Driving Value through Innovation in Biotech Manufacturing

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Connecting a World of Pharmaceutical Knowledge

Biogen

Agenda

- **Biopharma Legacy, Trends, & Challenges**
- **Maximizing Asset Productivity**
- **Creating Value Through Innovation**
  - Conventional technology improvements
  - Disruptive innovation
- **Conclusions**

Operations as a Value Driver in a Maturing Industry

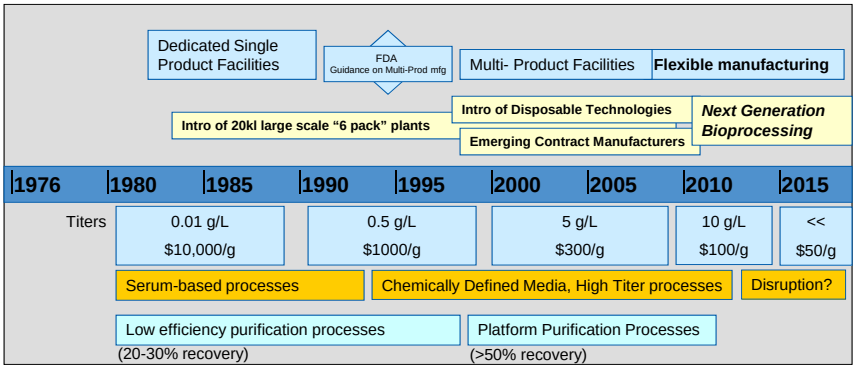
Pharmaceutical operations can advance from an outsourceable "necessary evil" to a true value creator in the biopharmaceutical industry by

- **Process Sciences:** Huge value has been captured from productivity increases in drug substance processing based on conventional technologies
- **Engineering:** advanced facility design and technology alignment improves facility utilization as a major source of value
- **Sustainable Compliance:** reliability of supply based on highly efficient and robust quality systems is an often underestimated value generator

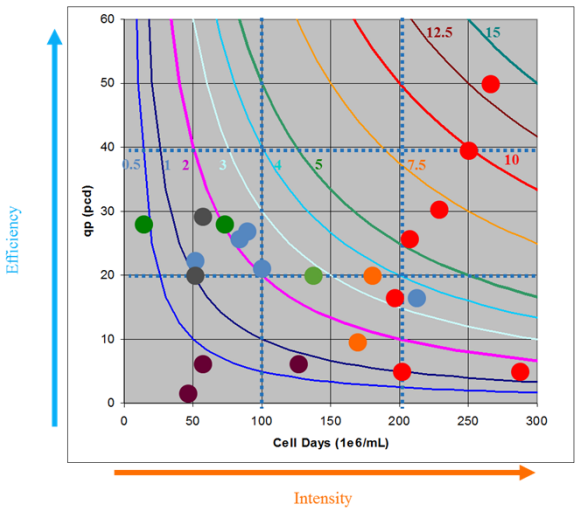
Process Sciences Have Captured Value Throughout the History of Biopharmaceuticals

- Titers have increased dramatically, enabling operations at a smaller scale
- Single-use technologies are growing rapidly
- Flexible manufacturing systems provide a low cost option for early clinical manufacturing

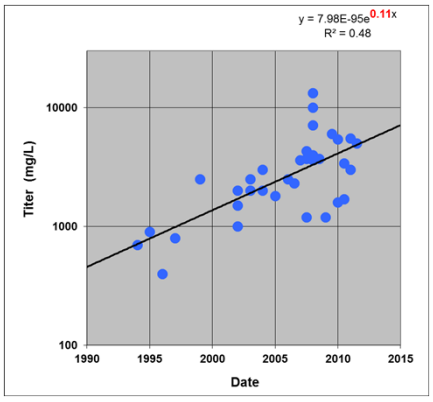
Evolution of Manufacturing Technologies



Cell Culture Process Productivity is Driven by Efficiency (Cell Engineering) and Intensity (Process Engineering)



Cell Culture Productivity Increases Have Delivered Huge Value



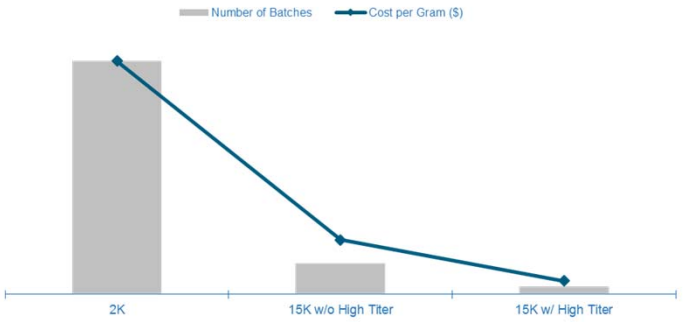
Growth Rate of 0.11 / year
Doubling Time of 6.3 years

