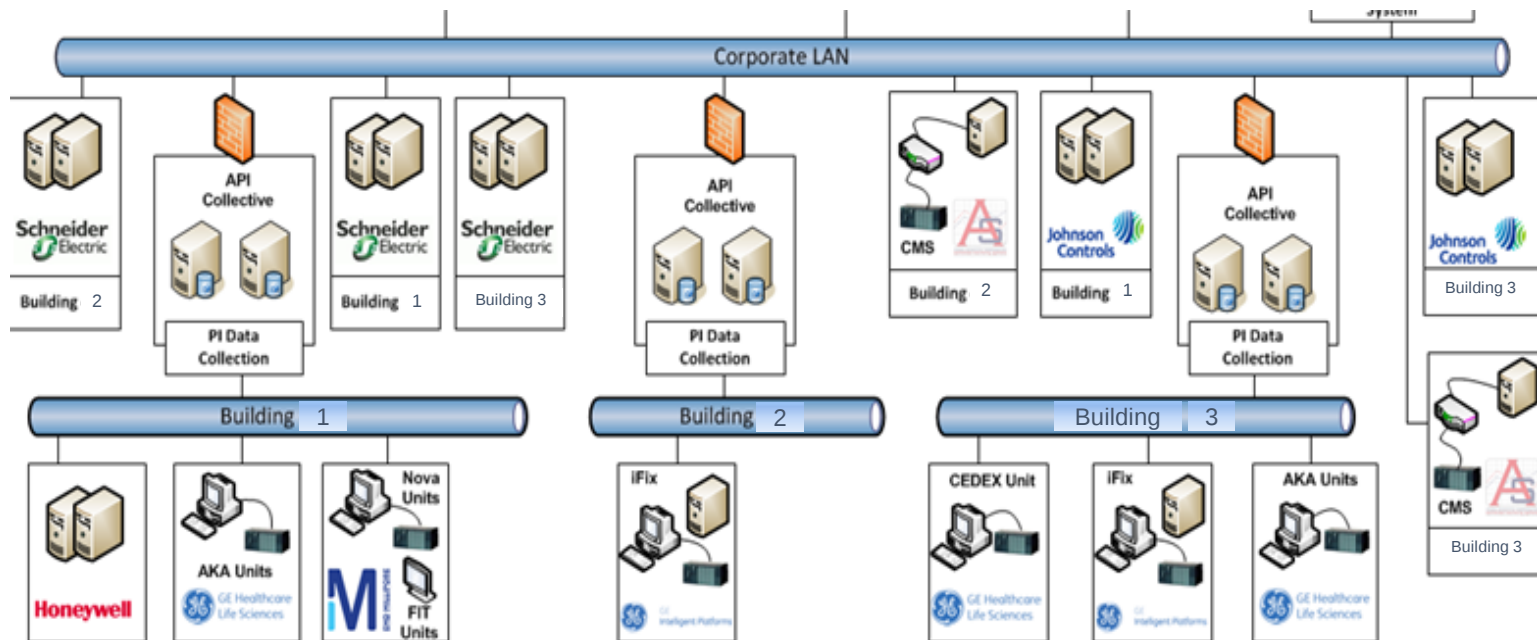


Initial Process Monitoring System Vision



Takeda Infrastructure: What modifications are needed for Process Monitoring System?

- Significant work already completed to get data acquisition from multiple automation sources into OSIsoft PI System and contextualized with AF and EF.



Data Contextualization

- Ideal data configuration due to OSIsoft PI System Event Frames offering strong batch functionality
 - Data linked with specific batch and phase

Search Parameters

Find:

Include: ☐ Running ☐ Completed ☒ Both

Batch ID:

Product:

Unit Name:

Time Range and Duration:

Active:

Any Length:

Search

Clear

Advanced Search

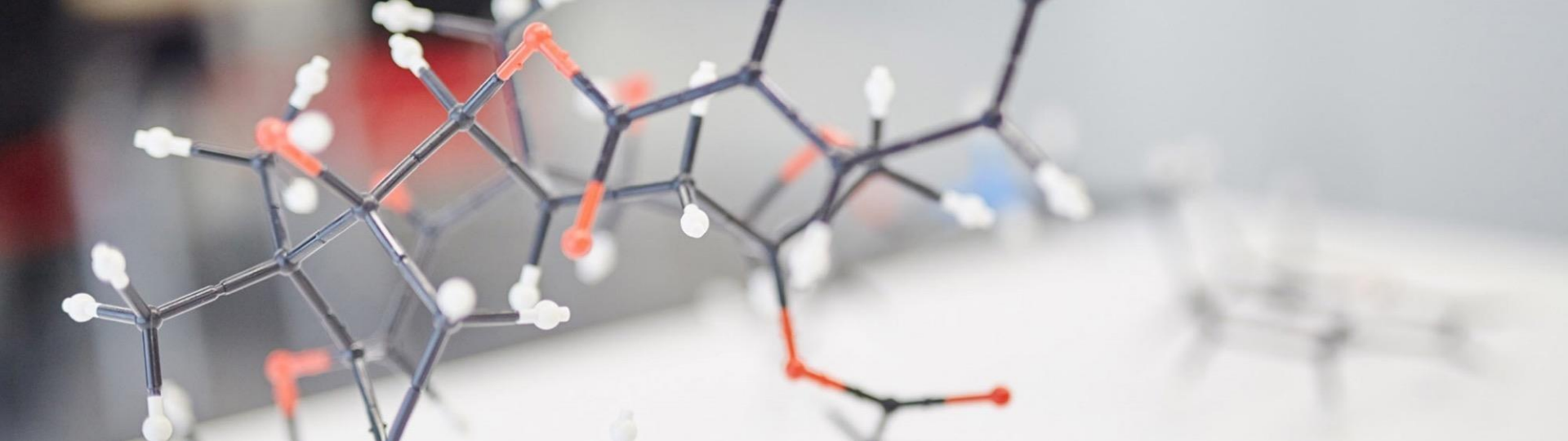
☐ Edit...

