Manufacturing Matters in Cell Therapy

Market Brief January 2016

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NB Research Report

Overview

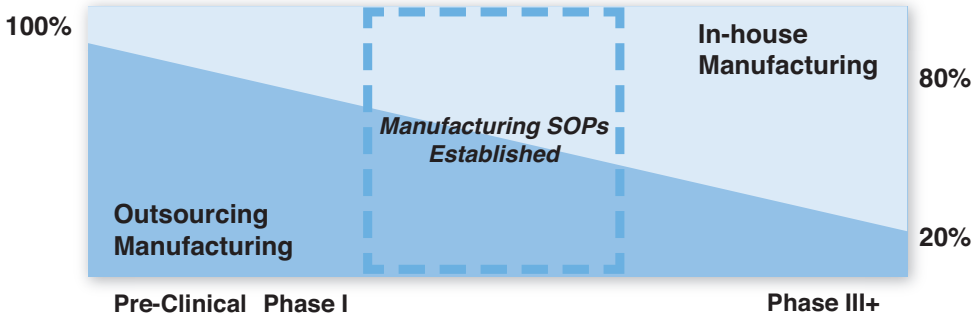
Rapid growth in the cell therapy industry is driving demand in cellular manufacturing. However, manufacturing of cell-based therapeutics, particularly the transition from early preclinical to late commercial stages, remains one of the most significant challenges faced by the industry. A major factor contributing to this challenge is that ***there is no typical, one-size-fits-all manufacturing solution.***

Despite the variability in protocols, there are typical manufacturing transitions that occur, through clinical development and during scale-up, where critical decisions regarding manufacturing in cell therapy are made. For companies providing manufacturing services and solutions, understanding when, where, and how these transitions occur provides key entry points to gain and retain new customers. For companies developing cellular therapeutics, planning for successful manufacturing transitions before they become costly can make the difference between clinical and commercial success.

This brief report provides an overview of the key phases where transitions in manufacturing occur, and factors influencing decisions on manufacturing from start-up to commercial scale. In addition, this report will touch on industry trends geared towards developing more efficient and cost-effective manufacturing solutions to support the growth and success of the cell therapy industry. A full Market Report will be available online at *www.nelsenbiomedical.com* beginning February 29, 2016.

I. Fundamental Manufacturing Decisions Occur Before Phase II Trials

The growth in cell-based therapeutic research over the past decade has stimulated academic institutions to establish or expand on-campus bioprocessing facilities. These academic manufacturing facilities are the outsourcing vendors of choice for manufacturing of pre-Investigational New Drug ("pre-IND") through Phase II studies. In fact, our market research showed that 80% of young companies use academic institutions, typically those affiliated with their scientific founders, for their manufacturing needs. Companies cited access and price point as the key determinants in their use of institutional manufacturing facilities. Unfortunately, decisions made early in the development of therapies can have a long-lasting effect on commercial success.



Rather than geographical convenience, young companies would benefit from opting to manufacture at one of the handful of "high profile" institutional facilities report that up to 50-60% of their clients are commercial entities (See Full Report for a list of these organizations). What differentiates these more commercially focused and successful institutional manufacturing centers from their counterparts? We found three distinguishing characteristics:

80% of early stage cell therapy companies outsource their manufacturing for pre-IND through Phase II.

1. Typically they have retained staff with commercial manufacturing backgrounds experienced in moving manufacturing from research scale to large-scale in an FDA compliant manner.
2. They have an ability to provide adaptive solutions and develop SOPs. This is particularly valuable given that cell therapy companies are continually learning about the biology informing the cellular requirements of a particular therapy, which in turn necessitates system modifications and adaptations.
3. They demonstrate interest, investment, and incorporation of novel systems and solutions for manufacturing.

These highly focused Institutional Centers should be the point of starting point for both early-stage cell therapies companies, and corporations providing new manufacturing solutions.

