LEVERAGING CONTINUOUS PROCESS DATA

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BioMarin Pharmaceutical Inc.
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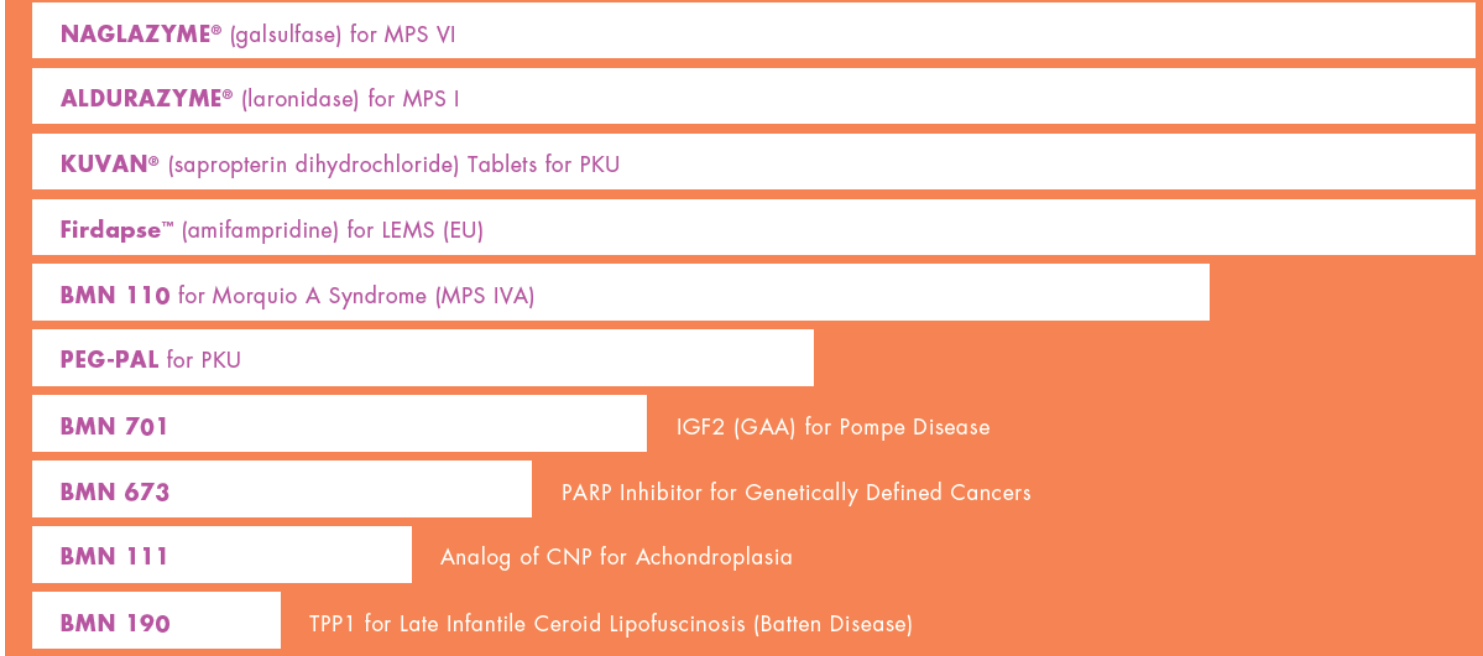
BioMarin at a Glance

BioMarin Pharmaceutical Inc. (Nasdaq: BMRN) develops and commercializes promising first-in-class or best-in-class therapeutics for patients with serious diseases and medical conditions

BioMarin Pipeline



*For the most current pipeline info, please visit www.BMRN.com

How we adopted it: Beginning

- Implemented new historian to capture data in 2 facilities
- Accessed Historian through Excel
- Used Batch Context for lot release

How we adopted it: Middle

VIMIZIM®
(elosulfase alfa)

- Increased production run rates and had new drug approval!
  - Integrated historical data with analytical tools
  - Began to use continuous process data for planning and scheduling

How we adopted it: Current



- Added a 3rd facility and went global
- Enterprise Agreement allowed for:
  - Troubleshooting Data Streams
  - Leveraging COE for global MFG network architecture
  - Additional data points for equipment with no $$ hurdles
- Began to use Multi-variate online monitoring
- Began to use templates as a harmonization tool

How we adopted it: Summary

We have been able to grow our historical data needs with the growth of the company

Analytics

- Specific analytical tool (most analyses are not in historian)
  Why?
  - More out of the box functionality (t-test, anova, etc)
  - Contextualization of data into manufacturing process
  - Lineage

