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
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

Realtime Data Acquisition

• Model constructed using univariate data from previous batches that demonstrated appropriate control and process outputs

• Enables development of a MVA Process Monitoring system without a significant upfront investment.

Current Batch Data

PI System

Historical Data Collection/Cleaning

SIMCA Modeling Software

Near Real Time Monitoring

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

BioReactor Model: Predicted Predicted Scores [Comp. 1]

Filter clogging visible well before change out

Air Overlay left Off following filter change
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.
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

• Same models employed for the on-line system as the off-line system.
Online System Implementation

Initial Timeline:

- Dec: Funding Approved
- Jan: Server Configured
- Feb: SIMCA-online up and running
- Mar: All initial issues resolved
- Mar: Expanded users to a small technical support team.

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
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.

  - SIMCA online system now deployed at 6 sites within the Takeda network
Overall Summary of Process Monitoring Roadmap

Discover Off-line Models

- Define unit operations
- Define parameters
- Generate useful data
- Batch context
- Collect historical data
- "Basic trending (univariate) from historian and other data sources (for raw materials"
- Using basic PI functionality
- Acquire additional data needed

Develop Off-line Models

- Select target operations
- Acquire SIMCA licenses
- Develop MV models
- Familiarize organization with the value of models and use of the system
- Initiate compliance requirements around models and their use

Develop and Expand On-line Models for Selected Unit Ops

- Integrate/test data acquisition from historian into SIMCA on-line
- Transfer off-line models to on-line tool and test monitoring using on-line equipment models
- Familiarize organization with the value of continuous monitoring using on-line equipment models
- Define compliance constraints

Expand Use of On-line Models

- Define new steps
- Obtain additional licenses
- Training
- Documentation of intended use under GMP

On-line data availability in right context

- Define unit operations
- Collect historical data
- Batch context
- Generate useful data
- Using basic PI functionality
- Acquire additional data needed

Costs and resource requirements for system need to be justified. Utilize historical issues and show the detection power of the system.
Minimal Process Monitoring

**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 loses.
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