MANUFACTURING TECHNOLOGIES: INSOURCING VERSUS OUTSOURCING

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Patheon, part of Thermo Fisher Scientific
December 5th 2017

Agenda

- Introduction
- Market Dynamics and Forecasting Challenges
- Cost Models and Supply Chain Quandaries
- Impact of Throughput
- Three Case Studies
  - Early phase flex
  - Late phase redesign
  - A need for speed!
- Conclusion
**Why come together – to create the industry's most fully integrated drug development and manufacturing solution**

Built on a proven foundation of quality systems and commitment to continuous improvement, Thermo Fisher Pharma Services has the capabilities and expertise to help you achieve success at every milestone.

- **Create or source your ingredient**
  - Route Scouting
  - Cell Line Development
  - Analytical Methods
  - Process Development
  - Commercial Manufacturing
  - More than 250 large & small APIs developed or manufactured

- **Design the ideal formulation**
  - Quick to Clinic
  - Complex Formulations
  - Solubility Enhancement
  - Analytical Methods
  - Process Development
  - Oral Solid & Sterile Development
  - More than 1,000 molecules developed 40+ dosage forms

- **Scale to your next milestone**
  - Pre-clinical
  - Early Phase Development
  - Clinical Trial Material Manufacture
  - Late Phase Trials
  - Commercialization
  - 143 technology transfers in 2016
  - 37 Drug Substance
  - 14 Development
  - 92 Commercial

- **Develop clinical supply chain strategy**
  - Clinical Supply Optimization
  - Compliance Management & Risk Mitigation
  - Comparator Sourcing
  - Label Translation & Planning
  - 11,000+ unique clinical packaging lots in 2016

- **Accelerate clinical research**
  - Primary & Secondary Packaging
  - Labeling
  - Storage & Distribution
  - Global Network
  - Cold Chain Material Management
  - Logistics & Transportation
  - More than 500,000 clinical shipments completed in 2016
  - 112 NDAs 2007-2016

- **Deliver a successful commercial launch**
  - +95% Right First Time delivery
  - 75% of all dosage forms
  - Oral Solid Dose
  - Sterile Injectable
  - Softgels
  - Flexible Business Models
  - +95% Right First Time delivery

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**Pharma Services Group - Patheon global locations**

More than 25 locations across North America, Europe, Latin America & Australia

- Whitby, Canada
- Toronto, Canada
- Cincinnati, OH USA
- Boston, MA USA
- Durham, NC USA
- High Point, NC USA
- Greenville, NC USA
- Princeton, NJ USA
- St. Louis, MO USA
- Bend, OR USA
- Florence, SC USA
- Greenville SC, USA
- Manati, Puerto Rico
- Monza, Italy
- Ferentino, Italy
- Milton Park, UK
- Swindon, UK
- Bourgoin, France
- Groningen, Netherlands
- Amsterdam, Netherlands
- Tilburg, Netherlands
- Linz, Austria
- Regensburg, Germany
- Tokyo, Japan
- Shanghai, China
- Brisbane, Australia
**MARKET DYNAMICS AND FORECASTING CHALLENGES**

Today's biologic pipeline doesn’t fit yesterday’s capacity

**Biologics market is changing...**

- More Complex Therapeutic Classes
- Higher Titers, Product Yields
- Improvements in upstream processing are producing higher yields

**In the future, more commercial product will be supplied from smaller bioreactors**

- 50% of all products in development will require 5kL or smaller bioreactor
- Multiplexing, SU, high titer fed batch, perfusion technology...

Biopharma no longer needs to rely on a one-size-fits-all solution
Forecasting for biomanufacturing is a challenge

Key drivers for forecast inaccuracy

- Dosage
- Titer
- Price
- Market size

Actual

- Delays in clinic
- Tied up capital
- Forego profit

You need to consider several sales curves

### Sales forecast

- **Actual high**
  - Can’t fulfill demand
  - Too much capacity

- **Actual low**

- **Forecast**

### Timing forecast

- **Market development**
- **Actual ahead**
- **Actual behind**
- **Ahead of curve**

- **Forecast**

- **Time**
Biopharma no longer needs to rely on a one-size-fits-all solution.