- Steady Progress made on Process Productivity
- Improved Raw Material Control and Safety
- Reduced Development Times and Required Resources

Process Sciences Have Transformed Bulk Manufacturing Output

94% Reduction in $/gram of drug substance through scale and process productivity

$100/gram of monoclonal readily achieved



Asset Utilization Impacts Cost of Goods

Process productivity alone does not assure COGS reduction

Increased facility utilization immediately improves COGS

Chart: Relative Cost per g of Product

Titer (g/L) \ Facility Utilization	35%	50%	70%	90%
1	1	0.7	0.5	0.4
2	0.5	0.35	0.25	0.19
4	0.25	0.18	0.12	0.1
6	0.17	0.11	0.08	0.07

Productivity Improvement

Utilization Improvement

Engineering Creates Value Through Flexible Manufacturing Assets

- Key points for maximized asset utilization
  - Manufacturing platforms: seamless process transfer between sites
  - Robust scale-up: seamless transfer between scales
  - Minimized changeover between campaigns and between batches
  - Match process step duration, avoid single step bottlenecks
- Engineering's key contributions to asset utilization
  - Technology alignment
  - Equipment modeling for understanding of scale-effects
  - Facility and process analytics
  - Reliability centered maintenance for minimal downtime (shut downs, failure)

Maximizing Utilization Through a Flexible Hybrid Model

Future Factory advantages:

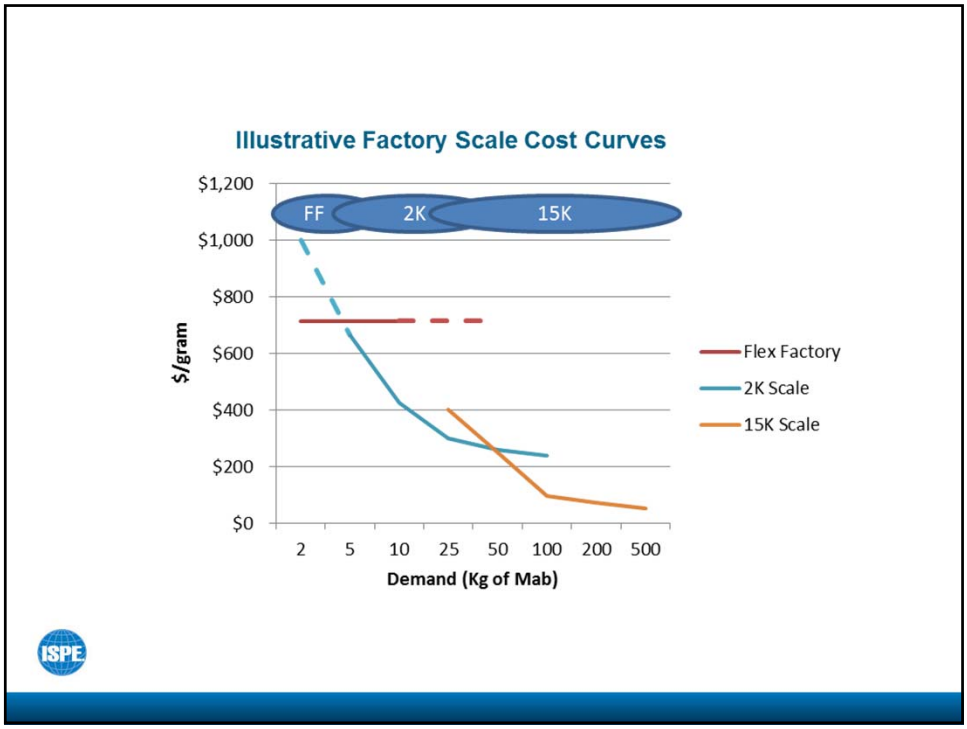
- Cost Effective for small quantities (clinical)
- Portable, lower capital investment, reduced footprint, etc.