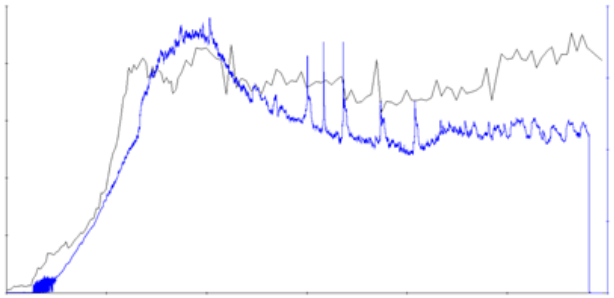
- Integrated historian and analytical tool
  Why?
  - Correlations: O2 flow rate in bioreactor is correlated with a critical quality attribute

  - Calculations:

$$Qp = \frac{\left(\frac{dTiter}{dt} + \frac{Harvest\ Flow\ Rate}{Vessel\ Volume}\right)}{Viable\ Cell\ Density}$$

Quality
Historian
Offline

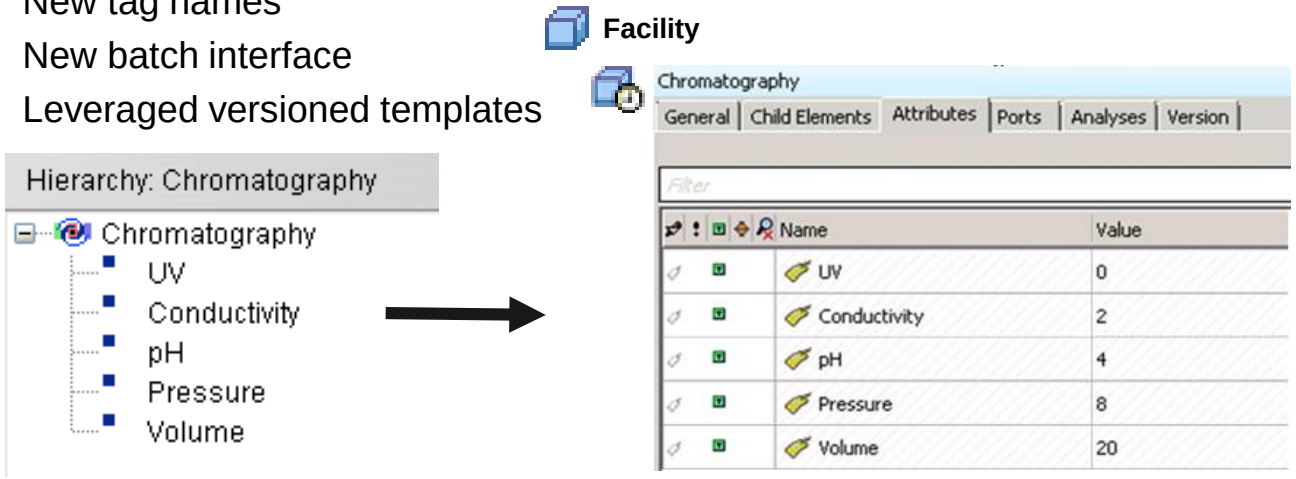
  - Trending:



- Result = **Increased Process Knowledge**

Templates as a Harmonization Tool

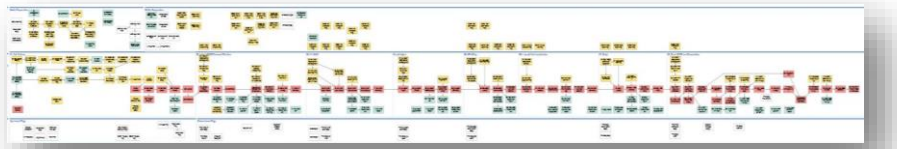
- Integrating historian with the analytical tool can be complex
- Templates vastly simplify this integration
  - Ex: replaced equipment
    - New tag names
    - New batch interface
    - Leveraged versioned templates



    - Detailed configuration takes place in the historian
  - Ex: differing naming conventions in different facilities
    - **Facility 1: SK####.AIT04.PV**
    - **Facility 2: 11-LHS-###-01.AIT04A.ADVal**

→ **\\FacilityServer\%@SkidPrefix%.%@UV_Postfix%**

Planning & Scheduling

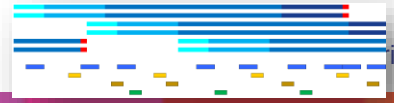


- Specific production process simulation tool
  - Flexible, customizable platform can simulate an array of operational modes (batch, fed-batch, and perfusion) and factor in site-specific resources and constraints
  - Used for long-range planning, scenario testing, identifying bottlenecks and optimization opportunities, and performing finite scheduling

- Integrate with continuous process data
  - Incorporate historical performance and variability into production simulations
  - Increase the accuracy of our projections

- High-level planning
  - Perform long-range planning with an understanding of historical performance
  - Answer a variety of questions, such as:
    - How can we make more/faster Product X in its licensed facility? What resources become constrained?
    - With a mix of manufacturing lines drawing from shared utilities, can the supply of utilities support the projected demand?