II. Cost and Control Determine Outsourcing Versus In-House Manufacturing

Outsourcing manufacturing offers the advantages of instant access to facilities and experienced personnel. But this comes at a cost beyond dollars for many young companies. **The greater cost is control.** Rather than a company's own employees gaining manufacturing expertise, it is the CMO's staff who are developing a working knowledge of the company's protocols. This can lead to a challenging transition later if a decision is made to bring manufacturing in-house. On the other hand, in-house manufacturing offers the highest degree of control and the ability to adapt and adjust protocols

The majority of later stage companies (greater than 75%) turn away from outsourcing all together and develop in-house manufacturing facilities.

Early Stage	Late Stage	
Academic Facility	**CMO**	**In-House**
⊕ Process adaptability ⊕ Easy transition to internal ⊕ Reasonable price point ⊖ Limited scale-up capacity	⊕ Large-scale capabilities ⊕ Experienced personnel ⊕ Process control ⊖ High Cost	⊕ Process control and adaptability ⊖ Expensive and uncertain return on investment ⊖ Expertise difficult to retain

as needed, but building and validating a system from scratch is very expensive and finding qualified staff to operate the facility is challenging. Furthermore, facilities may only be used sporadically during certain phases of clinical development, meaning that a satisfactory return on investment may not be realized until far into the future. For companies that are venture-backed, this investment is typically discouraged. But for many, despite the high initial expense, in-house manufacturing is the preferred manufacturing option in later clinical phases. New manufacturing systems in development will increase process control and adaptability so that trade-offs and transitions between the two options will become less of a barrier. Moreover, these new manufacturing systems could enhance the use of CMOs to establish manufacturing SOPs that can then be easily transferred to an in-house facility when needed. The quickly shifting landscape in manufacturing solutions is likely to reduce manufacturing costs, whether outsourcing or manufacturing in-house.

III. The Shift to Closed, Automated Systems

Dendreon provided an excellent (if unfortunate) example of a company that was clinically successful but a failure commercially due to the high cost of manufacturing. The cost of a single cleanroom for manufacturing cells from a single donor, or for a single program, is one of the bottlenecks associated with current cell manufacturing systems (from both a time and cost perspective). Scaling up a manual, cleanroom-based process involves installing additional cleanrooms, but cleanrooms are expensive to build and maintain, and simultaneous production of cells from multiple donors is impossible. One CMO we interviewed stated that to improve manufacturing efficiencies for both large and small-scale cellular therapeutics, the industry is headed away from clean rooms and toward automated, fully enclosed systems that can manufacture cells from multiple patients, or for multiple programs, simultaneously.

"If a single company we are involved with has success with all of their programs, they would need 100 clean rooms. This is just not feasible."

The emphasis is on single-use, disposables and a small footprint. The variety of manufacturing solutions improve efficiency by increasing cell density, reducing media and supplements use, decreasing sources of contamination, reducing human error and decreasing labor requirements. More improvements are on the way. The FDA is encouraging the industry to move to closed, separated and automated manufacturing systems as alternatives to clean rooms. In fact, regulators highly recommend that new manufacturing facilities look for and incorporate "closed and separated" systems, so that they can be producing things in a smaller scale, utilizing closed and automated formats. This shift is essential in the cell therapy industry where the cost of goods sold has been a significant barrier to success.

- Biomanufacturing is moving to disposable, small-footprint solutions.
- Implementing semi- or fully-automated, entirely enclosed manufacturing systems has become the future.
- This shift will enable cell therapy companies' transitions from outsourcing manufacturing, to building in-house capabilities.

Summary Recommendations

Manufacturing decisions can make or break the commercial success of cell therapies. Key fundamentals for manufacturing are established before Phase II clinical trials.

If you are a cell therapy company:

- Partner with commercially trained staff early in process development.
- Adopt new manufacturing systems that are efficient, cost-effective and scalable.
- Opt for manufacturing systems as automated and enclosed as possible. These are readily transferrable in-house manufacturing or CMOs in later stages.

If you are a company providing manufacturing systems:

- Target therapeutics customers early in life, before Phase II, to drive adoption and market share.
- Focus on high-profile Institutional (academic) manufacturing facilities for use and adoption of new systems.
- Manage the cost-versus-control conundrum by providing rental programs or other low-cost options for getting your systems in-use early.

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Our full Research Report will be available on February 29, 2016.
For ordering information, visit www.nelsenbiomedical.com