Biopharma has access to flexibility and more choices than ever before.

- **Single Use Systems**: x1
  - High titer fed batch
  - Perfusion technology
  - High density cell culture

- **Maturing Process Technology**
- **Smaller Bioreactors**
  - 50% of the clinical pipeline can be supplied from 5KL or smaller bioreactors
- **Multiplexing**
  - Processing multiple bioreactors in a single downstream batch

Design your supply chain based on your product or portfolio strategy. Optimize for unit cost, responsiveness and flexibility, or both.

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**COST MODELS AND SUPPLY CHAIN QUANDARIES**
Develop an understanding of

- How does process development best approach new processes from an economic perspective?
- What drivers will enhance productivity the most?
- How do we address scale-up?
- How does Patheon approach single use vs. stainless steel?
- How to think of a network?
- Clinical vs. commercial?
- Where and how to invest money?

Patheon cost model – For information only

**ASSUMPTIONS**

- Fed-batch
- Labor will vary across utilization
- Labor cost $150,000 per FTE
- CAPEX is cost of building new
- Expansion of existing site
- Material costs from existing processes
- Depreciation 20 year life
- Hybrid configuration has prep systems in SS
- Resin life 50 cycles or 2 years
- Media cost $15 / liter
- Facilities costs 5% of capex
- Other Costs 25% of facilities costs
- 10% material handling cost
- No taxes or interest
- $6 material cost per gram of protein produced

**KEY ASSUMPTIONS**

- 3 g / L titer
- 70% yield
- $1.3 MM Service Fee @2K
- $2.3 MM Service Fee @5K
- $3.5 MM Service Fee @15K
- 2K L Hybrid
- 5K L Stainless
- 15K L Stainless
- Robust process
- 7 day downstream cycle
**Make vs Buy cost ($ / g)**

Scale, utilization, and throughput have significant impact on cost.

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**Total annual cost for the drug substance ($ M per year)**

- **2000 L scale very viable**
- **Many options are viable in the “Middle”**
- **Need big tanks**
- **Differential creates driver for change**

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**Make vs Buy cost ($ / g)**

- **2-6 2000 L Own ($/g)**
- **2000 L Outsource ($/g)**
- **2 x 5000 L Own ($/g)**
- **5000 L Outsource ($/g)**
- **6 x 5000 L Own ($/g)**
- **6 x 15000 L Own ($/g)**
- **6 x 15000 L Outsource ($/g)**

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**Make vs. Buy total annual cost**

![Graph showing Make vs. Buy total annual cost](image)

- **2000 L scale very viable**
- **Many Potential Pathways**
- **Financial Driver for Change**

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<tr>
<th>Total annual cost for the drug substance ($ M per year)</th>
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<th>40</th>
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**Biologics companies have many manufacturing options**

**Biopharma manufacturing executives have many options for meeting capacity, including:**

- Insourcing / dedicated
- Single use technologies
- One-step development
- Large scale
- Existing capacity
- Outsourcing / shared
- Stainless steel
- Two-step development
- Small scale
- New capacity
Solve for volume and scale first - Outsource / Shared

2 K L cell culture batch

- $1.9 M with materials
- 4.2 kg API at 3 g/l & 70% yield
- $450/g
- Pay more per unit
- May not have enough product

15 K L cell culture batch

- $4.3 M with materials
- 32 kg API at 3 g/l & 70% yield
- >50% cheaper per kg on large scale
- 3 validation batches = expensive
- More product than you need

Solve for volume and scale first - Insource / Dedicated

2 K L cell culture batch

- $0.85 M* with materials
- 4.2 kg API at 3 g/l & 70% yield
- $200/g
- Pay more per unit
- May not have enough product