Output Cell

Batch ID	Start Time	End Time	Product	Unit Name	Procedure
Batch 1	9/8/2016 2:54:3...	10/11/2016 10:1...			
Media Addition	9/8/2016 2:54:4...	9/9/2016 10:08:...			
Inoculation	9/9/2016 10:08:...	9/9/2016 11:26:...			
Growth	9/9/2016 11:26:...	9/17/2016 9:53:...			
Transition	9/17/2016 9:53:...	9/19/2016 9:56:...			
Production	9/19/2016 9:56:...	10/11/2016 10:1...			
Batch 2	7/24/2016 11:25...	8/27/2016 11:05...			
Batch 3	5/30/2016 8:45:...	7/1/2016 11:34:...			

Initial Process Monitoring System

- Overall PI infrastructure suitable for development
- Process for development of monitoring system :
 - Obtain historical dataset
 - Clean dataset to develop a robust model
 - Current batch obtain data
 - Predict into SIMCA model and assess performance for current batch
- System summary:
 - Pros:
 - Relatively inexpensive
 - Clearly identifies process excursions
 - Shows how an online system could quickly and easily identify process perturbations
 - Cons
 - Very labor intensive

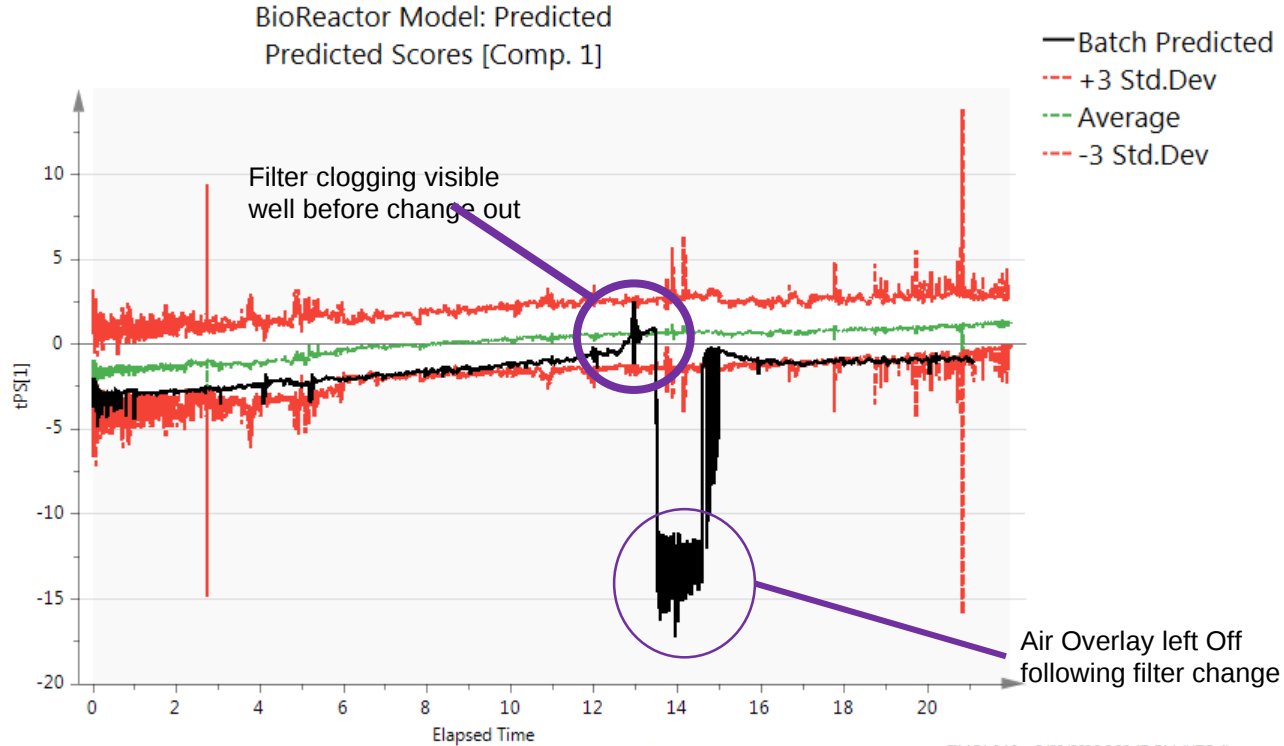


Manufacturing Case Studies



Better Health, Brighter Future

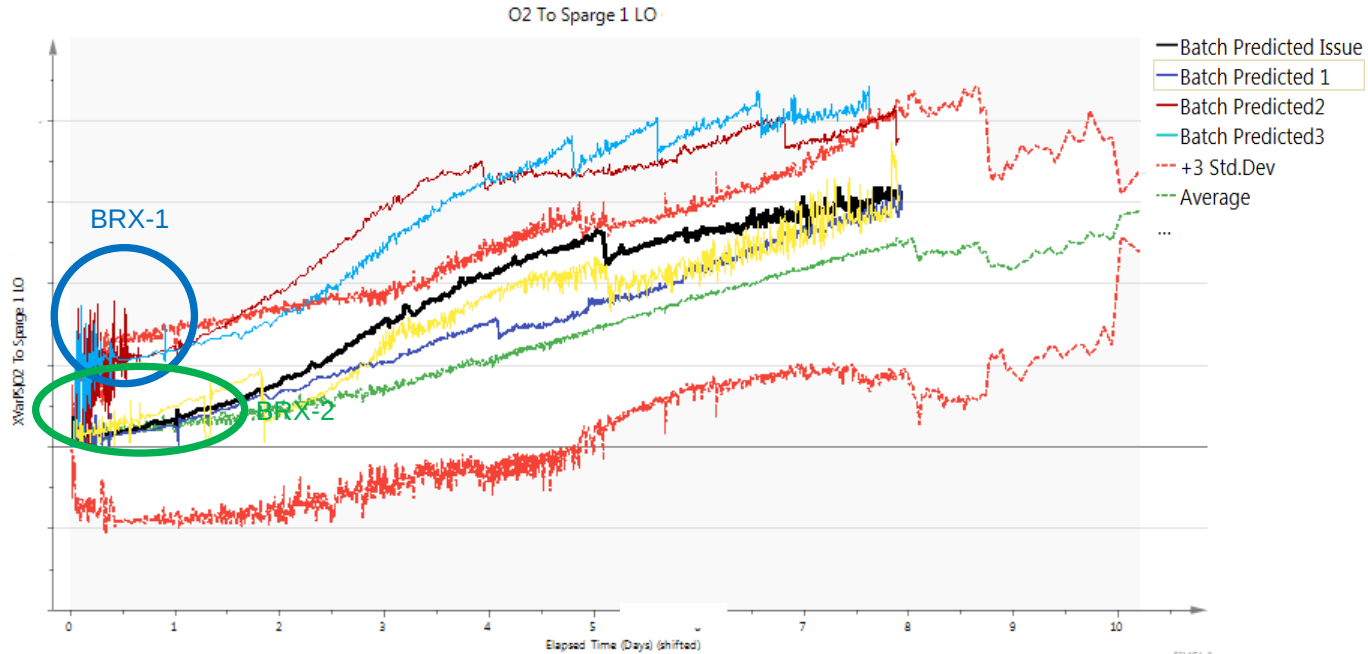
Case Study 1: Process and Operator Errors (Filter Clogging and Air Overlay Issue)



SIMCA 14.1 - 3/29/2016 2:32:47 PM (UTC-4)

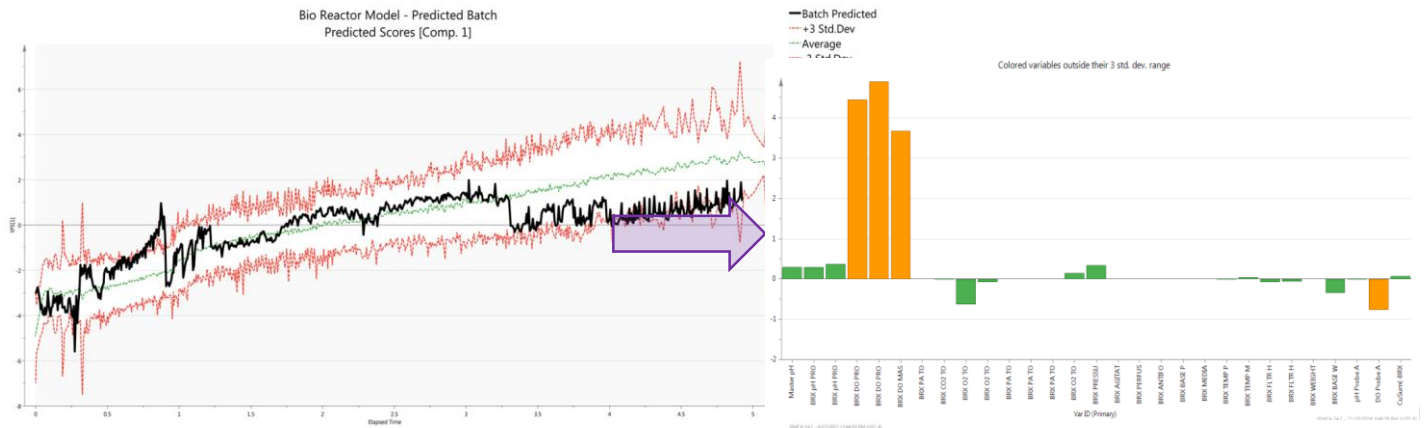
Case Study 2: Equipment Issue (Oxygen Leak on an air line)