Stainless Steel advantages:

- Cost effective for high volume and throughput
- Relatively Low variable costs
- Sunk costs for many companies

Our Hybrid Model: Optimizing existing network and new technologies

- Future Factory -- for early phase production and to accommodate demand variability
- 2K Scale – ideal for high titer late stage clinical and commercial production
- 15K Scale – ideal for high demand products



The Role of Innovation in Biogen's Hybrid MFG Network

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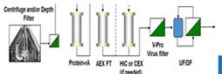
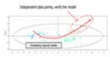
Creating Value Through Innovation in Biomanufacturing



Efficiency Through Incremental Technology Improvements

- Improve Existing MFG Technology



Efficiency Through Better Control

- Advanced Process Monitoring and Control

Efficiency Through Flexibility

- Facility Design & Scale-up Excellence

Improving Existing MFG Technology in the Near Term Through Sustaining Innovation

BIOLOGY

Increased productivity of cell lines

PROCESS & EQUIPMENT TECHNOLOGY INNOVATION

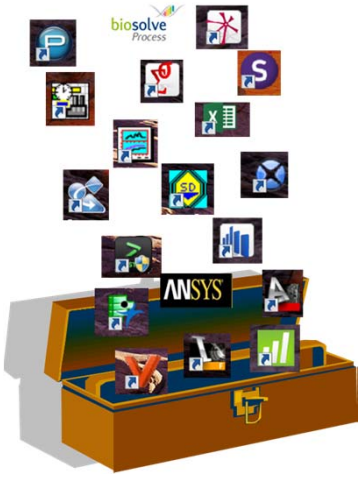
N-1 perfusion to optimize seed train productivity
High-capacity purification
Buffer concentrates
Single pass tangential flow filtration

In combination, incremental improvements can drive dramatic productivity increase

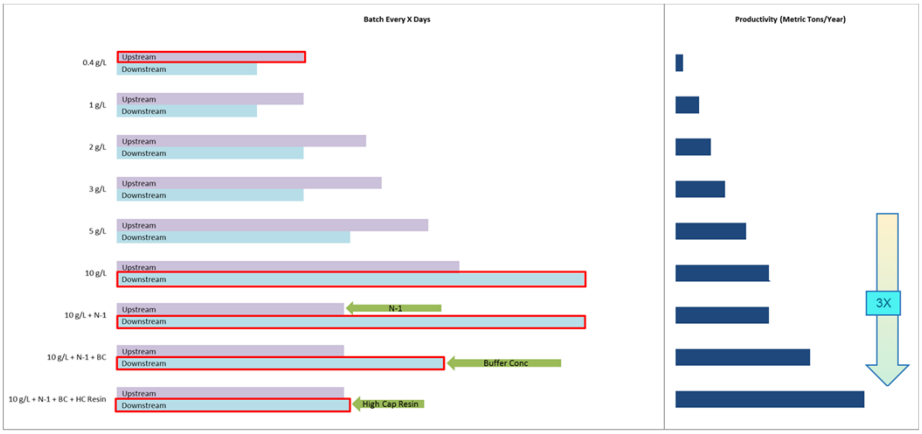
Modeling Provides Crucial Insights to Direct Innovation

Engineering Sciences provides:

- Computational Fluid Dynamics Modeling
- Process Modeling
- Dynamic Facility Modeling
- Statistical Modeling

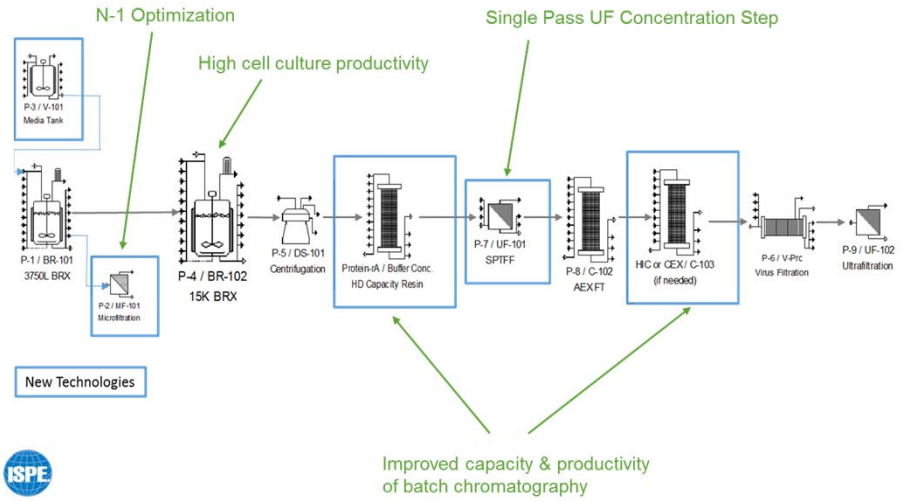


Facility Analytics Drive Strategic Improvement Programs

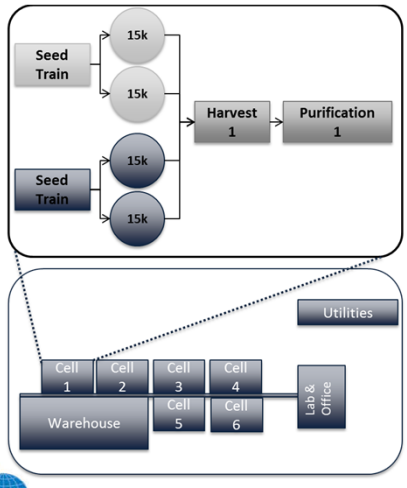


NOTE: Processing Bottleneck indicated with red bar

Where Can Conventional Process Technology Be Improved?