15 K L cell culture batch

- $2.6 M* with materials
- 32 kg API at 3 g/l & 70% yield
- >50% cheaper per kg on large scale
- 3 validation batches = expensive
- More product than you need

* With major investment
Make vs Buy cost ($ / g) - summary

Scale, utilization, and throughput have significant impact on cost

- Scale selection at high demand and low demand are simple
- Mid range options are plentiful and the decisions can be complicated
- As utilization goes down, the viability of owning is significantly diminished
- Larger scale does not always result in lower costs
- Outsourcing is better suited for driving variabilized costs

CASE STUDIES
- EARLY PHASE FLEX
- LATE PHASE REDESIGN
- A NEED FOR SPEED!
Case Study 1: Early phase flex

Background: Customer came to us with multiple Phase I projects and highly uncertain market demand. Customer was located in a “high cost” location and didn’t want to manufacture internally.

Process characteristics:
- Typical mAb processes and titers
- Highly conserved raw martial demand/type from molecule to molecule
- Highly uncertain long term (and short term) demand

Case Study 1: Early phase manufacturing still offer unique opportunities

Solution: We were able to work with this customer to set aside manufacturing space that could be allocated among different projects. In essence, we aggregated demand to get on the curve.

In general if you are in the early phases its about avoiding costs associated with building a manufacturing plant... because if you don’t use it, you still pay for it!
Case Study 2: Late phase redesign

Background: Customer came to just prior to Phase III clinical trials, and had previous been operating at the 1000L Scale.

Process Characteristics
- Historical process successfully transferred from 1000L to 2000L scale
- Low titer requiring > 2000L Scale for commercial demand
- Process was poorly characterized
- Clinical results were very promising but CMC was way behind

Upstream Development Scope of Work

Late-phase Development
Technical transfer occurred at start of Phase III

Monoclonal Antibody
Needed a higher titer to make the process viable

Undesirable RM in Media
Needed to remove

Focus on COGS
Willing to do PD despite tight timeline
Upstream Development

Media Adaptation
Screened 10 chemical defined media

Ambr15™ Run #1
Screened 7 feeds across 6 new media.

Ambr15™ Run #2
DOE to identify CPPs with new media and feed

2 Rounds of DOE @ 10L Scale
14 reactor runs utilizing scale down model

Upstream Development Results

Improved Titer
2X in Ambr15™ studies / 2.5X in 10L DOE optimization

Peak VCD Increase
1.6X increase in peak VCD / 2X increase in IVCD.

Shorter Seed Train Scale Up
Reduced by 5 days

Enhanced Product Quality
Removed ADRM / specific glycoform decrease
Case Study 2: Outcome

Solution: By increasing the process titer this customer was able to “shift the curve” and enter their PPQ batches (now complete) with a much more economically viable process.

There is still the opportunity to multiplex and “jump” to the 5000L curve

![Graph showing process titer vs cost]

- Drove the cost cure down via development
- Maintain the option to jump from the 2kL to the 5kL curve via multiplexing

Case Study 3: A need for speed!

Background: Customer came to us with a desire to enter PPQ batches on a highly accelerated time line< 6mo. There was a need for a high level of flexibility in terms of total product demand due to potential competition.
Case Study 3: Solution make it happen and lean it out later

Solution: When you’re racing to launch it’s all about speed, speed and speed. You need to find open capacity where you can.

That being said there are still efficiencies to be gained, it not just about titer. The DSP cadence can substantially impact your costs of goods as well.

<table>
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<th>DSP Cadence</th>
<th>14 days</th>
<th>12 days</th>
<th>9 days</th>
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<td>Total Bench</td>
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Summary

- The overall framework of the biologics market is growing rapidly
- Forecasting and planning is difficult at best
- There are many different options available to approach the challenges
- Supply chain decisions can have a major financial impact
- Depending on your molecule there are many levers you can pull to find an efficient solution
Questions & Thank you