- SIMCA identified an oxygen leak on a bioreactor
 - Fitting at flow meter was loose – went unnoticed for a year prior to assessment with SIMCA

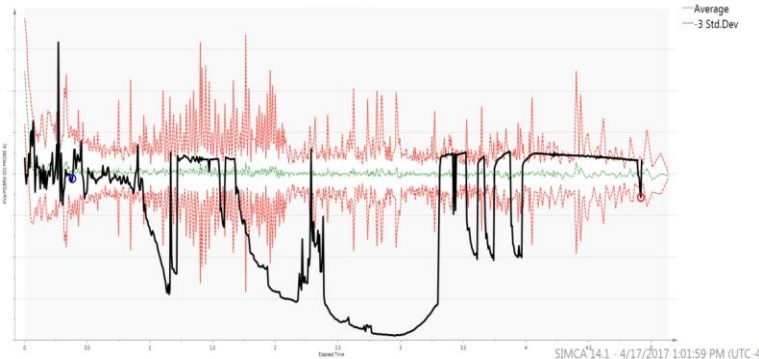


Case Study 3: Equipment Issue (DO Probe)

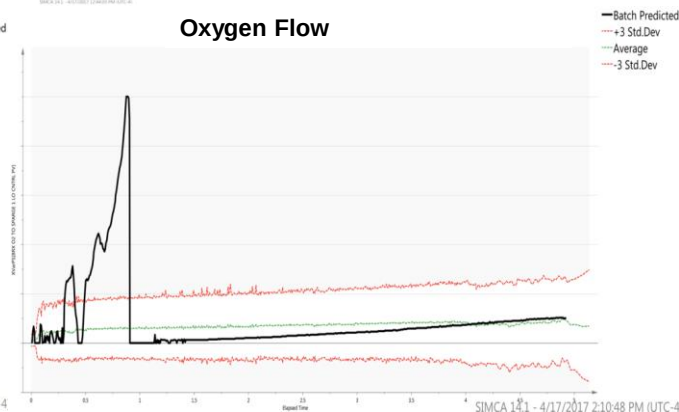
- SIMCA used to help save a batch
 - Controlling DO probe was faulty leading to excessive oxygen addition.



Initial Controlling DO Probe



Oxygen Flow



- Case Study 3: Equipment Issue (DO Probe)

SIMCA clearly identified an issue with a DO probe.

- Once all the batch data was analyzed it was clear that probe A (the controlling probe) was faulty.
- Used SIMCA to justify to QA the switch to DO probe B
- Switch was done and process parameters returned to historical ranges.

Off-line system helped save the batch, but a deviation still occurred.

Online SIMCA system would have detected this 12 hours earlier and likely prevented a deviation.

- Off-line analysis was performed at 15:30 and then the following morning at 7:00.
 - Unfortunately the issue started around 18:00 that night.

Initial Phase of Process Monitoring System

Off-line system:

- Took approximately 4 months and 1.5 FTE to develop
- Included all bioreactor, harvest, and chromatography operations