- Finite scheduling example
  - Enhance scheduling capabilities of a perfusion process when the downstream operations cadence is a function of the perfusion rate

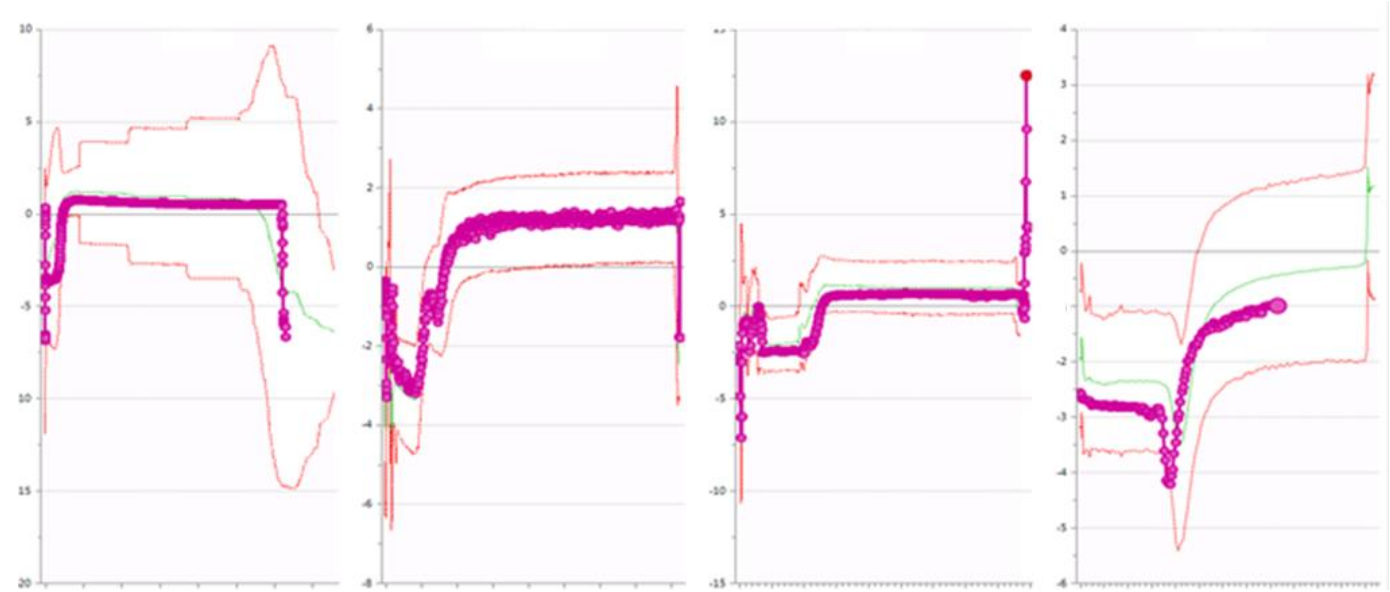


Real Time Multivariate Monitoring

- Benefits of Real Time Multivariate Monitoring:
  - Simplicity
    - One parameter to watch