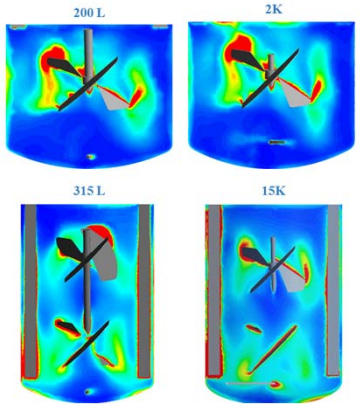
Large Scale MFG Design Considerations

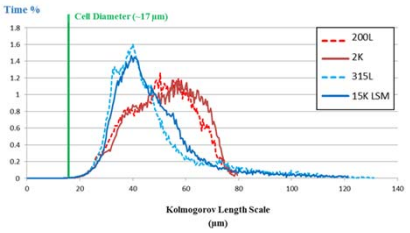


BIOGEN'S TEN METRIC TON ANTIBODY PRODUCTION CELL

- Modular design, optimized for throughput
- Build capacity in units of production cells;
- Deployment in phases to reduce investment risk
- Faster delivery post initial investment
- Each cell designed for up to 15 g/L and high throughput

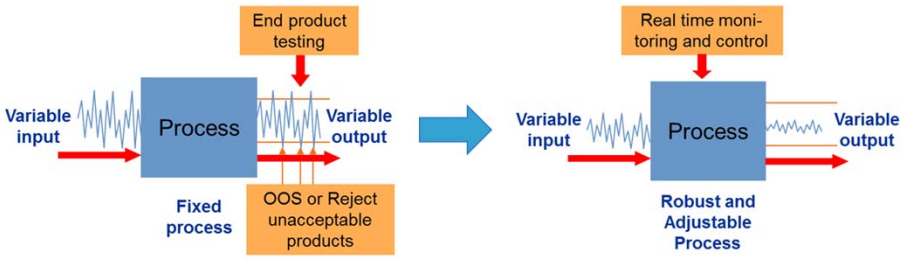
Quantitative Understanding of Scale Effects Enables Flexible Process Transfer for Maximum Asset Utilization





CFD simulations provide depth to bioreactor scalability analysis.

Engineering Creates Value Through Process Control



Present State

Future State

Process Control Vision

Raw Material Control
- Analytical fingerprinting
- Automated genealogy monitoring
- MVA models for feedforward control

Upstream Control
- Cell growth based feed control and transfers
- Automated set point glucose control

Downstream Control
- Adaptive feed forward control
- UF/DF refractive index feed back control

Analytical / Process Analytics
- Rapid and decisive multi-attribute methods
- In-line/On-line/At-line sensors*
- MVA models for disposition decisions

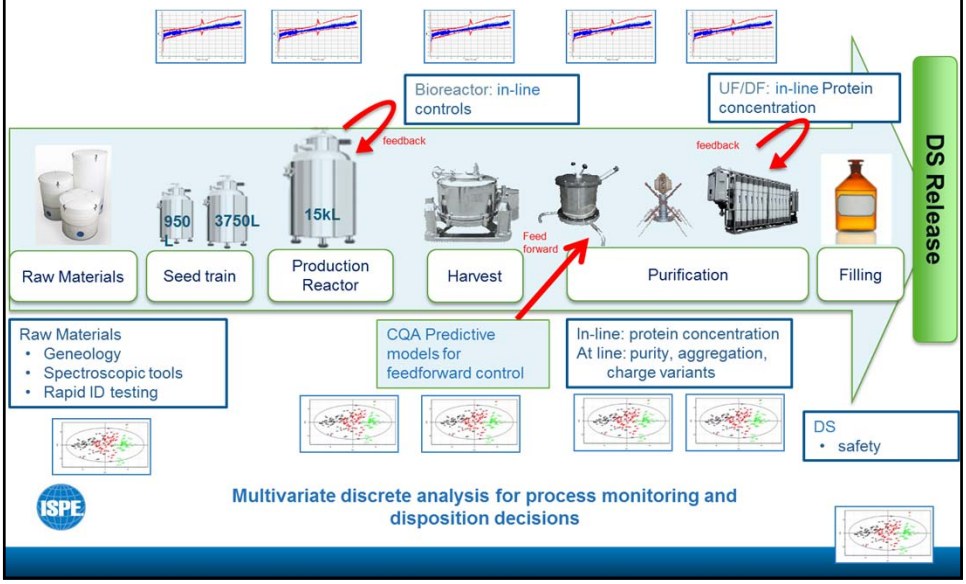
Benefit:
- Increased visibility to raw material variation
- Proactive control