Resulting system provided

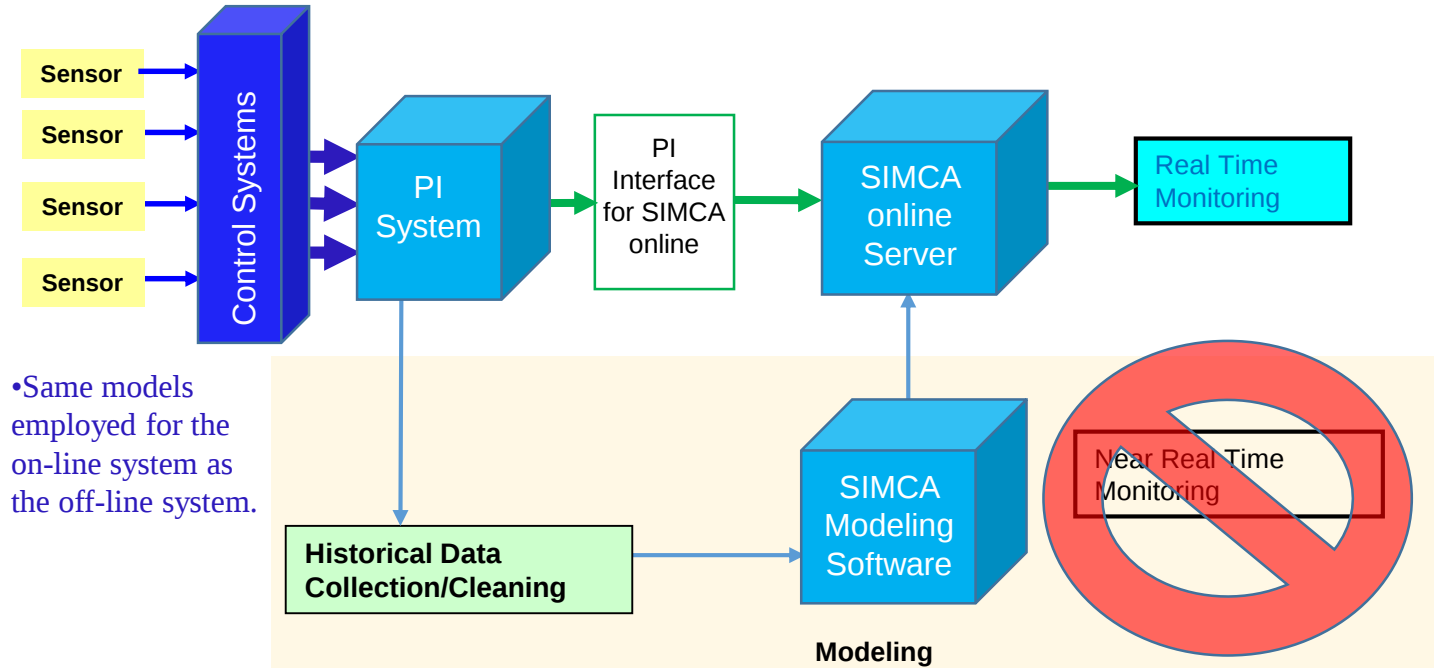
- Substantial benefits including saving a batch
- Concrete examples of the benefits of a process monitoring system
 - Invaluable and substantially better than theoretical arguments
- Justification for SIMCA-online system

Resulted in approval of funding for SIMCA-online

- Proof of concept project
- Initial approval only for bioreactor operations
 - Only unit operations fully configured for online system
 - Decision - Quickest way to show benefit/system performance

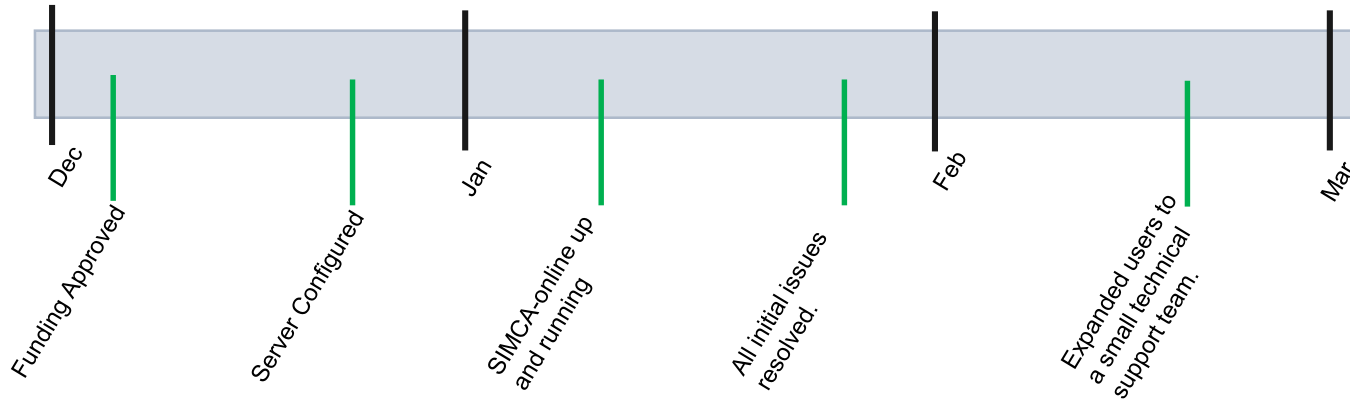
Online Process Monitoring System Infrastructure

Realtime Data Acquisition



Online System Implementation

Initial Timeline:



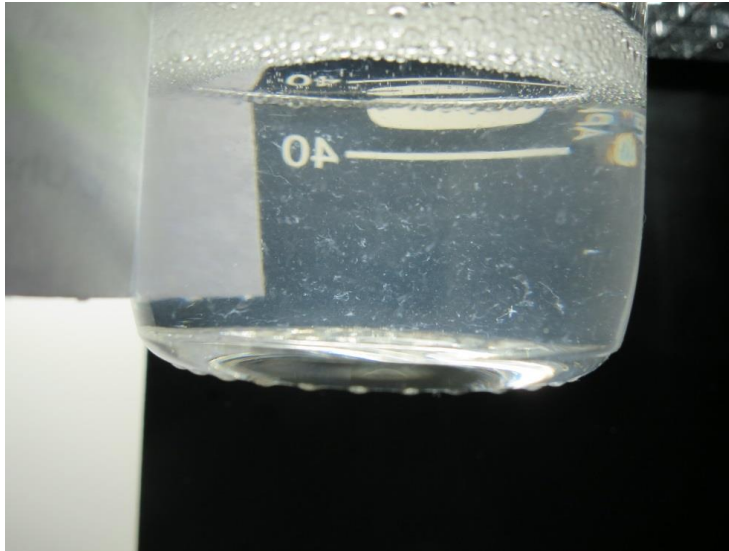
Subsequent Steps:

- Expanded use to a second manufacturing facility in Apr
- Expanded users to manufacturing in Jul

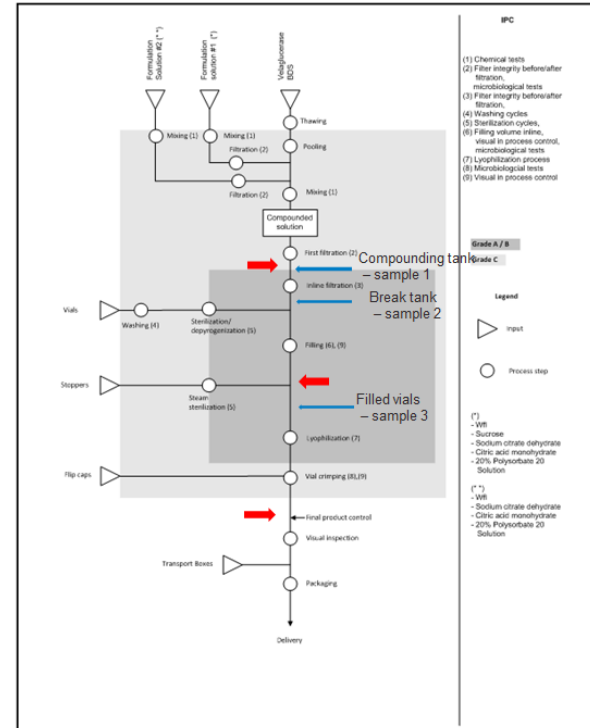
Despite proven benefits post implementation system expansion still moved slowly.

Global Initiative Trigger

- Particle issue during Drug Product (DP) processing
- Issue occurred in 2 consecutive drug product batches