    - Drill down functionality

  - Golden Batch Comparison
    - Easy to compare



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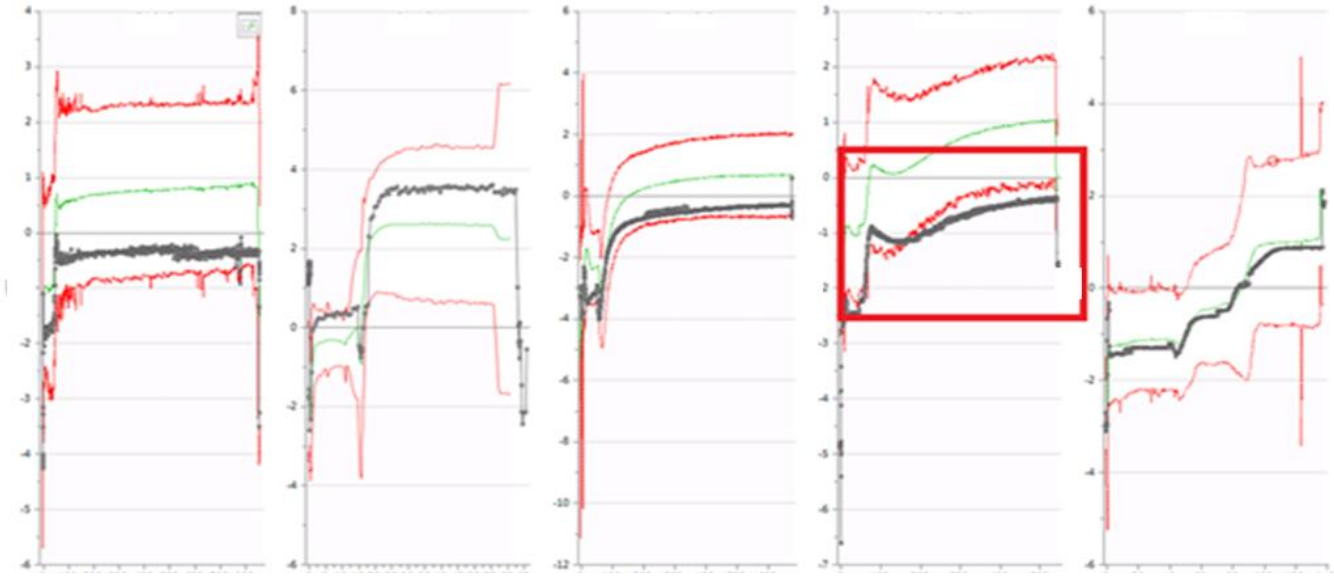

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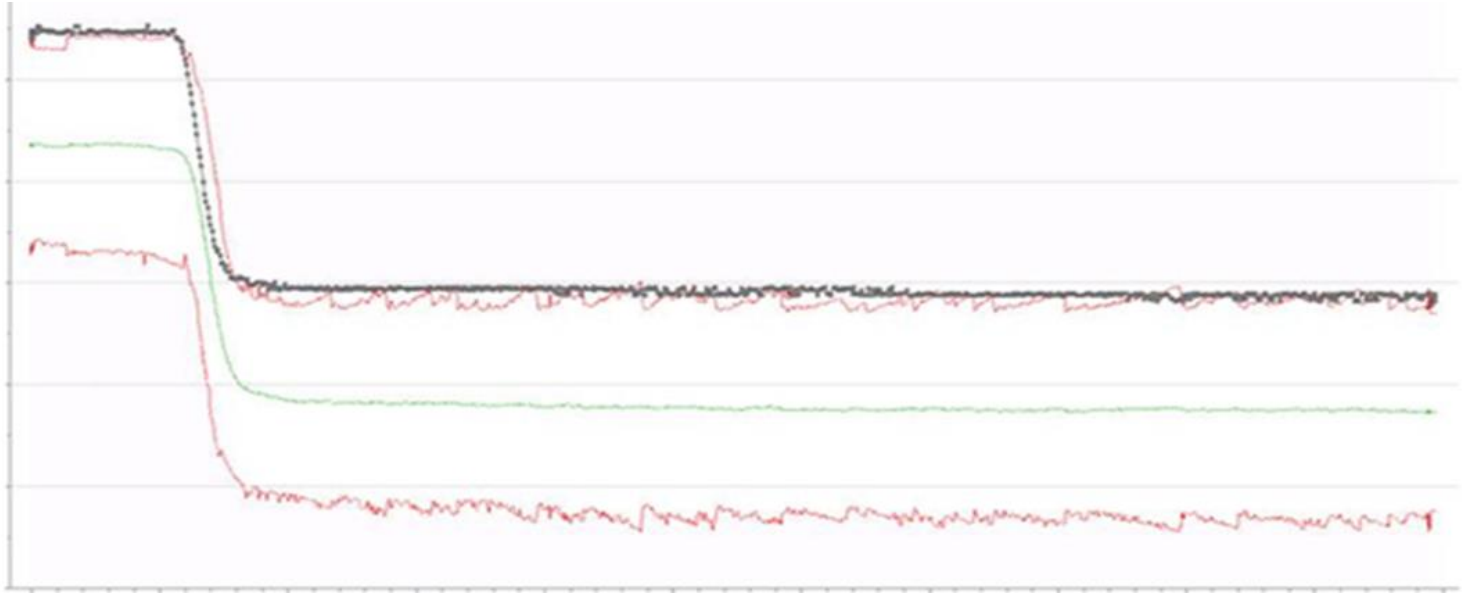

Future State of Continuous Process Data

- Re-architect historical data collection system for our Global Manufacturing Network
- Leverage Continuous Process data for company Sustainability goals
- Continuous to build out and leverage templates to harmonize across all global facilities