Next Generation Biologics Manufacturing: Delivering the Vision

Presented by Timothy Alosi
The driver behind Biogen’s Next Generation Manufacturing

Alzheimer’s Disease

5.3 million people in the US, and 25 million worldwide live with Alzheimer’s

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 m² 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!*

<table>
<thead>
<tr>
<th>Limitations in legacy manufacturing</th>
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<tbody>
<tr>
<td>Output of manufacturing process per unit time</td>
</tr>
<tr>
<td>Requirement to wait for testing and to react to process variation</td>
</tr>
<tr>
<td>Manual transfer of information between systems, waiting for batch release</td>
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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**

1-2 weeks → 2-3 weeks → 1-2 weeks

4-7 weeks

= ✓ ×

= ✓ ×
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

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

RM = Raw material
PQ = Product Quality
MA = Multivariate assay
DS = Drug substance
RLS = release
Next Generation Drug Substance CofA

<table>
<thead>
<tr>
<th>Category</th>
<th>Current State</th>
<th>Future State</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>What</strong></td>
<td><strong>What</strong></td>
</tr>
<tr>
<td>General</td>
<td>pH</td>
<td>Inline pH</td>
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<td></td>
<td>Osmolality</td>
<td>Inline Conductivity</td>
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<td></td>
<td>Color (visual)</td>
<td>Color by HunterLab</td>
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<td></td>
<td>Turbidity (visual)</td>
<td>Turbidity Meter</td>
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<tr>
<td>Quantity</td>
<td>Protein Conc by RI</td>
<td>Protein Conc by SoloVPE</td>
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<tr>
<td>Identity</td>
<td>ICIEF &amp; Binding Assay</td>
<td>Dot Blot ID</td>
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<td>Purity/Impurities</td>
<td>UPLC-SEC</td>
<td>UPLC SEC</td>
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<td>Non-Reducing CE-SDS</td>
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<td></td>
<td>Imaging Capillary IEF</td>
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<tr>
<td>Biological Activity</td>
<td>Binding Assays</td>
<td>Binding w/ Automation</td>
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<tr>
<td>Safety</td>
<td>Bioburden (plates)</td>
<td>Bioburden by GrowthDirect</td>
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<td></td>
<td>Endotoxin (turbidimetric)</td>
<td>NGS for Adventitious Virus</td>
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<td>In-Vitro Adventitious Virus</td>
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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

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

- Manufacturing Processes
- Quality Event Management
- Document Management
- Production Scheduling
- Asset Management
- Batch and Process Events
- Operator Entered Data
- Process Parameters
- Diagnostic Parameters
- Environmental Conditions

ERP and Warehouse Management

Syncade

- Integrated Solution
- Integrated Recipe

Oracle

Swisslog

Infor

Labware

MyCIMS

TrackWise

Lims Eln

DeltaV

SynTQ

Umetrics
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!

**CHALLENGE**

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**Single and complete source of Context**

... from multiple systems ... linked in PI EF
Capturing a single version of truth enables critical business processes

- Investigations and CPV
- Process Optimization
- Closed Loop APC / PAT
- Critical Alarm Notification
- Real-Time Review by Exception

**Benefits**
- Regulatory
- Cost
- Performance
- Efficiency

**Applications**
- PI Vision
- ARC
- AF
- EF

**Operational Support**
- PI System Connector
- MCN Firewall

**Site Applications**
- MES
- Automation
- BMS

**Global Applications**
- Production Scheduling
- Energy and Sustainability
- Reporting
- Real-Time Predictive Modeling
- Real-Time Environmental Monitoring

**Tools**
- TIBCO Statistica
- synTQ
- TOPVIEW
- SYNCAD

**Brands**
- OSIsoft
- EMEA USERS CONFERENCE 2017 LONDON

#OSISOFTUC ©2017 OSIsoft, LLC
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.

Events sourced from all systems

Context and criticality captured in EF

Quality Events

Event Frames with Criticality

Quality & Critical Alarms & Events

Real-Time workflow

Notifications for Critical Alerts

Events sourced from all systems

Alarm and Event Generation

MES

BMS

Automation

MES

BMS

SYNCADE

SYNCADE

VOIP/Email/SMS

Critical Alarms

TOPVIEW

Notifications for Critical Alerts

Real-Time workflow
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.

Real-Time performance prediction

Closed Loop PAT based Control

Predicted CPPs And Control Actions
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.

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**Common Manufacturing Context** from PI EF

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

- Process trending and Continued Process Validation (CPV)
- Investigation Support Root Cause, ANOVA
- Advanced Analytics for process optimization (ML, MV)

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**ODBC/JDBC**

**MCN Firewall**

**PI AF Connector**

**LIMS**

**CAPA**

**ERP**

**ARC**

**AF**

**EF**

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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.

Easier access to data for users and enterprise applications

Consistent global analytics & KPIs

Real-Time Data for Production Scheduling

Graphics, Ad-Hoc Trending, and Data Link Access

Enterprise Historian

MCN Firewall

Local Site Historians

Infometric InfoBatch Reporting

Energy

- ARC
- AF
- EF

PI Vision

- ARC
- AF
- EF
## 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.

### 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
Timothy Alosi
Tim.Alosi@Biogen.com
https://www.linkedin.com/in/timalosi/
Head – Data Analytics
Biogen

Acknowledgements: Rob Guenard, Canping Jiang, Jim Kenyon, Greg Pittman, Jyotika Sharma, Michael Farrow, Dan Hill, Roland Zhou, Gus Green, Dan Keelor, Curt Coury, Dave Burke, Jordan Croteau, Matt Haines
Questions

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

State your name & company.
Thank You