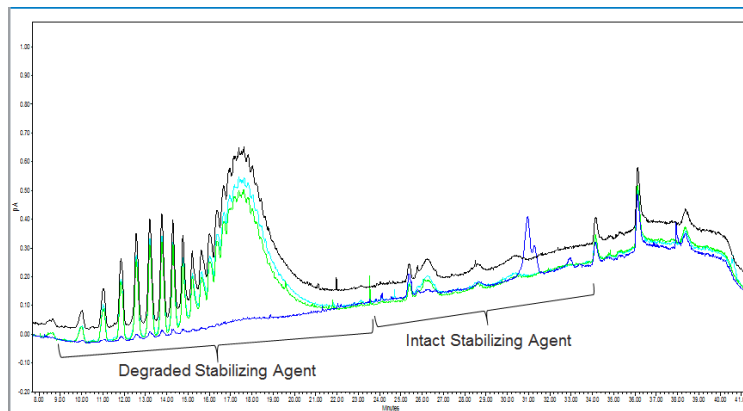


PROCESS FLOW CHART & PROCESS STEPS



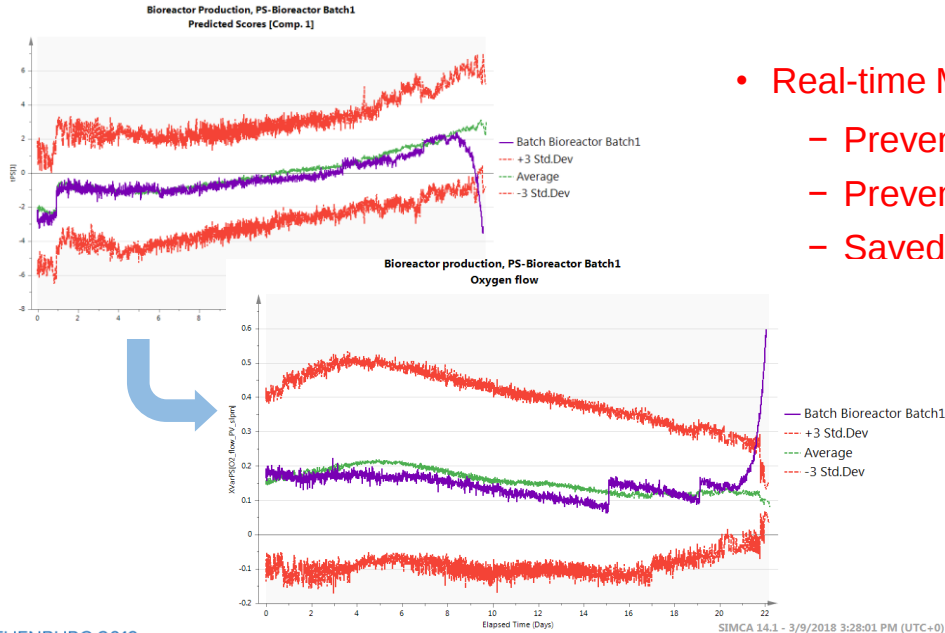
Global Initiative Trigger

- Drug Product Investigation (2 months)
 - Concluded that it was related to the Drug Substance (DS)
 - DS was breaking down stabilizing agent utilized in DS and DP formulation
- Drug Substance Investigation
 - No issues identified in the processing of DS utilized in the 2 DP batches
 - Testing shows DS has ability to break down stabilizing agent
 - DS batches all contained one specific upstream lot



Global Initiative Trigger - SIMCA

- Review of upstream process and data
 - SIMCA analysis signs of a possible slow contamination
 - Batch occurred before use of SIMCA
 - No alarms or process excursions (pH, DO, etc. were in operating ranges)
 - Ultimately retain samples showed presence of a facultative anaerobe

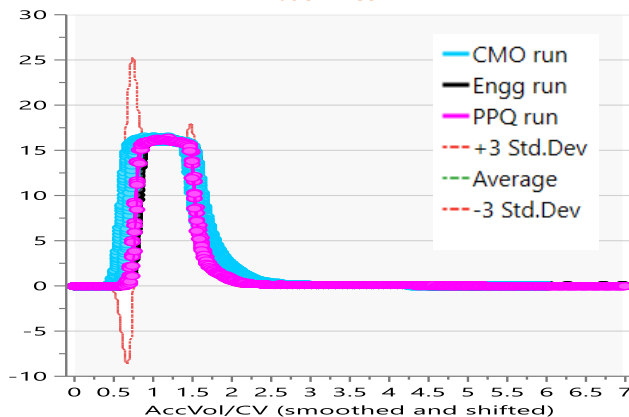


- Real-time MVA Analysis would have:
 - Prevented processing of 3 DS & 2DP batches
 - Prevented a 6-month investigation
 - Saved \$\$\$

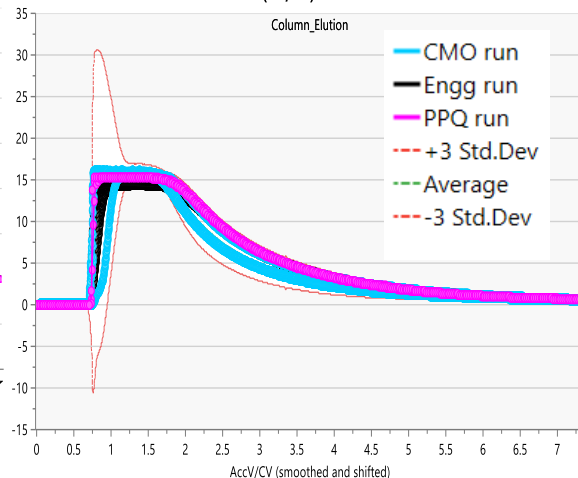
Global Adoption of System – How is it being used today?

- Utilized SIMCA for process comparability with CMO during a tech transfer
 - SIMCA models were built from CMO Unicorn data (R-scripting used to process data to SIMCA format) and projects configured on SIMCA-online to assess performance
 - Leveraged internal OSIsoft PI System to show that recovery and purification processes were comparable to CMO real-time.

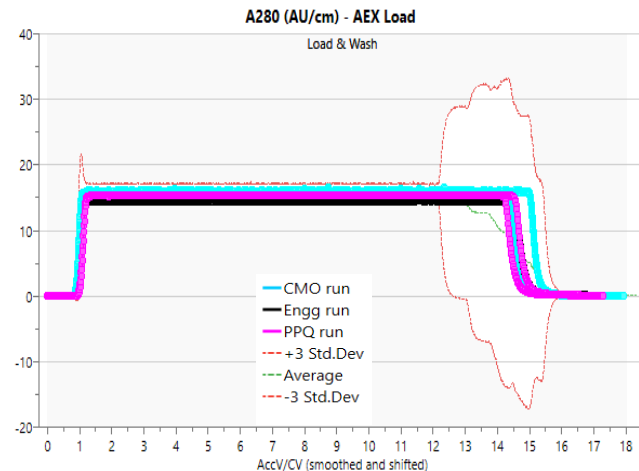
Clinical product – Column 1 (SIMCA Online)
Elution A280