Benefit:
- Consistent cell growth for consistent product quality and titer
- Control glycation

Benefit:
- Mitigate cell culture variation
- Better control of protein concentration

Benefit:
- Reduced sampling
- Real-time process data for release testing and adaptive control

Process Control For Real Time Release



Flexible Volume Facility Expands Asset Utilization

Single use technologies well-proven

Disposable bioreactors fully demonstrated in our prototype labs up to 10 g/L

Closed system technologies enable simplified infrastructure support

Flexibility, Cost Efficiency, Speed

Cell Culture Unit:
- Disposable 1000 – 2000 L bioreactors
- Harvest unit
- Overall productivity: 5 – 20 kg/batch

Intermediate Storage Unit:
- Storage of solid intermediate
- Batch size adapted to capacity of downstream unit

Purification Unit:
- Sized to optimize cost vs. clinical demand

Drug Substance Storage:
- Long term storage of Drug Substance

Operating a Disposable Process as a Closed System in General Pharmaceutical Manufacturing Space (GPMS)

- Closed System: Prevents ingress or egress of adventitious contaminants into the process stream
- Closed system achieved in GPMS through several methods
- Vendor qualified closed system components. Ex: gamma irradiated bags and tube sets using Readymate connectors or sterile welding.
- Open connections that were followed by appropriate cleaning or sanitization.
- Systems assembled and autoclaved or connections made in a class 100 hood.
- Closed system verification was performed to demonstrate closed system approach including effectiveness of connected unit operations

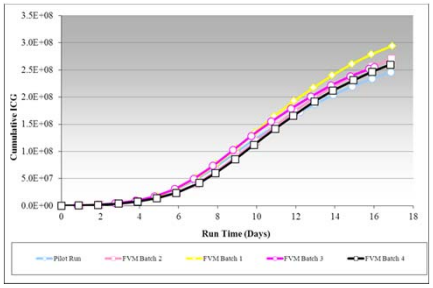
Closed System Verification

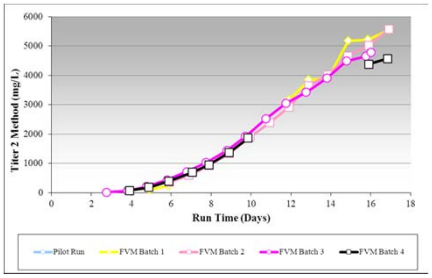
- Used proven growth promoting media (yeastolate)
- Simulation included all major processing steps including additions such as nutrient feed and buffers.
- Each unit op was evaluated for connection types and each type (Readymate, triclamp, etc) was used at least once.
- Number and type were evaluated and represented but was not required to be worst case.
- Sampled at specified locations and/or intervals and tested for growth promotion and microorganisms.
- Acceptance criteria- Upstream = No growth, Purification <100 CFU per 100 ml

Results of Closed System Verification

- Systems Challenged
  - Inoc (wave bag)
  - All SUBs
  - SUM to SUM (Single Use Mixer) transfers
  - Chrom Skid
  - Filtration (PODs)
  - UF/DF
  - Bulk fill
- All systems passed acceptance criteria

Results of Process Verification





Do We Need Disruptive Innovation in Biomanufacturing?

Sustaining versus Disrupting

You'll know when it's too late???

Steel Industry: A relevant case study?

Traditional Vertically Integrated Batch Mode
Continuous Casting and Minimills Disruption

Time for Disruption in Bioprocessing?

Capacity Constraints, Pipelines, At-Risk Capital Implications
=> A vision to "commoditize" biologics manufacturing?

Summary

- Question: Can we continue to drive the same value by doing more of the same?
- Suggestion: Manufacturing infrastructure investments may require new thinking
- Observation: productivity increases have allowed our industry to add flexible capacity to its rigid network
- Suggestion: we need innovation in operations and process technology to support the highest possible capacity utilization
- Conclusion: Existing stainless infrastructure remains a valued asset. A hybrid approach will become the “dominant design” at Biogen
- Suggestion: Even within conventional technology there is room for significant productivity improvements. Advanced process and facility analytics lead the way to targeted innovation.
- The big question: will we need disruptive innovation in Bioprocess technology?