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

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<thead>
<tr>
<th>Preclinical Testing</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>BLA</th>
<th>NDA</th>
<th>MAA</th>
<th>Commercialization</th>
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<tbody>
<tr>
<td>NAGLAZYME® (galsulfase) for MPS VI</td>
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<td>ALDURAZYME® (laronidase) for MPS I</td>
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<td>KUVAN® (sapropterin dihydrochloride) Tablets for PKU</td>
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<td>Firdapse® (amifampridine) for LEMS (EU)</td>
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<td>BMN 110 for Morquio A Syndrome (MPS IVA)</td>
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<td>PEG-PAL for PKU</td>
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<td>BMN 701</td>
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<td>IGF2 (GAA) for Pompe Disease</td>
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<td>BMN 673</td>
<td>PARP Inhibitor for Genetically Defined Cancers</td>
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<td>BMN 111</td>
<td>Analog of CNP for Achondroplasia</td>
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<td>BMN 190</td>
<td>TPP1 for Late Infantile Ceroid Lipofuscinosis (Batten Disease)</td>
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*For the most current pipeline info, please visit www.BMRN.com.*

April 7, 2016
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

- 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:

  \[ Q_p = \left( \frac{dTiter}{dt} + \frac{Harvest \ Flow \ Rate}{Vessel \ Volume} \right) \times \frac{Viable \ Cell \ Density}{Vessel \ Volume} \]

• 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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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