Clinical product – Column 2
A280 (AU/cm) - Elution



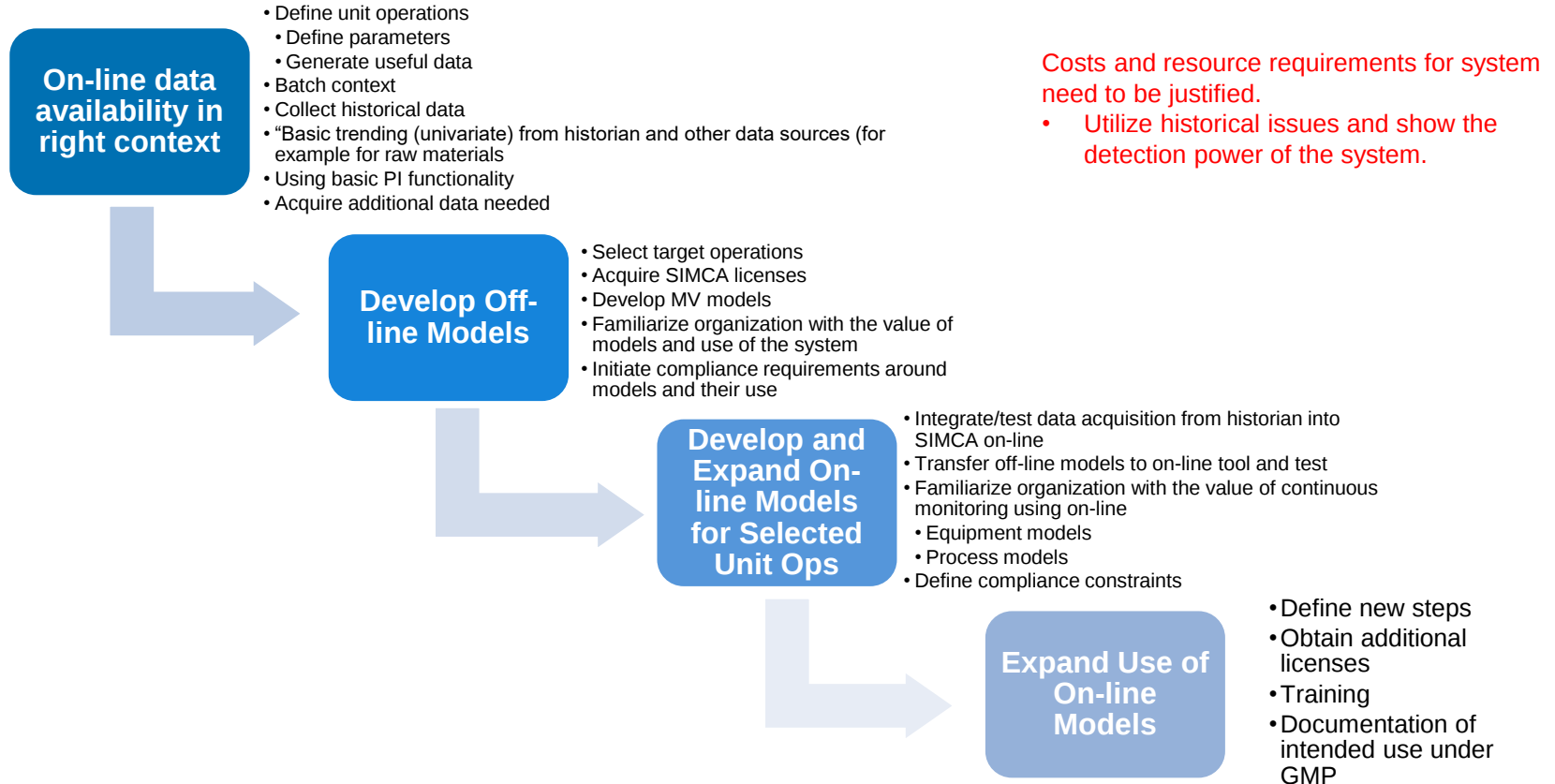
Clinical product – Column 3



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- SIMCA online system now deployed at 6 sites within the Takeda network

Overall Summary of Process Monitoring Roadmap



CHALLENGES

- Large amounts of process data not examined
- Multiple methods employed for analysis
- Very reactive culture
- Univariate approach ignores correlations between variables

SOLUTION

- Development of a process monitoring system
 - Leveraging data availability and configuration of OSIsoft PI System
 - Along with multivariate functionality of SIMCA
- A step wise approach shows benefits without significant investment

BENEFITS

- Decreased MFG risk
 - Preventing batch failures (\$MMs saved)
- Increase process understanding throughout organization
- Shift towards a proactive culture
- Provides efficient trouble shooting capabilities

Financial justification is always the most difficult part and unfortunately usually requires a significant failure. Leveraging historical issues can help provide justification without additional financial losses.

Acknowledgements

Thank you to the project team that made this possible:

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